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Toxicological Review of Formaldehyde—Inhalation

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Integrated Risk Information System
Center for Public Health and Environmental Assessment
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ABBREVIATIONS

ACA	activated carbon aerosol
ACTH	adrenocorticotropic hormone
ADAF	age-dependent adjustment factor
ADH	alcohol dehydrogenase
ADME	absorption, distribution, metabolism, excretion
ALDH2	aldehyde dehydrogenase 2
ALI	air-liquid interface
ALL	acute lymphoblastic leukemia
ALM	anterior lateral meatus
ALS	amyotrophic lateral sclerosis
AML	acute myeloid leukemia
ANOVA	analysis of variance
AOP	adverse outcome pathways
AON	adverse outcome network
ATS	American Thoracic Society
ATSDR	Agency for Toxic Substances and Disease Registry
BAL	bronchoalveolar lavage
BALF	bronchoalveolar lavage fluid
BBDR	biologically based dose-response
BER	base excision repair
BM-MSC	bone marrow mesenchymal stem cell
BMC	benchmark concentration
BMCL	benchmark concentration, lower confidence bound
BMD	benchmark dose
BMDL	benchmark dose lower limit
BMI	body mass index
BMR	benchmark response
BrdU	5-bromodeoxyuridine
BTPS	body temperature and ambient pressure saturated (with water vapor)
BW	body weight
CA	chromosomal aberration
CASN	Chemical Abstracts Service Number
CASRN	Chemical Abstracts Service Registry Number
CDC	Centers for Disease Control and Prevention
CE	cumulative exposure
CFD	computational fluid dynamic(s)
CFU	colony-forming unit
CFU-GM	colony-forming unit-granulocytes and macrophages
CGRP	calcitonin gene related protein
CI	confidence interval
CIIT	Chemical Industry Institute of Toxicology
CLL	chronic lymphatic leukemia
CML	chronic myeloid leukemia
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
COSMIC	Catalogue of Somatic Mutations in Cancer
cRfC	candidate reference concentration
CRH	corticotropin-releasing hormone
CS	conditioned stimulus
CTL	cytotoxic T lymphocytes
CV	coefficient of variation

DDC	DNA crosslink
DG	dentate gyrus
DNA	deoxyribonucleic acid
DPX	DNA-protein crosslink
DSB	double strand break
EA	ethyl acetate
EBV	Epstein-Barr virus
EC	effective concentration
ECHRS	European Community Respiratory Health Survey
EEG	electroencephalogram
EI	exposure index
EMG	electromyelogram
EPA	Environmental Protection Agency
ER	endoplasmic reticulum
ETS	environmental tobacco smoke
FANC	Fanconi anemia family
FDR	fecundability density ratio
FEF	forced expiratory flow
FEV	forced expiratory volume
FSH	follicle-stimulating hormone
FVC	forced vital capacity
GD	gestational day
GLP	good laboratory practice
GM	granulocyte, monocyte
GSNO	S-nitrosoglutathione
GSNOR	S-nitrosoglutathione reductase
GSD	geometric standard deviation
GSH	glutathione
HCHO	formaldehyde
HCL	hairy cell leukemia
HDM	house dust mite
HEC	human equivalent concentrations
HERO	Health and Environmental Research Online
HHRA	Human Health Risk Assessment
HIC	highest ineffective concentrations
HL	Hodgkin lymphoma
hmDNA	hypermethylated DNA
HPA	hypothalamic-pituitary-adrenal
HPG	hypothalamic-pituitary-gonadal
HPO	hypothalamic-pituitary-ovarian
HR	hazard ratio
HSC	hematopoietic stem cells
HSPC	hematopoietic stem and progenitor cells
HUVEC	and umbilical vein endothelial cells
IARC	International Agency for Research on Cancer
IB	information bias
ICD	International Classification of Disease
IFN	interferon
i.p.	intraperitoneal
IQR	interquartile range
IRIS	Integrated Risk Information System
ISAAC	International Study of Arthritis and Allergies in Children
IUR	inhalation unit risk
JEM	job-exposure matrix
JNK	Jun N-terminal protein kinase

LEC	lowest effective concentration
LI	labeling index
LH	luteinizing hormone
LHP	lymphohematopoietic
LM	lateral meatus
LOAEL	lowest-observed-adverse-effect level
LOD	limit of detection
LOQ	limit of quantification
LRT	lower respiratory tract
M1dG	malondialdehyde-deoxyguanosine
MAP	mitogen activated protein
MEF	mid-expiratory flow
MDA	malondialdehyde
MDS	myelodysplastic syndrome
mRNA	messenger RNA
miRNA	microRNA
ML	myeloid leukemia
MLE	maximum likelihood estimate
MM	multiple myeloma
MMEF	maximum mid-expiratory flow
MN	micronuclei
MOA	mode of action
MOR	mortality odds ratio
MS	mass spectrometry
MSC	Mesenchymal stem cell
NADP	Nicotinamide adenine dinucleotide phosphate (NADPH), reduced form
NALT	nasal-associated lymphoid tissues
NAS	National Academy of Sciences
NASA	National Aeronautics and Space Administration
NATA	National-Scale Air Toxics Assessment
NCEA	National Center for Environmental Assessment
NCHS	National Center for Health Statistics
NCI	National Cancer Institute
NER	nucleotide excision repair
NHL	non-Hodgkin lymphomas
NIOSH	National Institute for Occupational Safety and Health
NK	natural killer
NLMS	National Longitudinal Mortality Study
NMDA	*N*-methyl-D-aspartate receptor
NO	nitric oxide
NOAEL	no-observed-adverse-effect level
NOS	Nitric oxide synthase
NO_X	nitrogen oxides
NP	nonprotein
NPC	nasopharyngeal cancer
NRC	National Research Council
NREMS	nonrapid eye movement sleep
NTP	National Toxicology Program
OB	olfactory bulb
OE	olfactory epithelium
OHPC	oropharyngeal/hypopharyngeal cancer
OR	odds ratio
ORD	Office of Research and Development
OSB	oriented strand board
osRfC	organ/system reference concentration

OVA	ovalbumin
PA	polypoid adenoma
PBL	peripheral blood lymphocytes
PBPK	physiologically based pharmacokinetic
PECO	Populations, Exposures, Comparisons, Outcomes
PEF	peak expiratory flow
PEFR	peak expiratory flow rate
PG	periglomerular
PMR	proportionate mortality ratio
PND	postnatal day
POD	point of departure
POD_{ADJ}	point of departure, adjusted
POD_{HEC}	point of departure, human equivalent concentration
POE	portal of entry
PTM	posttranslational modification
PPL	prolymphocytic leukemia
ppm	parts per million
RANTES	regulated on activation, normal T-cell expressed and secreted
RE	respiratory epithelium
REMS	rapid eye movement sleep
RC	room control
RfC	reference concentration
RfD	oral reference dose
RIL	recommended indoor limit
ROS	reactive oxygen species
RR	relative risk
SA	spontaneous abortion
SB	selection bias
SCC	squamous cell carcinoma
SCE	sister chromatid exchange
SCF	stem-cell factor
SD	standard deviation
SE	standard error
SEER	Surveillance, Epidemiology, and End Results
SEM	standard error of the mean
SES	socioeconomic status
SIR	standardized incidence ratio
SMR	standardized mortality ratio
SNC	sinonasal cancer
SNP	single nucleotide polymorphism
SOD	superoxide dismutase
SPES	symptom questionnaire (German translation)
SPIR	Standardized Proportional Incidence Ratio
SPT	skin prick tests
SRR	summary relative risk
SSB	strand breaks
TCL	T cell lymphoma
TE	transitional epithelium
TH	tyrosine hydroxylase
THF	tetrahydrofolate
TLV	threshold limit value
TNF	tumor necrosis factor
TPA	12 O tetradecanoylphorbol-13-acetate
TRP	transient receptor potential (channel)
TSCE	two-stage clonal expansion

TSFE	time since first exposure
TSLP	thymic stromal lymphopoietin
TTP	time-to-pregnancy
TWA	time-weighted average
UCL	upper confidence limit
UCOD	underlying cause of death
UDS	unscheduled DNA synthesis
UF	uncertainty factor
UF_A	uncertainty factor, interspecies
UF_C	uncertainty factor, composite
UF_D	uncertainty factor, database
UFFI	urea foam insulation
UF_H	uncertainty factor, intraspecies
UF_L	uncertainty factor, LOAEL-to-NOAEL
UF_S	uncertainty factor, subchronic-to-chronic
UFFI	urea formaldehyde foam insulation
ULLI	unit length labeling index
URT	upper respiratory tract
U.S.	United States of America
UV	ultraviolet
VAS	visual analogue scale
VC	vital capacity
VOC	volatile organic compound
WBC	white blood cell
XRCC	X-ray repair cross-complementing

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Office of Chemical Safety and Pollution Prevention/Office of Pesticide Programs
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This assessment was provided for review to other federal agencies and Executive Offices of the President. Comments were submitted by:

Department of Defense
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Department of Health and Human Services/National Institute of Environmental Health Sciences
Department of Health and Human Services/National Institute for Occupational Safety and Health
Executive Office of the President/Office of Management and Budget
Small Business Administration Office of Advocacy

This assessment was released for public comment on [month] [day], [year] and comments were due on [month] [day], [year]. The public comments are available on the IRIS website. A summary and EPA's disposition of the comments from the public is included in Appendix [X] and is also available on the IRIS website. Comments were received from the following entities:

COMPANY NAME	Location
COMPANY NAME	Location

This assessment was peer reviewed by independent expert scientists external to EPA (specify NAS panel) and a peer-review meeting was held on [month] [day], [year]. The external peer-review comments are available on the IRIS website. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix [X] and is also available on the IRIS website.

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PREFACE ON ASSESSMENT METHODS AND ORGANIZATION

This Preface presents information to orient the reader to the assessment, including background information on the development of the Toxicological Review of Formaldehyde—Inhalation and a description of the focus and underlying framework for this assessment. The evaluation of formaldehyde's toxicity was informed by what is known about the toxicokinetics of inhaled formaldehyde (see Section 1.1.3 and Appendix A.2), and this knowledge is reflected in the organization of the Hazard Identification section. This Preface summarizes the approaches and methods for the identification of the literature and evaluation of study methods, syntheses of results for specific health hazard categories within streams of evidence, and integration of the evidence across human, experimental animal, and mechanistic studies. Finally, the approach used to select studies and their data for deriving quantitative (dose-response) values is described.

BACKGROUND INFORMATION

The Toxicological Review was prepared under the auspices of the U.S. Environmental Protection Agency's (EPA's) Integrated Risk Information System (IRIS) program. Assessment development was based on EPA guidelines as well as standard IRIS procedures (U.S. EPA, 2020) that were reviewed by the National Academy of Sciences, Engineering, and Medicine (NASEM[1]) (NASEM, 2021). In 1990 and 1991, an oral reference dose (RfD) (reference value for ingested formaldehyde) and an inhalation unit risk (IUR) value for cancer, respectively, were developed for formaldehyde. A previous draft of the inhalation assessment was developed between 1998 and 2010. That document was reviewed by an external peer-review panel convened by the National Research Council (NRC) between June 2010 and April 2011 (NRC, 2011). The newly developed, current assessment addresses the comments from the NRC panel on that prior draft (see Appendix D).

For additional information about this assessment or for general questions regarding IRIS, please contact EPA's IRIS Hotline at 202-566-1676 (phone), 202-566-1749 (fax), or hotline.iris@epa.gov.

[1] This Toxicological Review and related assessment documents refer to NASEM as well as the National Academy of Sciences (NAS) and National Research Council (NRC). These names apply to the same organization during different timeframes (generally with different panel members on the different review panels).

GENERAL ASSESSMENT ORGANIZATION

The Toxicological Review critically reviews the publicly available studies relevant to human health hazards that may result from formaldehyde inhalation and describes the level of confidence in the supporting evidence. When there was sufficient confidence in the evidence supporting a hazard and appropriate studies and data were available, toxicity values were derived using either analyses of dose-response or selected no-observed-adverse-effect or lowest-observed-adverse-effect levels (NOAELs or LOAELs). Although this review focused on exposure through inhalation, general population exposure to formaldehyde can occur via inhalation, ingestion, and dermal contact.

The Toxicological Review is organized into the following sections: Introduction (consisting of a Preface and an Executive Summary); Hazard Identification; and Dose-Response Analysis. Supplemental Information to the Toxicological Review is provided in a separate document, *Supplemental Information to the Toxicological Review of Formaldehyde—Inhalation*, containing appendices that support hazard identification and dose-response evaluation. The appendices include a description of the chemical properties and uses of formaldehyde; information specifically addressing exposure, toxicokinetics, and genotoxicity; supporting information for health hazard conclusions in the Toxicological Review (i.e., literature search strategies and results for each health hazard; conclusions of the evaluation of study methodology; additional analyses); dose-response modeling; a list of previous legislation and assessments by other agencies; and responses to external peer-review comments on a prior draft IRIS assessment. In addition, an abridged version of the main assessment conclusions and underlying analyses is provided in a third document, the *Assessment Overview*. Additional documents produced during assessment development are available on the IRIS website (http://www.epa.gov/iris).

The NRC recommendations on the 2010 draft IRIS assessment (NRC, 2011) were substantive and prompted development of a new (from scratch) assessment using a framework for evidence identification, evaluation, and integration to provide a more systematic and transparent process. As a result, different decisions were made, some as a response to the comments received and others as part of the systematic approach to evaluating the available evidence.

For the purposes of this assessment, potential human health hazards from formaldehyde exposure were identified and evaluated. These include sensory irritation; decreased pulmonary function; respiratory tract pathology; immune-mediated conditions, focusing on allergies and asthma; nervous system effects; reproductive and developmental toxicity; and carcinogenicity. These health outcomes were identified based on previous reviews of formaldehyde toxicity and health assessments by other agencies, including the International Agency for Research on Cancer (IARC), Agency for Toxic Substances and Disease Registry (ATSDR), and the National Toxicology Program (NTP) (NTP, 2014; IARC, 2012; ATSDR, 2010, 1999). For each health hazard, the literature regarding specific health effects was synthesized within each of the human, animal, and mechanistic streams of evidence and then integrated across the streams of evidence. The evidence integration

includes a narrative summary of the key evidence and a corresponding level of evidence judgment (i.e., **evidence demonstrates**, **evidence indicates [likely], evidence suggests**, or **evidence inadequate**[2]) as to whether formaldehyde inhalation exposure may pose a human hazard for specific types of cancer or individual noncancer health effects, given appropriate exposure circumstances. The assessment provides evidence integration judgments for each unit of analysis that can be reasonably supported by the available health effect-specific evidence base, so that a given health hazard may have a single judgment or multiple judgments at more granular outcome groupings. The evidence integration for cancer concludes with a descriptor summarizing the weight of evidence for cancer according to EPA's cancer guidelines (U.S. EPA, 2005a). For each credible hazard identified (in this assessment, judgments of **evidence demonstrates** or **evidence indicates** [likely]), the "appropriate exposure circumstances" alluded to during hazard identification in Section 1 are more fully evaluated and defined through dose-response analysis in Section 2 (including, depending on the evidence available, the derivation of toxicity values).

Based on the current understanding of the toxicokinetics of formaldehyde inhalation exposure (see Appendix A.2), several practical working assumptions were applied to this assessment. Although some uncertainties remain, the organization and analyses in the assessment assume that inhaled formaldehyde is not distributed to an appreciable extent beyond the respiratory tract to distal tissues; thus, it is assumed that inhaled formaldehyde acts via a pathway different from a direct interaction with tissues distal to the portal of entry (POE) to elicit observed systemic effects. Similarly, it is assumed that formaldehyde does not cause appreciable changes in normal metabolic processes associated with formaldehyde in distal tissues. Thus, studies examining potential associations between levels of formaldehyde or formaldehyde byproducts in tissues distal to the POE (e.g., formate in blood or urine, brain formaldehyde levels) and health outcomes are not considered relevant here to interpreting the human health hazards of inhaled formaldehyde.

The Toxicological Review includes an inhalation reference concentration (RfC) value for lifetime exposure. The inhalation RfC (expressed in units of μg of substance/m^3 air) is defined as an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous daily exposure of formaldehyde to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. A carcinogenicity assessment was also performed, including derivation of an inhalation unit risk value (IUR), which is an upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 μg/m^3 in air. In addition, organ/system-specific RfCs (osRfCs) were derived for the various noncancer health endpoints, when supported by the available evidence. These may be useful when considering cumulative risk scenarios. Multiple candidate RfCs (cRfCs) were

[2] These level of evidence judgments and their implications are described in detail in the IRIS Handbook (U.S. EPA, 2020). Note that none of the health effects evaluated in this assessment approached the level of evidence needed to support a judgment of **strong evidence supports no effect**, so this level is not discussed.

sometimes compared before choosing a representative osRfC. An osRfC was typically selected from cRfCs based on use of higher confidence studies, and higher confidence in the cRfC derivation (including point-of-departure [POD] selection). Where relevant, mechanistic understanding regarding the development of specific health effects (e.g., temporal progression, potential thresholds in dose-response), as well as knowledge of susceptibility, was used to inform approaches to derive points of departure (PODs), uncertainty factors, or confidence levels for the quantitative estimates (e.g., osRfCs, RfC, IUR). Where possible, the assessment attempts to describe the level of response observed across different exposure levels within the range of the data, and to discuss transparently the uncertainties and assumptions when deriving toxicity value estimates (e.g., cRfCs, IUR). In addition, as the temporal window of exposure relevant to particular outcomes may vary, the window of exposure expected to be most relevant to each toxicity value is discussed in Section 2, Dose-Response Analysis, when applicable.

A confidence level of **high**, **medium**, or **low** was assigned to each osRfC and the overall RfC based on the reliability of the associated POD and cRfC calculation(s). Confidence in the POD and cRfC calculation(s) included considerations of the quality, timing, and variability of the exposure estimates in an epidemiological study or the exposure protocols in an animal study. Moreover, higher confidence was placed in the osRfC when the POD was identified close to the range of the observed data. Finally, confidence in the coverage and quality of the database of studies that informed the hazard conclusion for that organ/system was assigned. The evidence base for different health outcomes varies in size, coverage of critical endpoints, and quality of the studies; this confidence level reflects database completeness for each of the organ systems.

SUMMARY OF ASSESSMENT METHODS AND APPROACHES

The approaches implemented throughout different stages of this assessment can be grouped into those used to (1) identify and evaluate individual studies; (2) synthesize and integrate the evidence, including interpreting the support for particular human health effects across different streams of evidence (i.e., human, animal, and mechanistic studies) and developing summary conclusions; and (3) select and analyze studies and data to derive quantitative (dose-response) values. The process for hazard identification, which involves hazard-specific literature searches, outcome/endpoint-specific evaluation of study methods, synthesis of information within each streams of evidence, and integration across streams of evidence, is displayed in Figure I. The process involves a successive focusing on the more informative outcomes/endpoints within each hazard domain and the most methodologically sound studies.

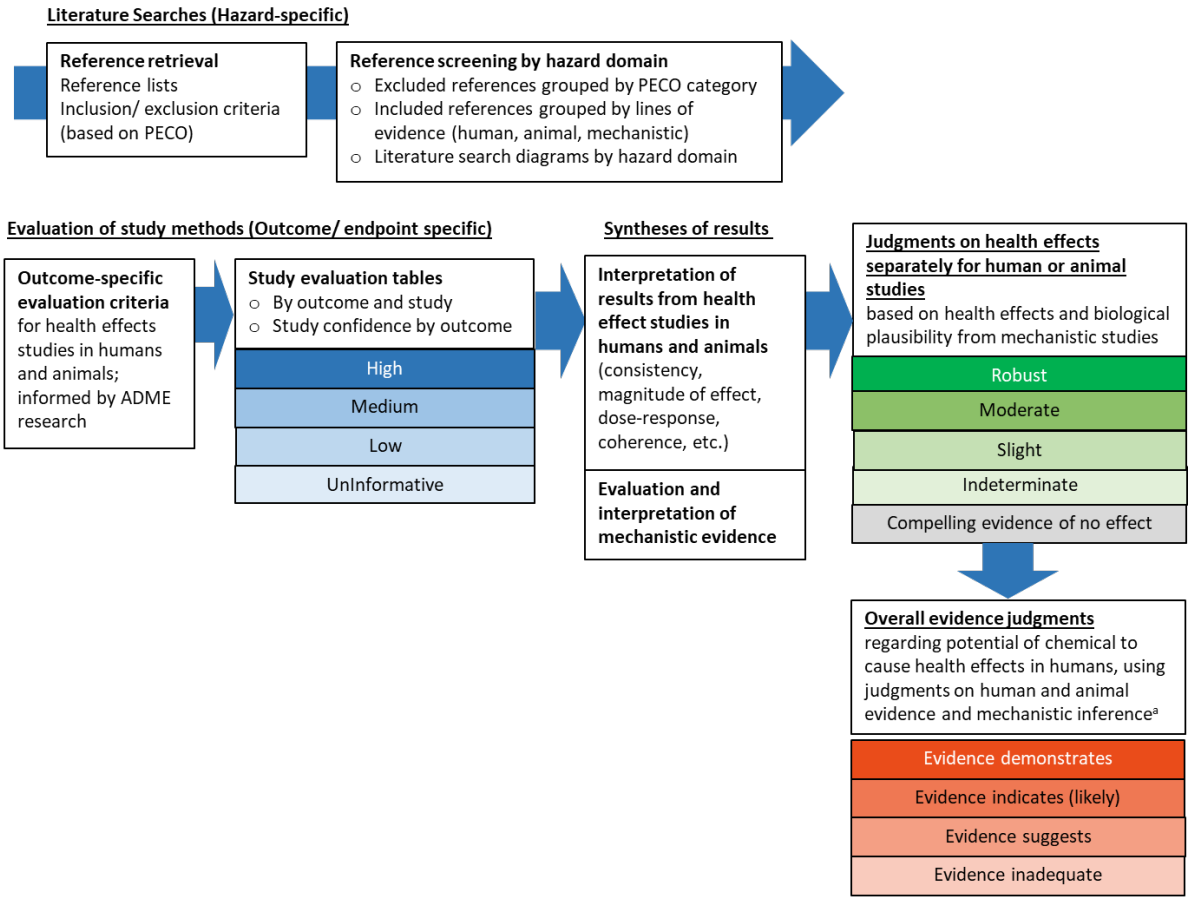


Figure I. Overview of assessment methods for hazard identification.

This figure illustrates the flow of evidence through the assessment, sequentially focusing on the most useful information, as well as the decision-making processes for arriving at evidence judgments regarding the potential for noncancer health effects and for developing specific types of cancer. [a]Mechanistic inference considered during evidence integration included biological plausibility or relevance of animal study results to humans and identification of susceptible groups. Notes: For this assessment, "compelling evidence of no effect" was not reached for any of the human or animal evidence evaluations; as such, criteria for evidence integration when compelling evidence of no effect was present are not discussed in this assessment. Importantly, hazard identification for carcinogenicity includes an additional step of assigning a descriptor regarding the potential for formaldehyde to cause cancer (this step is not shown but is discussed in this section below (see Table IX). Abbreviations: HERO = Health and Environmental Research Online; PECO = Populations, Exposures, Comparisons, Outcomes; ADME = absorption, distribution, metabolism, excretion; MOA = mode of action.

Literature Search Strategy

The literature search strategy used to identify primary research pertaining to formaldehyde inhalation was conducted using the databases and approaches listed in Table I. A separate search strategy was developed for each health hazard considered in the assessment. These strategies are described in detail in Appendix A.5, with PECO criteria, and literature flow diagrams depicting the systematic search and sorting process. Generally, health outcomes and search terms were selected

after reviewing the draft Toxicological Review for Formaldehyde (2010) and other relevant health assessments or reviews of formaldehyde toxicity. A series of comprehensive literature searches was conducted beginning in 2012 and updated annually through 2016, after which the completed 2017 Step 1 draft IRIS formaldehyde-inhalation assessment was suspended at the request of senior EPA management. When the IRIS assessment was unsuspended in March 2021 (http://www.epa.gov/sites/production/files/2021-03/documents/iris_program_outlook_mar2021.pdf), systematic evidence mapping (SEM) methods (Keshava et al., 2020; Wolffe et al., 2020) were employed to survey the newer literature and expedite updating the unsuspended draft (see Appendix F for the methods and results of the formaldehyde SEM update). In these searches, electronic database queries were supplemented using various approaches to identify additional papers, including review of reference lists in identified publications and national-level health assessments. Several meta-analyses of formaldehyde effects, with different conclusions, have been published for a few health outcomes. Reviews and meta-analyses were reviewed to identify relevant publications and background information.

Table I. General approach to literature search strategies

Databases[a]	Health hazard searches[b]
Web of Science ToxNet PubMed TSCATS2	(formaldehyde, formalin, paraformaldehyde, OR CASN 50-00-0) AND: Sensory Irritation[c] Pulmonary Function[c] Immune-Mediated Conditions, focusing on Allergies and Asthma Respiratory Tract Pathology Developmental and Reproductive Toxicity Nervous System Effects Cancer Inflammation and Immune Effects (mechanistic information)[d]

[a]PubMed: http://www.ncbi.nlm.nih.gov/pubmed/, Web of Science: http://apps.webofknowledge.com/WOS_GeneralSearch_input.do?product=WOS&search_mode=. ToxNet: toxicology information previously contained in ToxNet were integrated into other NLM products (see https://www.nlm.nih.gov/toxnet/index.html for where to access).

[b]Specific parameters and keywords for each hazard-specific database search strategy are included in Appendix A.5.

[c]A systematic search strategy was not applied to the database of animal studies on this health outcome. Sensory irritation in animals is a well-described phenomenon. For pulmonary function, there was an extensive set of research studies on humans, and therefore, the few studies on this endpoint in animals were not reviewed.

[d]This separate, systematic literature search was performed to augment the analyses of mechanisms relevant to other health effect-specific searches.

The citations returned from these literature searches were screened using health outcome-specific PECO criteria (see Appendix A.5). In general, although studies of other routes of exposure might inform the mechanistic understanding of potential health hazards, the formaldehyde literature database is extensive and the toxicokinetics following inhalation exposure is expected to

differ significantly from those observed after exposure via other routes; thus, the evaluations of potential health effects and mechanistic information focused on inhalation exposure studies (with the exception of genotoxicity). Publications were typically excluded if they contained no information about formaldehyde exposure or were descriptions of analytic methods using formaldehyde. Ambient levels of formaldehyde in outdoor air are significantly lower than those measured in the indoor air of workplaces or residences, and the exposure range was narrow in many epidemiological studies of ambient exposure (<0.005 mg/m^3), limiting their sensitivity to find any associations with health outcomes even if they existed. In addition, the potential for exposure misclassification for estimates of individual exposure using mean formaldehyde concentrations from central outside monitors is greater than from indoor formaldehyde measurements. Therefore, the few studies examining health effects in relation to outdoor formaldehyde concentrations were excluded. Other exclusions were based on specific criteria relating to each health hazard, which are summarized in each of the respective health hazard sections in Appendix A.5.

In addition to the health effects listed in Table I, relevant literature on additional topics (e.g., formaldehyde exposure, toxicokinetics, mechanisms of carcinogenesis) was identified. While a thorough effort was made to identify all relevant studies for each of these topic areas (see Appendix A for details), these discussions do not include specific tracking of the selection of individual studies (e.g., based on PECO criteria). The references identified and selected through the literature search process, including bibliographic information and abstracts, can be found on the formaldehyde page of the Health and Environmental Research Online (HERO) website[3]: http://hero.epa.gov/hero/index.cfm/project/page/project_id/4051.

For the literature update from 2016-2021 using SEM approaches (overlapping with the searches used for the 2017 draft), while the aforementioned description of the search and screening process was largely identical (see Appendix F) a few differences are important to note. Most notably, after screening the studies for PECO relevance, only those studies meeting the PECO criteria and judged as likely to have a potential impact on the conclusions or toxicity values described in the suspended 2017 draft are synthesized in this assessment. Studies meeting PECO criteria that were judged to have no impact on those conclusions or toxicity values are summarized in Appendix F, along with explanations for these decisions. These latter studies are not further discussed or synthesized in the assessment.

[3]HERO (Health and Environmental Research On-line) is a database of scientific studies and other references used to develop EPA's assessments that support critical decision-making and is aimed at understanding the health and environmental effects of pollutants and chemicals. It is developed and managed in EPA's Office of Research and Development (ORD) by the Center for Public Health and Environmental Assessment. The database includes more than 3,000,000 scientific articles and associated data from the peer-reviewed literature. New studies are added continuously to HERO.

Study Evaluations

All human and experimental animal health effect studies identified in the search and screening processes described above, without regard to study results, were considered for use in assessing the evidence for health effects associated with inhalation exposure to formaldehyde. This full body of evidence is discussed and evaluated in Section 1, Hazard Identification.

Study methods were evaluated to assign a level of confidence in the results of the study with respect to the hazard question under consideration. The study confidence levels were *high*, *medium*, and *low* confidence, and *not informative*, and are presented as italicized text in the body of the assessment. These evaluations were performed on a health outcome-specific basis, rather than a study-specific basis; thus, a single study was sometimes evaluated multiple times for different endpoints, sometimes involving slightly different considerations. *High* confidence studies generally had no notable methodological limitations for an outcome, while *medium* confidence studies were considered well conducted but had specific issues that might introduce a minor amount of uncertainty about attribution of the results solely to formaldehyde exposure on the health outcome in question. Methodological limitations of *low* confidence studies are considered to be significant, but the outcome-specific results might still be of limited use (e.g., as support for observations from other studies; to identify potential data gaps). The evaluations for studies identified as *not informative* were documented (see Appendix A.5), but these data are not discussed in the Toxicological Review. In general, if a study or individual analysis (e.g., when multiple health outcomes or cohorts were assessed) was judged to have multiple severe limitations, or if reporting deficiencies precluded the ability to conduct an evaluation, the experiment was concluded to be *not informative*. When potential limitations were identified, the evaluations considered the anticipated direction (i.e., bias toward or away from the null) and magnitude of the impact of the limitation(s) on the study results (when possible). Emphasis was placed on discerning limitations that would be expected to produce a substantive change in the results.

The evaluations focused on potential sources of bias or other limitations (including reduced sensitivity) that can affect the validity or interpretation of a study's results. Thus, the confidence conclusions for individual studies reflect an interpretation of the reliability of the study results for answering each particular hazard question. The general procedure involved evaluating specific methodological features (see below), although the categories differed somewhat between observational epidemiological, animal toxicological, and human-controlled exposure studies. The appendices contain summary evaluation tables developed for studies in each health hazard domain, which provide both relevant study characteristics and the conclusions of the evaluations. Evaluation conclusions also are included in the tables summarizing the evidence for each health effect in the Toxicological Review. In addition to the evaluations of the individual health effect studies, systematic evaluations of individual mechanistic studies were conducted in relation to several important health domains when this information could contribute to judgments about the human and animal evidence or hazard conclusions, specifically: biomarkers of genotoxicity in

exposed humans, mechanistic data related to potential respiratory health effects, and mechanistic data related to potential nervous system effects (see Appendix A.4.6, A.5.6, and A.5.7, respectively). Individual study evaluations for literature on exposure, toxicokinetics and other mechanistic data were not systematically conducted and documented.

In some situations, in which key study details or results were not presented, the study author(s) were contacted to obtain this information. Any additional study details obtained from the authors are noted in the evaluation summary tables and evidence tables.

Evaluation of Observational Epidemiology Studies

Classification scheme

For each type of health outcome examined, the epidemiological studies were evaluated for each of the categories of information relevant to internal validity (bias) that could lead to an under- or overestimate of risk and to other features that could affect the interpretation of the results or limit the ability to detect a true association (e.g., narrow exposure range). The categories used for the epidemiological studies included population selection, exposure (measurement and levels/range), outcome ascertainment, consideration of confounding, and analytic approach. The potential for selection bias, information bias (relating to exposure and to outcome), and confounding was evaluated. A pictorial summary of the conclusions from the outcome-specific evaluation process was created (see Figure II). Studies that evaluated more than one outcome might be categorized differently for each outcome. The classification of a study could also vary among different analytical groups within a study (e.g., studies of children and adults, with separate analyses for each group), depending on the information presented for the different analyses.

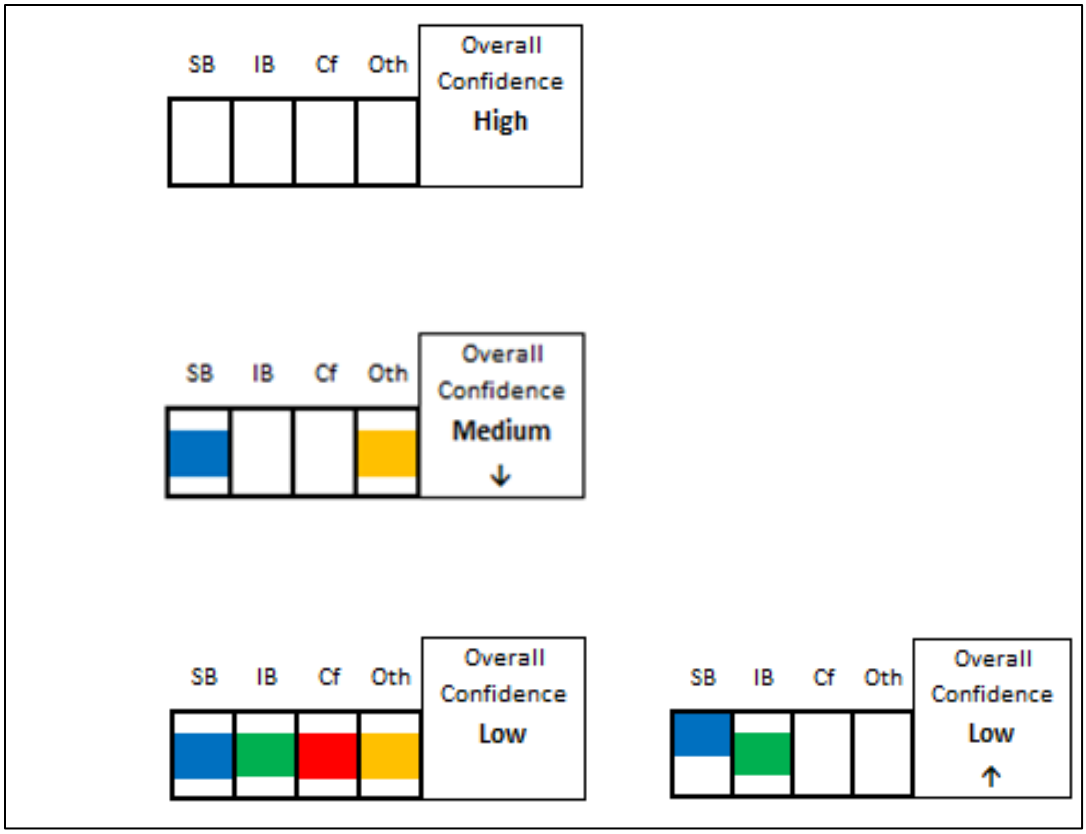


Figure II. Summary depictions of evaluation of epidemiology studies.

The extent of column shading reflects the degree of limitation. Different colors are intended to visually distinguish the columns and have no other meaning. The direction of anticipated bias is indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact would be likely to be away from the null (i.e., spurious or inflated effect estimate). Panel A: *High* confidence study; Panel B: *Medium* confidence study with likely attenuated effect estimate; Panel C: Two possible examples for a *low* confidence study. Color blocks that straddle the midline indicate that the direction of bias is unknown or not predictable. The depiction on the right indicates that selection bias (SB) likely resulted in an overestimate of the effect estimate, indicated by the colored block above the midline. Abbreviations: SB = selection bias; IB = information bias; Cf = confounding; Oth = other feature of design or analysis.

The synthesis of evidence (see next section) focuses on the *medium* and *high* confidence studies, if available, taking into account differences in populations and settings (e.g., children and adults; occupational, residential, or in schools), exposure levels, and other aspects of the studies.

<u>Formaldehyde exposure considerations specific to observational epidemiological studies</u>

All residential or school-based studies with measures of formaldehyde exposure were included in the hazard identification evaluation; because the database of studies with direct measurements is relatively large, residential studies with indirect measures of formaldehyde exposure (e.g., based on age of building or presence of plywood) were not included. Most of the included studies attempted to estimate average formaldehyde levels using area samples placed in

one or more locations; measurement periods ranged from 30 minutes to 2 weeks. A few studies included more than one sampling period (e.g., sampling on multiple days in different seasons over the course of a year). Studies in adults and in children indicate that area-based (e.g., residential or school) samples are highly correlated with personal samples (Lazenby et al., 2012; Gustafson et al., 2005); therefore, the use of measures based on residential (e.g., bedroom) samples rather than personal samples was not considered to be a limitation when evaluating a study.

There was also variation in the exposure measurements used within occupational settings. For hazard identification, an accurate characterization of "high" versus "low" exposure or "exposed" versus "nonexposed" may be able to provide a sufficient contrast to examine associations, even if there is considerable heterogeneity within the high exposure group. Exposure assessments in occupational studies involved one or more area samples in specific task areas, personal samples, or a combination of both. Sampling periods ranged from less than 1 hour to an entire work shift over 1 or more days. Concentrations were reported as an average of all samples for a particular location or as a time-weighted average (TWA) over the sampling period. Generally, a TWA concentration from a full-shift measurement using personal sampling was preferred as a more precise estimate of average exposure. Other occupational studies that used a formaldehyde-specific exposure definition or semiquantitative measure (e.g., duration, number of embalmings) also were included, although they were concluded to be limited to some extent by exposure misclassification. Studies of certain occupational groups with considerable exposure to formaldehyde (e.g., embalmers, pathologists, wood or garment workers) were included as proxies for formaldehyde exposure because formaldehyde is the predominant chemical exposure in these jobs and a large contrast is expected between exposed and unexposed groups.

Evaluation of controlled exposure studies in humans

A process incorporating aspects of the evaluation approaches used for epidemiological studies and experimental animal studies (see below) was used to evaluate controlled exposure studies in humans. The evaluation categories included exposure generation, outcome classification, consideration of possible bias (i.e., randomization and blinding), consideration of confounding (i.e., adequacy of randomization), and details of analysis and presentation of results. A study was judged to be *low* confidence if the exposure generation method resulted in exposure to substances other than formaldehyde (e.g., emissions from pressed wood products), allocation to the order of exposure categories was not random, or subjects were not blinded to their exposure order.

Evaluation of experimental studies

Classification scheme

Toxicological studies differ systematically from observational epidemiological studies because the former seek to control both the exposure and nonexposure conditions of an experiment. This leads to some differences in approach and interpretation. In general, however,

toxicological study evaluations considered similar categories to the epidemiological studies. The categories were based on the design of a toxicological study, including test animals, experimental design (e.g., duration of exposure, timing of endpoint evaluations, allocation procedures), exposure conduct, endpoint evaluation procedures, and data presentation and analysis. The specifics of the considerations applied were different for each type of health outcome examined (see Appendix A.5).

As the expectation is that experimental studies should attempt to control all variables, any study limitation interpreted as capable of influencing the data was considered to have negatively affected the quality (e.g., validity, accuracy) of the results. Thus, these "confounding factors" differ substantially from what would be deemed a potential "confounder" in epidemiological studies.

Formaldehyde exposure considerations specific to controlled exposure (animal or human) studies

Typical human exposures to formaldehyde can be complex and difficult to translate to experimental systems. Experimental exposure to formaldehyde by inhalation is typically achieved through volatilization of formalin or depolymerization of paraformaldehyde. Methanol, present in aqueous formaldehyde solutions to inhibit polymerization, is a potential confounder of associations between observed health outcomes and formaldehyde exposure via formalin. As experimental studies, including controlled exposure studies in either humans or animals should aim to control all variables other than the exposure or manipulations of interest; coexposure to methanol in these studies introduces uncertainty that the effects were caused by formaldehyde alone. Inhaled methanol could affect health endpoints or introduce quantitative uncertainty. An example of the former would be if methanol were distributed to different locations than inhaled formaldehyde, where it could either directly cause effects or, theoretically, be metabolized to formaldehyde and cause effects. An example of the latter would be that, because methanol is metabolized to formaldehyde in vivo, substantial coexposure to methanol could result in differences in tissue-specific formaldehyde levels at identical external formaldehyde exposure levels when different test articles are used. This limitation typically introduces a bias toward an effect and is of particular concern in studies observing systemic effects after exposure. Thus, the test article used to generate the formaldehyde atmosphere in experimental studies was critically evaluated (see Appendix A.5 for details), including consideration of whether a methanol-only control group was used.[4] Although

[4]While one study used a sprayer in a heated vessel to generate formaldehyde from a formalin solution containing a known concentration of methanol (Kamata et al., 1997), presumably resulting in the release of formaldehyde and methanol in proportions that would be conserved from liquid to gas (i.e., allowing air methanol levels to be relatively accurately estimated based on air formaldehyde levels), the remaining formalin studies generally evaporated formalin from solution. Notably, the liquid:air partitioning of methanol and formaldehyde is influenced by the proportions of these agents in aqueous solutions (Albert et al., 2000). Thus, as chamber methanol levels were not analytically measured in the other identified studies, a methanol control group may not eliminate uncertainty. Unfortunately, a calculation for estimating methanol levels released (e.g., by evaporation) from formalin solutions at different levels of inhaled formaldehyde was not identified.

this evaluation was applied to all experimental systems, conclusions about the level of uncertainty introduced by this coexposure varied by health outcome, with a far greater level of concern for potential impacts on nonrespiratory health effects (see Section 1.3, Nervous System Effects, developmental and reproductive system effects, and lymphohematopoietic (LHP) cancers), as compared to respiratory health effects (see Section 1.2). This disproportionate level of concern is primarily based on two factors: (1) as compared to formaldehyde, which does not appear to be distributed to distal sites in appreciable amounts, inhaled methanol would be readily transported beyond the portal of entry (POE) and could elicit direct effects at distal target tissues, and (2) certain systemic effects evaluated in this assessment (i.e., reproductive and developmental toxicity, nervous system effects) are health outcomes known to be a target of methanol toxicity, while other health outcomes, although generally less well studied, have not been clearly associated with methanol exposure (U.S. EPA, 2013). These issues are discussed further in each major endpoint discussion in Sections 1.2 and 1.3.

For certain health outcomes, the irritant and odorant nature of formaldehyde gas and the inescapable nature of these exposures (animals cannot terminate exposure at irritating levels), can complicate interpretations of causality. In addition, reflex bradypnea is an irritant response that exists in rodents, typically at formaldehyde concentrations exceeding 1 mg/m^3 (see Section 1.1.3), but not humans and can cause large variations between the administered and internal exposures. Although the understanding of irritation-related responses, including reflex bradypnea in rodents, is incomplete (e.g., responses following repeated and prolonged exposure are not well studied; see Appendix A.3), it is generally assumed that irritation- and odorant-specific changes are either short lived or markedly reduced shortly after formaldehyde exposure is removed. In light of these considerations, care was taken to consider in detail the specifics of the study protocols related to formaldehyde exposure (e.g., determining whether a sufficient duration was allotted between exposure and testing, evaluating whether the exposure levels tested were capable of introducing variables such as reflex bradypnea) for certain health outcomes.

Overall, as in observational studies in humans, considerations related to the quality of the exposure paradigms used in experimental studies typically had the strongest influence on study confidence determinations.

Evaluation of mechanistic studies

For the datasets described previously, evaluations of individual mechanistic studies involving formaldehyde inhalation in experimental animals or in vitro models of gaseous formaldehyde exposure considered the same general features evaluated for more apical measures of toxicity (i.e., evaluations of exposure quality and study design were emphasized). The specific criteria were simplified, however, to accommodate the increased heterogeneity of the available mechanistic studies, as compared to the data available for apical measures of toxicity. Similarly, study evaluations of individual mechanistic studies involving exposed humans emphasized consideration of exposure assessment, study design, outcome ascertainment, and comparison

groups for potential sources of bias and their potential impact. For the mechanistic studies related to potential noncancer respiratory effects, given the large number of studies identified, individual experiments were characterized as *high* or *medium* confidence, *low* confidence, or *not informative*. These evaluations emphasized exposure-related considerations and were designed to identify the mechanistic data most likely to be associated with constant, chronic inhalation exposure to formaldehyde (see Appendix A.5.6 for additional details). As these individual study evaluations were less endpoint specific than the evaluations of the individual health effect-specific studies, these evaluations were generally less rigorous. Subsequently, groupings of studies or related endpoints were evaluated to assess the strength of the evidence for different "mechanistic events" as robust, moderate, slight, or indeterminate. Likewise, potential associations between mechanistic events were judged based on the tissue(s)/region(s) assessed and known biological roles within those tissues for the identified mechanistic events. The criteria and presentation of decisions for the strength of the mechanistic evidence relating to potential respiratory health effects are illustrated in Table II. For studies of genotoxicity biomarkers in exposed humans, conclusions about bias and sensitivity were drawn using the same approach as for other epidemiological studies.

Table II. Criteria and presentation of strength of the evidence for each mechanistic event and for potential associations between events relating to potential respiratory health effects

	Evidence judgment[a]	Mechanistic events		Associations between mechanistic events	
		Criteria for conclusions	Presentation[b]	Criteria for conclusions	Presentation[b]
Strongest	Robust	Direct evidence supporting an effect in multiple, consistent *high or medium* confidence studies[b]	◉ Emphasized in Text	Formaldehyde-specific data demonstrate a linkage (i.e., inhibition of mechanistic event "A" prevents or reduces the occurrence of event "B"; events "A" and "B" are linked by concentration, location, or temporality)	→
	Moderate	Direct or indirect (e.g., genetic changes) evidence supporting an effect in at least one *high or medium* confidence study, with supporting evidence (e.g., consistent changes suggesting an effect in *low* confidence studies)[b]	○ Emphasized in Text	• An association between events "A" and "B" is known based on established (basic) biology • An association has been demonstrated for similar chemicals or effects	⇢
	Slight	• Evidence supporting an effect in one hypothesis-generating	◌	An association is justifiable, or even expected, based on	⇢

	Evidence judgment[a]	Mechanistic events		Associations between mechanistic events	
		Criteria for conclusions	Presentation[b]	Criteria for conclusions	Presentation[b]
		high or medium confidence study • Evidence suggesting an effect in multiple, reasonably consistent *low* confidence studies	Minimal Discussion in Text	underlying biology, but it has not been well established (note: events for which a biological association appears unlikely are not linked)	
Weakest	Indetermin-ate	• Evidence suggesting an effect in one *low* confidence study • A set of *low* confidence studies with inconsistent results	Not included in figures; may be noted in text	N/A	N/A
		• Evidence cannot be interpreted (no data; no pattern in results within or across studies) • Data suggest no change	Not included in figures or synthesis text	N/A	N/A

[a]For consistency, the words used to describe the judgments for apical health effect endpoints in human or animal studies were applied (see subsequent section, Evidence Integration and Confidence Conclusions for Noncancer and Cancer Health Outcomes), although the criteria herein are less rigorous (i.e., when evaluating sets of studies), unlike the conclusions for apical health effects.

[b]Supporting evidence and documentation for these decisions is provided in Appendix A.5.6, with only the evidence on mechanistic changes (irrespective of the results) most informative to the health effect-specific discussions presented in Sections 1.2.1–1.2.4.

[c]The presence of a comparable or stronger set of studies with directly conflicting evidence results in the identification of the next weaker evidence descriptor (e.g., robust evidence with conflicting data would be moderate); note that the purpose of this evaluation was not to identify mechanistic events for which there was robust evidence of no change; however, the plausibility of the pathways (considering evidence for a lack of changes in expected events) is discussed in later sections.

Synthesis of the Available Evidence for Each Health Outcome

Sections 1.2 and 1.3 include syntheses of the entire body of evidence for the following health hazard categories: sensory irritation; reduced pulmonary function, respiratory tract pathology, immune-mediated conditions, focusing on allergies and asthma; cancer (respiratory tract cancers, lymphohematopoietic cancers); nervous system effects (motor neuron disease, tests of general motor-related behaviors, neural sensitization, learning or memory, neuropathology); developmental and female reproductive toxicity; and male reproductive toxicity. Health hazard categories were chosen based on prior reviews, as well as the specifics of the available literature. The units of analysis within an overall hazard category for which a hazard conclusion was developed were determined based on biologic considerations (i.e., specific to an organ system and

considering the degree to which endpoints are related) and the number of studies that evaluated a particular outcome. Thus, hazard conclusions were developed for consolidated sets of related health endpoints within an overall hazard category in some instances (e.g., male reproductive toxicity).

For each unit of analysis (hazard category, or hazard subgrouping), and depending on the data available, separate syntheses were developed for each of the three streams of evidence: namely, human and animal health effect studies and mechanistic studies. These evidence syntheses, which incorporate the evaluations of the strengths and limitations of the available studies as well as considerations related to the toxicokinetics of inhaled formaldehyde, provide a discussion of the information provided by each stream of evidence regarding the potential for exposure to formaldehyde via inhalation to result in specific health effects. All informative studies (see above), regardless of the magnitude or direction of results (i.e., whether yielding positive or null results) were considered in assessing the evidence; however, the focus of the synthesis was on the *high* and *medium* confidence studies, when available. Descriptive information about study methods and detailed results are generally presented in tabular or graphical displays, with supportive text. The narrative summaries discuss the nature and breadth of the available literature, highlighting details that contribute to the analysis of the strength of evidence regarding causality in the next section.

The syntheses of the separate streams of evidence—human health effect studies, animal health effect studies, and mechanistic studies—involved related considerations that differed due to the nature of the study designs and applicability of the data (see Table III). Consistency, magnitude of effects, and dose-response gradients were emphasized in the synthesis of results of epidemiological and controlled human exposure studies. While the precision of effect estimates could add to the strength of evidence for a health effect, all of the results were summarized. Consistency between studies was examined by comparing study results by confidence level, specific methodological features that contributed to potential bias, exposure setting, and level of exposure. The primary considerations for synthesizing the results of animal studies were consistency (e.g., across species and across research groups, with consideration of study confidence), magnitude and severity of the effects, dose-response, and coherence of findings for related effects. The information from mechanistic studies in humans or animals relevant to each apical outcome was synthesized, highlighting information that could inform either biological plausibility, coherence, susceptibility, relevance to humans or an improved understanding of dose-response. Given the exposure-related issues specific to formaldehyde and the abundance of data available, the mechanistic evaluations in this assessment focused almost exclusively on in vivo studies of inhalation exposures, with rare exception (e.g., evaluation of in vitro genotoxicity studies).

Table III. Information most relevant to describing primary considerations informing causality during evidence syntheses

Consideration	Description and synthesis methods
Consistency	• Examines the similarity of results (e.g., direction; magnitude) across studies. When inconsistencies exist, the synthesis considers whether results were "conflicting" (i.e., unexplained positive and negative results in similarly exposed human populations or in similar animal models) or "differing" (i.e., mixed results explained by differences between human populations, animal models, exposure conditions, or study methods) (U.S. EPA, 2005a) based on analyses of potentially important explanatory factors such as: • Confidence in studies' results, including study sensitivity (e.g., some study results that appear to be inconsistent may be explained by potential biases or other attributes that affect sensitivity, resulting in variations in the degree of confidence accorded to the study results) • Exposure, including route (if applicable), levels, duration, etc. • Populations or species, including consideration of potential susceptible groups or differences across lifestages at exposure or endpoint assessment • Toxicokinetic information as an explanation for any observed differences in responses across route of exposure, other aspects of exposure, species, or lifestages The interpretation of the consistency of the evidence and the magnitude of the reported effects will emphasize biological significance as more relevant to the assessment than statistical significance. Statistical significance (as reported by p-values, etc.) provides no evidence about effect size or biological significance, and a lack of statistical significance will not be automatically interpreted as evidence of no effect.
Strength (effect magnitude) and precision	• Examines the effect magnitude or relative risk, based on what is known about the assessed endpoint(s), and considers the precision of the reported results based on analyses of variability (e.g., confidence intervals; standard error). In some cases, this may include consideration of the rarity or severity of the findings (in the context of the health effect being examined). Syntheses will analyze results both within and across studies and may consider the utility of combined analyses (e.g., meta-analysis). While larger effect magnitudes and precision (e.g., $p < 0.05$) help reduce concerns about chance, bias, or other factors as explanatory, syntheses should also consider the biological or population-level significance of small effect sizes. Thus, a lack of statistical significance should not be automatically interpreted as evidence of no effect.
Biological gradient/dose-response	• Examines whether the results (e.g., response magnitude, incidence, severity) change in a manner consistent with changes in exposure (e.g., level, duration), including consideration of changes in response after cessation of exposure. Syntheses will consider relationships both within and across studies, acknowledging that the dose-response (e.g., shape) can vary depending on other aspects of the experiment, including the outcome and the toxicokinetics of the chemical. Thus, when dose-response is lacking or unclear, the synthesis will also consider the potential influence of such factors on the response pattern.

Consideration	Description and synthesis methods
Coherence	• Examines the extent to which findings are cohesive across different endpoints that are known/expected to be related to, or dependent on, one another (e.g., based on known biology of the organ system or disease, or mechanistic understanding such as toxicokinetic/dynamic understanding of the chemical or related chemicals). In some instances, additional analyses of mechanistic evidence from research on the chemical under review or related chemicals that evaluate linkages between endpoints or organ-specific effects may be needed to interpret the evidence. These analyses may require additional literature search strategies. Syntheses will consider potentially related findings, both within and across studies, particularly when relationships are observed within a cohort or within a narrowly defined category (e.g., occupation, strain or sex, lifestage of exposure). Syntheses will emphasize evidence indicative of a progression of effects, such as temporal- or dose-dependent increases in the severity of the type of endpoint observed.
Mechanistic evidence related to biological plausibility	• There are multiple uses for mechanistic information (see 9.2), and this consideration overlaps with "coherence." This examines the biological support (or lack thereof) for findings from the human and animal health effect studies and becomes more impactful on the hazard conclusions when notable uncertainties in the strength of those sets of studies exist. These analyses can also improve understanding of dose- or duration-related development of the health effect. In the absence of human or animal evidence of apical health endpoints, the synthesis of mechanistic information will drive evidence integration conclusions (when such information is available). Syntheses can evaluate evidence on precursors, biomarkers, or other molecular or cellular changes related to the health effect(s) of interest to describe the likelihood that the observed effects result from exposure. This will be an analysis of existing evidence, and not simply whether a theoretical pathway can be postulated. This analysis may not be limited to evidence relevant to the PECO but may also include evaluations of biological pathways (e.g., for the health effect; established for other, possibly related, chemicals). The synthesis will consider the sensitivity of the mechanistic changes and the potential contribution of alternative or previously unidentified mechanisms of toxicity.
Natural experiments	• Specific to epidemiological studies and rarely available, these examine effects in populations that have experienced well-described, pronounced changes in exposure to the chemical of interest (e.g., blood lead levels before and after banning lead in gasoline).

Evidence Integration and Integration Judgments for Noncancer and Cancer Health Outcomes

For transparency in the sequential decision steps taken to draw overall evidence integration judgments, a two-step, sequential process was used (Figure III). First, judgments regarding the strength of the evidence from the available human and animal studies were made. These judgments incorporated mechanistic evidence (or MOA understanding) in exposed humans and animals, respectively, that informed the biological plausibility and coherence of the available human or animal health effect studies. Second, an overall conclusion(s) was drawn by integrating the animal and human evidence judgments and incorporating inferences regarding the human

relevance of the animal evidence (i.e., based on default assumptions or empirical evidence), coherence across the human and animal evidence, and susceptibility.

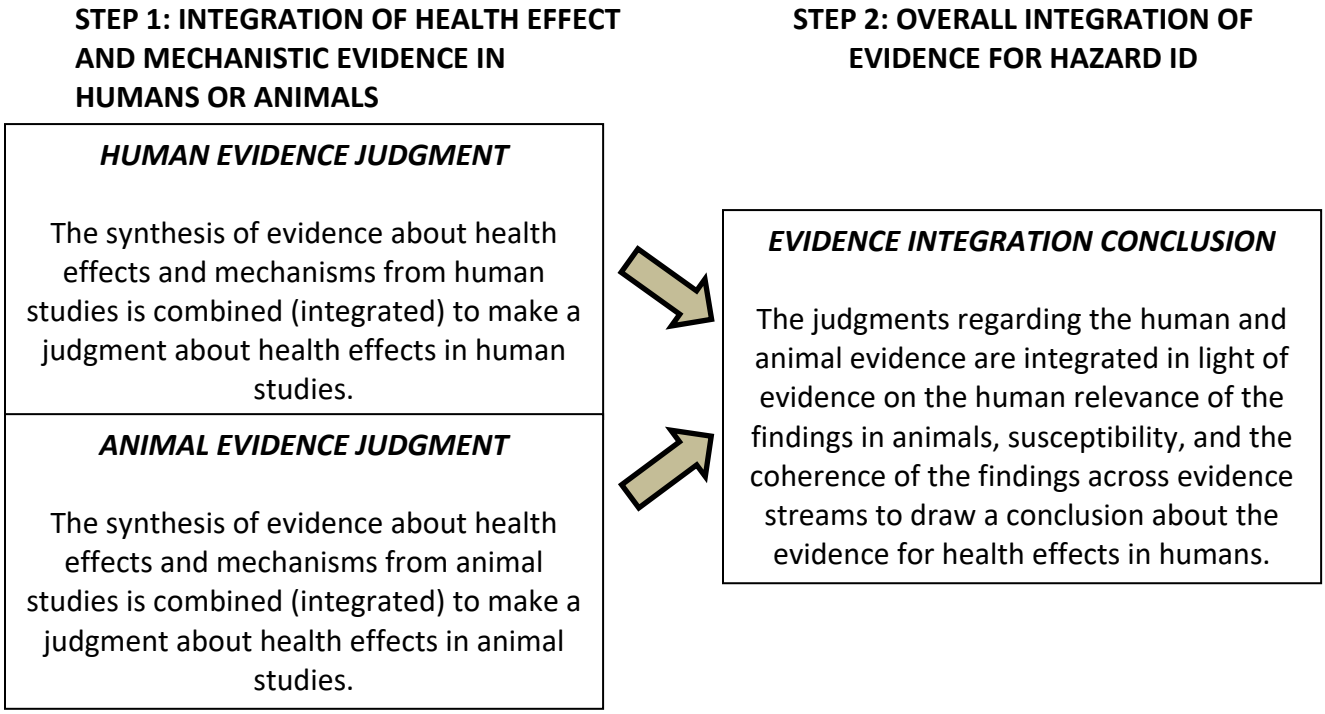


Figure III. Process for evidence integration.

Human and animal evidence judgments from Step 1 and the overall evidence integration conclusion from Step 2 were reached using decision frameworks (see Tables IV, V, and VI) adapted from considerations originally described by Austin Bradford Hill (Hill, 1965). In the first step, the strength of the human and, separately, the animal evidence (with consideration of mechanistic information in humans and animals, respectively, including in vitro or other relevant models) for each noncancer health effect (or groups of related effects) and specific cancer type (or groups of related cancer types) was summarized using the following terms: *robust, moderate, slight,* and *indeterminate*. The strength of the human and animal evidence was determined starting from the evidence syntheses that summarized the evidence from the available human and animal health effects studies, respectively, and then considering coherence of effects and biological plausibility based on mechanistic evidence, which could add to or detract from the strength of evidence. Syntheses of mechanistic data that might inform potential respiratory health effects (Section 1.2.1–1.2.4), which involved an integrated and systematic review process (see Appendix A.5.6), emphasize the sequence(s) of mechanistic events interpreted to have the most reliable evidence (e.g., mechanistic events and associations with robust evidence are preferred). Based on the known or presumed linkages, these events are organized from a "plausible initial effect of exposure" (e.g., a potential direct interaction between inhaled formaldehyde and biological materials) to each apical

toxicity endpoint in a linear fashion, regardless of tissue region. Additional details and other mechanistic changes that might contribute to the observed health effects are discussed in Appendix A.5.6. Note, however, that the lack of mechanistic data explaining an association did not discount results from human or animal health effect studies. To draw these judgments, a modified set of considerations was applied to evidence from studies in humans and animals (Table III). Examples of ways that mechanistic evidence was used in causal analyses and derivation of toxicity values are described in Table IV.

Table IV. Primary considerations for assessing the strength of evidence for the health effects studies in humans and, separately, animals[a]

Consideration	Increased evidence strength (of the human or animal evidence)	Decreased evidence strength (of the human or animal evidence)
The structured categories and criteria in Tables VI and VII will guide the application of strength-of-evidence judgments for an outcome or health effect. Evidence synthesis scenarios that do not warrant an increase or decrease in evidence strength will be considered "neutral."		
Risk of bias; sensitivity (across studies)	• An evidence base of *high* or *medium* confidence studies increases strength.	• An evidence base of mostly *low* confidence studies decreases strength. An exception to this is when the primary issues resulting in *low* confidence are related to insensitivity. This may increase evidence strength in cases where an association is identified because the expected impact of study insensitivity is toward the null. • Decisions to increase strength for other considerations in this table should generally not be made if there are serious concerns for risk of bias.
Consistency	• Similarity of findings for a given outcome (e.g., of a similar magnitude, direction) across independent studies or experiments increases strength, particularly when consistency is observed across populations (e.g., location) or exposure scenarios in human studies, and across laboratories, populations (e.g., species), or exposure scenarios (e.g., duration, route, timing) in animal studies.	• Unexplained inconsistency (conflicting evidence) decreases strength. Generally, strength should not be decreased if discrepant findings can be reasonably explained by study confidence conclusions, variation in population or species, sex, or lifestage, exposure patterns (e.g., intermittent or continuous), levels (low or high), duration or intensity. However, any decisions about decreased strength will be determined by the extent to which residual questions about the evidence may persist.
Strength (effect magnitude) and precision	• Evidence of a large magnitude effect (considered within or across studies), can increase strength. Effects of a concerning rarity or severity can also increase strength, even if they are small magnitude. • Precise results from individual studies or across the set of studies increases strength, noting that biological significance is prioritized over statistical significance.	• The presence of small effects is not typically used to decrease confidence in a body of studies. However, if effect sizes that are small in magnitude are concluded not to be biologically significant, or if there are only a few studies with imprecise results, then strength is decreased. • In animal studies, an example of evidence that can decrease strength involves an effect for which there is a lesser level of concern under some conditions (e.g., rapid reversibility after removal of exposure). Note that many reversible effects are of high concern. Such a decision is informed by factors such as the toxicokinetics of the chemical and the conditions of exposure (see U.S. EPA (1998)), judgments regarding the potential for delayed or secondary effects, as well as the exposure context focus of the assessment (e.g., addressing intermittent or short-term exposures).
Biological gradient/dose-response	• Evidence of dose-response increases strength. Dose-response may be demonstrated across studies or within studies and it can be dose or duration dependent. It may also not be a monotonic dose-response	• A lack of dose-response when expected based on biological understanding and having a wide range of doses/exposures evaluated in the evidence base can decrease strength.

Consideration	Increased evidence strength (of the human or animal evidence)	Decreased evidence strength (of the human or animal evidence)
	(monotonicity should not necessarily be expected), and the analysis will consider the extent to which this might be explained by the available evidence (e.g., different outcomes may be expected at low versus high doses due to activation of different mechanistic pathways or induction of systemic toxicity at very high doses). • Decreases in a response after cessation of exposure (e.g., symptoms of current asthma) also may increase strength by increasing certainty in a relationship between exposure and outcome (this is applicable to human observational studies, but not experimental studies).	• In rare cases, and typically only in toxicology studies, the duration of exposure might reveal an inverse association with effect magnitude (e.g., due to tolerance or acclimation). Similar to the discussion of reversibility above, a decision about whether this decreases strength depends on the exposure context focus of the assessment and other factors. • If the data are not adequate to evaluate a dose-response pattern, then strength is neither increased nor decreased.
Coherence	• Biologically related findings within an organ system, or across populations (e.g., sex) increase strength, particularly when a temporal- or dose-dependent progression of related effects is observed within or across studies, or when related findings of increasing severity are observed with increasing exposure.	• An observed lack of expected coherent changes (e.g., well-established biological relationships), particularly when observed for multiple related endpoints, will typically decrease evidence strength. The decision to decrease depends on the strength of the expected relationship(s), and considers factors (e.g., dose and duration of exposure) across studies of related changes.
Mechanistic evidence related to biological plausibility	• Mechanistic evidence of precursors or health effect biomarkers in well-conducted studies of exposed humans or animals, in appropriately exposed human or animal cells, or other relevant human or animal models (for the human or animal evidence, respectively) increases strength, particularly when this evidence is observed in the same cohort/population exhibiting the health outcome. • Evidence of changes in biological pathways or providing support for a proposed MOA in models also increases strength, particularly when support is provided for rate-limiting or key events, or changes are conserved across multiple components of the pathway or MOA.	• Mechanistic understanding is not a prerequisite for judging the evidence, and thus absence of knowledge should not be used a basis for decreasing strength NTP (2015); NRC (2014a).The human relevance of animal findings is assumed unless there is sufficient evidence to the contrary [see IARC (2006); U.S. EPA (2005a)]. • Mechanistic evidence in well-conducted studies that demonstrates that the health effect(s) are unlikely to occur, or only likely to occur under certain scenarios (e.g., above certain exposure levels), can decrease evidence strength. A decision to decrease depends on an evaluation of the strength of the mechanistic evidence supporting vs. opposing biological plausibility, as well as the strength of the health effect-specific findings (e.g., stronger health effect data require more certainty in mechanistic evidence opposing plausibility).

[a]These ideas build upon the discussion for assessing causality of disease in Hill (1965), although the use or interpretation of some of the terms differs.
[b]While humans are "exposed" and not "dosed," and nor are animals "dosed" via inhalation, "dose-response" is used for convention throughout the assessment, although it is acknowledged that 'exposure-response' may be more appropriate in many contexts.
[c]There is a clear overlap in the use of mechanistic evidence to interpret coherence (e.g., informing the relatedness or comparability of potentially coherent health findings) and biological plausibility. The available mechanistic information is also considered during the subsequent step of evidence integration across streams of evidence (see Table VIII).
[d]Although it is not separately listed, Hill's consideration of 'analogy' (information for a similar but different association that supports causation) is indirectly encompassed by the evaluation of coherence during the review of environmental health studies; however, this use of analogous chemicals or exposure scenarios is less common.

Table V. Examples of the interpretation and application of mechanistic evidence

Mechanistic inferences considered	Potential specific applications within the assessment
Biological plausibility: as applied herein, this applies to information that either strengthens or weakens an interpretation of the likelihood of an association between exposure and the health effect. Thus, in some instances, differing levels of biological plausibility (or certainty) might be drawn. It is important to note that the lack of mechanistic data explaining an association is not used to discount observations from human or animal studies. The interpretation of biological plausibility considers the existing knowledge for how the health effect develops and can involve analyses of information at different levels of biological organization (e.g., molecular, tissue).	***Evidence Integration (Animal or Human Health Effects)*** • Observations of important mechanistic changes in exposed humans or animals that are plausibly associated with the health outcome in question can strengthen the confidence in the health effect findings for either the human or animal evidence base, particularly when the changes are observed in the same exposed population presenting the health effect. • The absence of expected mechanistic changes in an exposed population might diminish the plausibility of an association. This considers the sensitivity of the changes and the potential contribution of alternative or unidentified toxicity mechanisms. • Inconsistent evidence (i.e., heterogeneous results) across different animal species or human populations might be explained by evidence that mechanisms differ or are not/less operant in the different populations (e.g., evidence demonstrating that certain populations cannot metabolize a chemical to its reactive metabolite; evidence that gene expression variability correlates with response variability).
Human relevance of findings in animals: in the absence of sufficiently justifiable mode of action (MOA) information, effects in animal models are assumed to be relevant to humans (U.S. EPA, 2005a). In this assessment, for potential health hazards where the evidence from animal models is likely to influence the overall hazard conclusion, the available mechanistic evidence was considered in light of human relevance.	***Evidence Integration (Overall Hazard Description)*** • Evidence establishing that the mechanisms underlying the animal response do not operate in humans, or that animal models do not suitably inform a specific human health outcome can support the view that the animal response is irrelevant to humans. In these cases, the animal response provides neither an argument for nor an argument against an overall hazard judgment. • Observations of mechanistic changes in exposed humans that are similar or coherent with mechanistic or toxicological changes in experimental animals (and which are interpreted to be associated with the health outcome under evaluation) strengthen the human relevance of the animal findings.
Potential susceptibilities: When a mechanistic understanding of how a health outcome develops, or MOA, is known or hypothesized, knowledge about the presence and sensitivity (e.g., across lifestages), or modifying factors (e.g., genetics) of important events in that MOA can help identify vulnerable groups.	***Susceptibility, Dose-Response Analysis, and Uncertainty*** • Identification of lifestages or groups potentially at greatest risk can add clarity to hazard descriptions and inform uncertainties on whether the most vulnerable populations have been adequately tested. • Knowledge of potential or expected vulnerabilities can inform selection of studies for quantitative analysis (e.g., prioritizing studies including such populations).

Mechanistic inferences considered	Potential specific applications within the assessment
Biological understanding, including the identification of precursor events: When mechanistic data can reasonably describe how effects develop, this information may inform the situations or scenarios expected to result in these effects. Further, well-studied MOAs can sometimes identify mechanistic precursor events that can be qualitatively or quantitatively linked to the apical health effect in question with reasonable confidence.	***Dose-Response Analysis*** • Understanding how effects develop might support the use of, for example, particular models (e.g., models assuming effects do not occur below certain levels; biologically based models; models integrating data across several closely related outcomes) or measures of exposure (e.g., different external or internal metrics). • Uncertainty in the dose-dependence of responses in animals or humans can be influenced by the occurrence of precursor events, which can add to or subtract from the plausibility of the findings for use in dose-response analyses. Relatedly, in rare instances, well-established precursor events might be used as surrogates in dose-responses analyses when the health effect-specific data are less certain.

Decision frameworks, with criteria described in Tables VI and VII were used to develop the judgments concerning the strength of evidence for a health effect within each of the human and animal evidence bases, weighing the strengths and weaknesses of both positive and null studies. These frameworks, which add clarity, consistency, and transparency to the evidence evaluations and conclusions, are consistent with generally accepted principles in epidemiology and toxicology and are meant to convey a distribution of confidence in each body of evidence pertaining to a hazard, a process that relies on expert judgment.

Table VI. Framework for strength of evidence judgments (human evidence)

Strength of evidence judgment	Description
Robust … evidence in human studies *(strong signal of effect with little residual uncertainty)*	A set of *high* or *medium* confidence independent studies reporting an association between the exposure and the health outcome, with reasonable confidence that alternative explanations, including chance, bias, and confounding, can be ruled out across studies. The set of studies is primarily consistent, with reasonable explanations when results differ; an exposure-response gradient is demonstrated; and the set of studies includes varied populations. Additional supporting evidence, such as associations with biologically related endpoints in human studies (coherence) or large estimates of risk or severity of the response, may increase confidence but are not required. In exceptional circumstances, a finding in one study may be considered to be *robust*, even when other studies are not available (e.g., analogous to the finding of angiosarcoma, an exceedingly rare liver cancer, in the vinyl chloride industry). Mechanistic evidence from exposed humans or human cells, if available, may add support informing considerations such as exposure-response, temporality, coherence, and MOA, thus raising the level of certainty to *robust* for a set of studies that otherwise would be described as *moderate*.
Moderate	A smaller number of studies (at least one *high* or *medium confidence* study with supporting evidence), or with some heterogeneous results, that do not reach the degree of confidence

Strength of evidence judgment	Description
… evidence in human studies *(signal of effect with some uncertainty)*	required for *robust.* For multiple studies, there is primarily consistent evidence of an association, but there may be lingering uncertainty due to potential chance, bias or confounding. For a single study, there is a large magnitude or severity of the effect, or a dose-response gradient, or other supporting evidence, and there are not serious residual methodological uncertainties. Supporting evidence could include associations with related endpoints, including mechanistic evidence from exposed humans or human cells, if available, based on considerations such as exposure-response, temporality, coherence, and MOA, thus raising the level of certainty to *moderate* for a set of studies that otherwise would be described as *slight*.
Slight *… evidence in human studies* *(signal of effect with large amount of uncertainty)*	One or more studies reporting an association between exposure and the health outcome, where considerable uncertainty exists. In general, only *low* confidence studies may be available, or considerable heterogeneity across studies may exist. Supporting coherent evidence is sparse. Strong biological support from mechanistic evidence in exposed humans or human cells may also be independently interpreted as s*light*. This also includes scenarios where there are serious residual uncertainties across studies (these uncertainties typically relate to exposure characterization or outcome ascertainment, including temporality) in a set of largely consistent medium or high confidence studies. This category serves primarily to encourage additional study where evidence does exist that might provide some support for an association, but for which the evidence does not reach the degree of confidence required for *moderate*.
Indeterminate *… evidence in human studies* *(signal cannot be determined for or against an effect)*	No studies available in humans or situations when the evidence is inconsistent or primarily of *low* confidence
Compelling evidence of no effect *… in human studies* *(strong signal for lack of an effect with little uncertainty)*	Several *high* confidence studies showing null results (for example, an odds ratio of 1.0), ruling out alternative explanations including chance, bias, and confounding with reasonable confidence. Each of the studies should have used an optimal outcome and exposure assessment and adequate sample size (specifically for higher exposure groups and for susceptible populations). The set as a whole should include the full range of levels of exposures that human beings are known to encounter, an evaluation of an exposure-response gradient, and an examination of at-risk populations and lifestages.

Table VII. Framework for strength of evidence judgments (animal evidence)

Strength of evidence judgment	Description
Robust … animal evidence	The set of *high* or *medium* confidence experiments includes consistent findings of adverse or toxicologically significant effects across multiple laboratories, exposure routes, experimental designs (e.g., a subchronic study and a two-generation study), or species, and the experiments can reasonably rule out the potential for nonspecific effects (e.g., resulting from toxicity) to have resulted in the findings. Any inconsistent evidence (evidence that cannot be reasonably explained by the respective study design or differences in animal model) is from a set of experiments of lower confidence. At least two of the following additional factors in the set of experiments increases certainty in the evidence for the health outcome(s): coherent effects across multiple related endpoints (may include mechanistic evidence); an unusual magnitude of effect, rarity, age at onset, or severity; a strong dose-response relationship; or consistent observations across animal lifestages, sexes, or strains. Alternatively, mechanistic data in animals or animal cells that address the above considerations or that provide experimental support for a MOA that supports causality with reasonable confidence may raise the level of certainty to *robust* for evidence that otherwise would be described as *moderate* or, exceptionally, *slight, or indeterminate*.
Moderate … animal evidence	A set of evidence that does not reach the degree of certainty required for *robust*, but which includes at least one *high* or *medium* confidence study and information strengthening the certainty in the evidence for the health outcome(s). Although the results are largely consistent, notable uncertainties remain. However, while inconsistent evidence or evidence indicating nonspecific effects (e.g., toxicity) may exist, it is not sufficient to reduce or discount the level of concern regarding the positive findings from the supportive experiments or it is from a set of experiments of lower confidence. The set of experiments supporting the effect provide additional information supporting causality, such as consistent effects across laboratories or species; coherent effects across multiple related endpoints (may include mechanistic evidence); an unusual magnitude of effect, rarity, age at onset, or severity; a strong dose-response relationship; or consistent observations across exposure scenarios (e.g., route, timing, duration), sexes, or animal strains. Mechanistic data in animals or animal cells that address the above considerations or that provide information supporting causality with reasonable confidence may raise the level of certainty to *moderate* for evidence that otherwise would be described as *slight*.
Slight … animal evidence	Scenarios in which there is a signal of a possible effect, but the evidence is conflicting or weak. Most commonly, this includes situations where only *low* confidence experiments are available and supporting coherent evidence is sparse. It also applies when one *medium* or *high* confidence experiment is available without additional information increasing the certainty in the evidence (e.g., corroboration within the same study or from other studies). Lastly, this includes scenarios in which there is evidence that would typically be characterized as *moderate*, but inconsistent evidence (evidence that cannot be reasonably explained by the respective study design or differences in animal model) from a set of experiments of higher confidence (may include mechanistic evidence) exists. Strong biological support from mechanistic studies in exposed animals or animal cells may also be independently interpreted as *slight*. Notably, to encourage additional research, it is important to describe situations where evidence exists that might provide some support for an association but is insufficient for a conclusion of *moderate*.

Strength of evidence judgment	Description
Indeterminate …animal evidence	No animal studies were available, or a set of *low* confidence animal studies exist that are not reasonably consistent or are not informative to the hazard question under evaluation.
Compelling evidence of no effect … in animal studies	A set of *high* confidence experiments examining a reasonable spectrum of endpoints relevant to a type of toxicity that demonstrate a lack of biologically significant effects across multiple species, both sexes, and a broad range of exposure levels. The data are compelling in that the experiments have examined the range of scenarios across which health effects in animals could be observed, and an alternative explanation (e.g., inadequately controlled features of the studies' experimental designs; inadequate sample sizes) for the observed lack of effects is not available. The experiments were designed to specifically test for effects of interest, including suitable exposure timing and duration, postexposure latency, and endpoint evaluation procedures, and to address potentially susceptible populations and lifestages.

In the next step (i.e., after judging the strength of the human and animal evidence separately), the entire body of evidence was integrated across the human and animal evidence, considering mechanistic information on the human relevance of the animal evidence and coherence of the findings across streams of evidence, to arrive at an overall evidence integration judgment regarding the evidence for causation (Table VIII). This evidence integration framework interprets the instructions and examples provided in the cancer guidelines (U.S. EPA, 2005a) to allow clarity and consistency in the evaluation of each potential human hazard. The evidence integration framework is consistent with the cancer guidelines in that evidence in humans generally has greater weight than evidence in animals. In the absence of sufficiently justifiable MOA information, effects in animal models are assumed to be relevant to humans. In this assessment, for potential health hazards where the evidence from animal models influenced the overall evidence integration judgment, the available mechanistic evidence was considered to inform human relevance.

For each potential health effect evaluated, a narrative evidence integration summary and judgment was developed. The overall evidence integration judgments of **evidence demonstrates**, **evidence indicates [likely]**, **evidence suggests** and **evidence inadequate** (to judge hazard) are defined in Table VIII and presented as bolded text throughout the assessment, accompanied by a description of the conditions of expression (e.g., exposure levels, exposure patterns) in the studies that served as the basis for the judgment. Importantly, for the purposes of this assessment, the same evidence integration approach was used to draw evidence integration judgments for both noncancer health effects and specific cancer types. This approach uses the methods and considerations and described in the EPA cancer guidelines (U.S. EPA, 2005a). Consistent with these guidelines, for carcinogenicity, a final step of categorizing the totality of the evidence using a "descriptor" was performed, as described in Table IX.

Table VIII. Overall evidence integration judgments for characterizing potential human health hazards (noncancer health effects and cancer outcomes) in the evidence integration narrative

Overall evidence integration judgment in narrative	Explanation and example scenarios
Evidence demonstrates	This signifies a very high level of certainty that formaldehyde exposure causes the health effect in humans. • This category was[a] used if there was *robust* human evidence supporting an effect. • This category could also be used with *moderate* human evidence and *robust* animal evidence if there was strong mechanistic evidence that MOAs and key precursors identified in animals were anticipated to occur and progress in humans.
Evidence indicates (likely)[b]	This reflects a reasonable certainty that the relationship between formaldehyde exposure and the health outcome is causal, although there may be some outstanding questions that remain. • This category was used if there is *robust* animal evidence supporting an effect and *slight*-to-*indeterminate* human evidence, or with *moderate* human evidence when strong mechanistic evidence was lacking. • This category could also be used with *moderate* human evidence supporting an effect and *slight or indeterminate* animal evidence, or with *moderate* animal evidence supporting an effect and *slight* or *indeterminate* human evidence. In these scenarios, any uncertainties in the *moderate* evidence were not sufficient to reduce or discount the level of concern, or mechanistic evidence in the *slight* or *indeterminate* evidence base (e.g., precursors) existed to increase confidence in the *moderate* evidence.
Evidence suggests (but is not sufficient to infer)[c]	This conveys some concern that formaldehyde may cause a particular health effect in humans, but there were very few studies that contributed to the evaluation, the evidence was very weak or conflicting, or the methodological conduct of the studies was poor. Given the substantial degree of uncertainty, additional research would provide valuable information for future evaluations. • This category was used if there was *slight* human evidence and *slight-to-indeterminate* animal evidence. • This conclusion level was also used with *slight* animal evidence and *slight-to-indeterminate* human evidence. • This category could also be used with *moderate* human evidence and *slight or indeterminate* animal evidence, or with *moderate* animal evidence and *slight* or *indeterminate* human evidence. In these scenarios, there were outstanding issues regarding the *moderate* evidence that reduced the level of concern or confidence in the reliability of the findings, or mechanistic evidence in the *slight* or *indeterminate* evidence base (e.g., null results in well-conducted evaluations of precursors) existed to decrease confidence in the *moderate* evidence. • Exceptionally, when there is general scientific understanding of mechanistic events that result in a hazard, this category could also be used if there was strong mechanistic evidence that was sufficient to identify a cause for concern—in the

Overall evidence integration judgment in narrative	Explanation and example scenarios
	absence of adequate conventional studies in humans or in animals (i.e., *indeterminate* evidence in both).
Evidence inadequate[d]	This conveys either a lack of information or an inability to interpret the available evidence. • This category was used if there was *indeterminate* human and animal evidence. • This category could also be used with *slight*-to-*robust* animal evidence and *indeterminate* human evidence if strong mechanistic information indicated that the animal evidence was unlikely to be relevant to humans. A conclusion of **inadequate** is not a determination that the agent does not cause adverse health outcomes or is safe. It generally indicates that further research is needed.

Note: This table does not supersede or alter direction provided in EPA guidelines. It is meant only to provide added transparency for conclusions drawn regarding the level of evidence from human, animal, and mechanistic studies.
[a]Terminology of "was" refers to the default option; terminology of "could also be" refers to alternative options.
[b]For some applications, such as benefit-cost analysis, to better differentiate the categories of **evidence demonstrates** and **evidence indicates (likely)**, the latter category should be interpreted as evidence that supports an exposure-effect linkage that is likely to be causal.
[c]Health effects characterized as having evidence demonstrates and evidence indicates (likely) (and, in some cases, **evidence suggests**) are evaluated for use in dose-response assessment. When the database includes at least one well-conducted study and a judgment of **evidence suggests** is drawn, quantitative analyses may still be useful for some purposes (e.g., providing a sense of the magnitude and uncertainty of estimates for health effects of potential concern, ranking potential hazards, or setting research priorities), but not for others [see related discussions in U.S. EPA (2005b)]. It is critical to transparently convey the extreme uncertainty in any such estimates.
[d]Specific narratives for each of the health effects with an evidence integration judgment of **evidence inadequate** may be deemed unnecessary.

For carcinogenesis only, the weight of evidence as to whether formaldehyde inhalation exposure is carcinogenic to humans was summarized using descriptors, consistent with EPA guidelines (U.S. EPA, 2005a) (Table IX). For this assessment, the descriptors build upon the overall evidence integration judgments for individual cancer types, as described in Table VIII; however, this does not alter or supersede direction provided in EPA guidelines. These descriptors are bolded and italicized.

Table IX. Criteria for applying cancer descriptors to overall confidence conclusions for cancer types

Cancer descriptor	Criteria
Carcinogenic to humans	This descriptor was used if the **evidence demonstrates** that, for at least one cancer type, formaldehyde inhalation exposure caused the increase in cancer incidence or mortality.

Cancer descriptor	Criteria
	This descriptor could also be used in rare instances if the **evidence indicates** that formaldehyde inhalation exposure likely causes different cancer types across evidence bases (e.g., when one type of cancer is based on human evidence and tumors at another site is supported by animal evidence), consistent with EPA guidelines (U.S. EPA, 2005a) that site concordance is not required. Such a decision would depend on mechanistic understanding (i.e., in this example, the decision would consider differences in tumor types or ADME across species).
Likely to be carcinogenic to humans	This descriptor was used if the **evidence indicates** that, for at least one cancer type, formaldehyde inhalation exposure likely caused the increase in cancer incidence or mortality. Similar to the rationale provided above, this descriptor could also be used in rare instances when the **evidence suggests** formaldehyde inhalation exposure may cause multiple tumor types, depending on mechanistic inference.
Suggestive evidence of carcinogenic potential	This descriptor was used if, for the evidence relating to carcinogenicity, the **evidence** was only **suggestive** that formaldehyde inhalation exposure may cause any of the observed increases in cancer incidence or mortality for any cancer type. This would reflect a substantial degree of uncertainty in any potential causal inference.
Inadequate evidence to assess carcinogenic potential	This descriptor was used if the **evidence** was **inadequate** to draw a conclusion regarding cancers of any type with any confidence. This might reflect a lack of information or highly conflicting information.
Not Likely to be carcinogenic to humans	This descriptor conveys a high degree of certainty that there is negligible concern for carcinogenic effects. A substantial amount of evidence would be required to support this descriptor (see (U.S. EPA, 2005a).

Quantitative Dose-Response Assessment

This formaldehyde assessment includes development of organ/system-specific RfCs (osRfC) and an overall RfC for noncancer effects, as well as an IUR for carcinogenic effects, presented in units of μg/m^3.[5] From among the body of evidence used for the hazard identification assessment, selection of the studies for dose-response assessment used information from the study confidence evaluations, with particular emphasis on conclusions regarding the characteristics of the study population (considering potential susceptible groups) and the accuracy of formaldehyde exposure, the severity of the observed effects, and the exposure levels analyzed (see Appendix B). Based on the data available in this assessment, the subset of studies used to develop RfCs and unit risk estimates were from those noncancer health outcomes and specific cancer types with an overall **evidence demonstrates** or **evidence indicates [likely]** judgment regarding the potential for formaldehyde inhalation to cause those effects (see Section 2).

For each health effect for which a value was derived, one or more studies were determined to be suitable for use in quantitative exposure-response assessment, and these are discussed in Section 2.1 for effects other than cancer and in Section 2.2 for specific cancer types. A POD was

[5] Throughout this assessment, a conversion of 1 ppm = 1.23 mg/m^3 formaldehyde is used.

determined for several health effects, including sensory irritation, pulmonary function, respiratory tract pathology, prevalence of current asthma, allergic conditions, developmental and female reproductive toxicity, male reproductive toxicity, respiratory tract cancers (i.e., nasopharyngeal cancer), and lymphohematopoietic cancers (i.e., myeloid leukemia). In some cases, estimates considered information from mechanistic studies (see Table ES-2, footnote c for examples of how these data were considered quantitatively). Specifically, for some outcomes (i.e., nasal cancers; noncancer respiratory tract pathology), analyses included efforts to apply dosimetry models estimating the uptake of inhaled formaldehyde, including an evaluation of modeling efforts to account for the potential contribution of endogenous formaldehyde on uptake (see Section 2.2). Candidate osRfCs or cancer unit risk values were estimated for each of these noncancer or cancer health outcomes, respectively, and the associated uncertainties were discussed. In addition to the overall evidence integration judgment for concluding that formaldehyde inhalation results in specific health effects (which incorporates the individual study confidence), a confidence level of **high**, **medium**, or **low** was assigned to each osRfC regarding the reliability of the associated POD calculation(s). Confidence in the completeness of the database for each osRfC was also assigned. These judgments were used to select the RfC, draw an overall level of confidence in the RfC, and determine the completeness of the formaldehyde literature database. For noncancer health hazards, multiple graphical depictions were developed to display PODs, uncertainty factors, and candidate osRfCs across outcomes and studies, as well as the context of these estimates (e.g., in relation to the study-specific results, in relation to known human exposures to formaldehyde). Organ/system-specific RfCs, a single, overall RfC, and unit risk were selected; the specific rationale is described in Section 2, Dose-Response Analysis. For the derivation of the cancer inhalation unit risk (IUR) estimate, exposure-response analyses for nasopharyngeal cancer (NPC) from an occupational cohort study and cancers of the nose across two bioassays in rats, and for lymphohematopoietic malignancies from an occupational cohort study, were considered. The IUR was based on the preferred unit risk estimate for NPC and application of age-dependent adjustment factors (see Section 2.2.6). An overall level of confidence was assigned to the IUR. For one mechanism that contributes to cancer risk, cytotoxicity-induced regenerative proliferation, a contributing mechanism which appears to involve a threshold, cRfCs were derived using different data sets from rat bioassays.

Table X. Considerations for study selection for quantification of dose-response and derivation of toxicity values

Factor	Considerations
Overall Confidence Conclusion	For this assessment, if the data were amenable, a toxicity value was estimated for health effects with evidence integration judgments of **evidence demonstrates** or **evidence indicates [likely]**. Although it may sometimes be possible to develop toxicity values for judgments of **evidence suggests**, given the particulars of the available data in this assessment, toxicity values were not estimated.

Factor	Considerations
Study Confidence	Studies with appropriate study designs (e.g., long-term bioassays were preferred for animal studies of most health effects), reasonably complete reporting of results, and with no identified sources of selection bias, information bias, or confounding that would substantially alter interpretation of study results.
Population	Human studies were preferred over animal studies. Dose-response information for the most susceptible subgroups was evaluated, if appropriate.
Exposure information	Studies with risk estimates for multiple exposure levels or regression coefficients per unit of formaldehyde concentration were generally preferred over LOAELs or NOAELs because they provided information about the shape of the concentration-response curve and allowed for benchmark dose modeling.

The role of endogenously generated formaldehyde in human diseases is largely unknown. This includes endogenous formaldehyde generated during normal cellular metabolic processes, as well as formaldehyde produced endogenously within cells (e.g., in the liver) as a breakdown product of external exposures to other chemicals, including ingestion of caffeine (Summers et al., 2012; Hohnloser et al., 1980) and methanol-rich foods or beverages, such as fruit-based liquors (Riess et al., 2010). The mode of action by which toxicity at distal sites, such as bone marrow or reproductive tissues, may occur in response to inhalation of formaldehyde over long periods, also is not known. Once formaldehyde is inhaled and interacts with extracellular aqueous matrices such as mucus in nasal passages and is hydrated, the biochemical reactivity of inhaled formaldehyde and endogenous formaldehyde are likely to be very similar, given that there are no differences in chemical structure. However, no specific data are available to inform whether there may be differences in interactions with specific extracellular or intracellular macromolecular targets in vivo. While the rate of cellular detoxification of exogenous formaldehyde remains unknown, the production and subsequent detoxification of endogenous formaldehyde appears to be kept under strict control and has been well described (Burgos-Barragan et al., 2017b).

The focus of the assessment is to estimate the risk over background that results from only the exogenous exposure, and the assessment assumes that background incidence of cancer or other health hazard that may potentially be attributed to endogenous formaldehyde is already accounted for in the background. Endogenous formaldehyde might be responsible for some portion of background risks for some health outcomes, particularly when normal detoxification pathways are deficient (e.g., Pontel et al., 2015); but that possibility is not the purpose of this review. This assessment does consider and discuss the potential impact of normal levels of endogenous formaldehyde on the penetration and distribution of inhaled formaldehyde, based on recent dosimetric models ((Campbell Jr et al., 2020; Schroeter et al., 2014); see Section 2.2). In addition, efforts to incorporate the unknown contribution of endogenous formaldehyde to background cancer incidence in an attempt to bound low-dose human cancer risks from formaldehyde exposure have been published using a measure of internal dose for inhaled formaldehyde. These papers are discussed in Section 2.2 and Appendix B.2.3.

EXECUTIVE SUMMARY

ES.1 OVERALL SUMMARY

This IRIS health assessment presents a systematic evaluation of the publicly available studies relevant to inhalation exposure to formaldehyde and potential adverse health outcomes. The purpose of the review was to identify hazards that may result from formaldehyde inhalation and to describe the level of confidence in each conclusion. When there was sufficient confidence in a hazard and the studies and data available, toxicity values were derived using either analyses of dose-response or selected no-observed-adverse-effect or lowest-observed-adverse-effect levels (NOAEL or LOAEL). The conclusions of the assessment are summarized in Tables ES-1 and ES-2.

The evidence identification, evaluation, and integration framework depicted in Figure I was used to conduct the assessment. Potential health hazards were evaluated, including sensory irritation; reduced pulmonary function; immune system effects, focusing on allergic conditions and asthma; respiratory tract pathology; nervous system effects; reproductive and developmental toxicity; and cancer. Several extensively studied cancer sites were specifically evaluated, including cancers of the upper respiratory tract (i.e., nasopharyngeal cancer, sinonasal cancer, cancers of the oropharynx/hypopharynx, and laryngeal cancer) and of the lymphohematopoietic system (i.e., Hodgkin lymphoma, multiple myeloma, myeloid leukemia, and lymphatic leukemia).

Table ES-1. Evidence integration judgments for noncancer health effects and the reference concentration (RfC)

Noncancer health effect	Confidence in health effect	POD basis	Confidence in POD	UF_C	osRfC (mg/m^3)
Decreased pulmonary function	**evidence indicates [likely]**[c]	Human	*high*	3	0.007
Allergic conditions	**evidence indicates [likely]**	Human	*high*	3	0.008
Current asthma symptoms or degree of asthma control	**evidence indicates [likely]**	Human	*medium*	10[d]	0.006[d]
Sensory irritation	**evidence demonstrates**	Human	*medium*	10	0.009
Female reproductive or developmental toxicity	**evidence indicates [likely]**	Human	*low*	10	0.01
Respiratory tract pathology	**evidence demonstrates**	Rat	*medium*	30[d]	0.003[d]
Male reproductive toxicity	**evidence indicates [likely]**	Rat	*low*	3000	0.001
Nervous system effects[a]	**evidence suggests**	Not Derived	-	-	-

	Confidence in health effects	PODs basis	Confidence in PODs	UF_C	Confidence in database	RfC (mg/m^3)	Overall confidence
RfC[b]:	*Medium* or *High*	Human	*Medium* or *High*	3 or 10[d]	*High*	0.007	**High**

Abbreviations and definitions: RfC = reference concentration: An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure of a chemical to the human population (including sensitive subpopulations), that is likely to be without risk of deleterious noncancer effects during a lifetime. osRfC = organ- or system-specific RfC: an RfC based on the evidence for effects on that particular organ or system. UF_C = composite (total) uncertainty factor; POD = point of departure.

[a]Three separate judgments were drawn for nervous system effects, all **evidence suggests**; specifically, the **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation might cause increases in amyotrophic lateral sclerosis incidence or mortality, developmental neurotoxicity, or behavioral toxicity.

[b]Basis for RfC—sensory irritation, decreased pulmonary function, current asthma symptoms or degree of asthma control, and allergic conditions. The corresponding osRfCs (i.e., based on human studies with *medium* or *high* confidence in the health effects and PODs) are highlighted in gray, which also have the lowest UF_C values.

[c]For decreased pulmonary function, the judgment **evidence indicates [likely]** was drawn for long-term exposure durations. For acute or intermediate exposure durations (hrs to wks), the **evidence** is **inadequate** to draw judgments.

[d]These two osRFCs and the RfC are based on multiple studies and candidate values, sometimes with different UFCs applied. The UFC values shown in this table and Figure 2-2 reflect the candidate values selected to represent each osRfC [i.e., the UFC applied to the POD from Krzyzanowski et al. (1990) for asthma and from Woutersen et al. (1989) for respiratory pathology].

Table ES-2. Cancer evidence integration judgments, carcinogenicity descriptor, and inhalation unit risk (IUR) for cancer incidence

Cancer type investigated	Evidence integration judgment for cancer type risk	Unit risk estimate basis	Unit risk estimate (per µg/m^3)	ADAF-adjusted unit risk estimate (per µg/m^3)[a]	Confidence in the unit risk estimate
Nasopharyngeal cancer (or nasal cancer in animals)	**evidence demonstrates**[b]	Human	6.4×10^{-6}	1.1×10^{-5}	*medium*
		Animal[c]	8.9×10^{-6} to 1.8×10^{-5}	NA[d]	*medium*
Myeloid leukemia	**evidence demonstrates**[e]	Human	3.4×10^{-5}	NA[f]	*low*
Sinonasal cancer	**evidence demonstrates**[g]	No usable data	-	-	
Oropharyngeal/Hypo-pharyngeal cancer	**evidence suggests**	Not derived	-	-	
Multiple myeloma	**evidence suggests**	Not derived	-	-	
Hodgkin lymphoma	**evidence suggests**	Not derived	-	-	
Laryngeal cancer	**evidence inadequate**	Not derived	-	-	
Lymphatic leukemia	**evidence inadequate**	Not derived	-	-	
Carcinogenicity Descriptor:	***Carcinogenic* to Humans**				
Total cancer risk (IUR)[h]:	**1.1×10^{-5} per µg/m^3;** Confidence in the IUR is **Medium**				

Abbreviations and definitions: IUR = inhalation unit risk: the upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 µg/m^3 in air; ADAF = age-dependent adjustment factor.

[a]ADAF adjustments are recommended for cancers for which there is sufficient evidence that formaldehyde has, at least in part, a mutagenic MOA (see Section 2.2.4).

[b]The judgment of **evidence demonstrates** for NPC cancer is based on *robust* human evidence of increased risk in groups exposed to occupational formaldehyde levels, and *robust* animal evidence of nasal cancers in rats and mice that exhibits steeply increasing incidence at high formaldehyde levels. Strong mechanistic support is provided across species (primarily rats, but also mice, monkeys, and humans), including genotoxicity, epithelial damage or remodeling, and cellular proliferation that are consistent with neoplastic development in a regional, temporal, and dose-related fashion.

[c]While the preferred unit risk estimate for NPC is based on a cancer mortality study in humans, several estimates in general agreement with each other were also derived based on animal nasal tumor incidence. These estimates used multiple mechanistic and statistical models, including biologically based dose-response (BBDR) modeling (see Section 2.2.2). In addition, an RfC for one mechanism contributing to nasal cancer development, specifically cytotoxicity-induced regenerative cell proliferation, was estimated to be between 0.006 and 0.018 mg/m^3 based on calculations using animal data. Specifically, this narrow RfC range was estimated based on cRfCs from a pathology study of hyperplasia, labeling studies of proliferating cells, and BBDR modeling results (see Section 2.2.2).

[d]NA = not applicable; an ADAF-adjusted value was not calculated for the unit risk estimates based on the animal data on nasal cancer, as the human unit risk estimate for NPC was the preferred estimate.

[e] The judgment of **evidence demonstrates** for myeloid leukemia is based on *robust* human evidence of increased risk in groups exposed to occupational formaldehyde levels. Supporting mechanistic evidence consistent with leukemia development is provided across numerous studies of peripheral blood isolated from exposed workers, including evidence of mutagenicity and

other genotoxic damage in lymphocytes and myeloid progenitors, and perturbations to immune cell populations. The animal evidence is *inadequate* and the findings to date suggest that there may be a lack of concordance across species for leukemia, as leukemia was not increased in two well-conducted chronic bioassays of rats or mice, and the available animal data provide weak mechanistic support for LHP cancers. No MOA has been established to explain how formaldehyde inhalation can cause myeloid leukemia without systemic distribution (inhaled formaldehyde does not appear to be distributed to an appreciable extent beyond the respiratory tract to distal tissues).

[f]NA = not applicable; no ADAF adjustment is recommended for myeloid leukemia because the MOA is unknown (see Section 1.3.3).

[g]The judgment of **evidence demonstrates** for sinonasal cancer is based primarily on *robust* human evidence of increased risk in groups exposed to occupational formaldehyde levels. The strong animal and mechanistic evidence for nasal cancers across species is interpreted to provide *moderate* evidence supportive of sinonasal cancer (a judgment of *moderate* rather than *robust* reflects some uncertainty in interpreting the nasal cavity findings in animals as fully applicable to the specific human disease of sinonasal cancer; see Section 1.2.5).

[h]The full lifetime (ADAF-adjusted) IUR estimate is based on the ADAF-adjusted estimate for nasopharyngeal cancer (which includes a mutagenic MOA; see Section 1.2.5). Less-than-lifetime exposure scenarios with a very large fraction of exposure during adulthood may not warrant ADAF adjustment, and one may choose to use the unadjusted unit risk estimate of 6.4×10^{-6} per $\mu g/m^3$. Otherwise, see Table 2-39 for an illustration of how to apply the ADAFs to obtain total cancer risk estimates for less-than-lifetime exposure scenarios (see Section 2.2.4).

ES.2 HAZARD ASSESSMENT SUMMARY

ES.2.1. Noncancer Effects

Overall, the integrated **evidence demonstrates** that inhalation of formaldehyde causes increased sensory irritation and respiratory tract pathology in humans, given appropriate exposure circumstances. Well-conducted studies in humans and animals support these hazard conclusions, and strong mechanistic evidence in animals provides plausible modes of action (MOAs) for the identified endpoints.

The available **evidence indicates** that formaldehyde inhalation likely causes decreased pulmonary function, an increased frequency of current asthma symptoms or difficulty controlling asthma, and increased allergic responses in humans, given appropriate exposure circumstances. These conclusions were supported primarily by evidence in exposed humans, with supportive mechanistic evidence indicating that formaldehyde inhalation results in biological changes related to these outcomes in exposed animals. In addition, the **evidence indicates** that inhalation of formaldehyde likely causes female reproductive or developmental toxicity and reproductive toxicity in men, given appropriate exposure circumstances. The conclusion for female reproductive or developmental toxicity is supported by evidence in humans, specifically increases in time-to-pregnancy (TTP) and spontaneous abortion risk; mechanistic evidence explaining such effects without systemic distribution of formaldehyde is lacking. The conclusion for male reproductive toxicity is supported primarily by coherent evidence of several alterations to the male reproductive system in animals exposed to very high levels of formaldehyde (>6 mg/m^3), with some corroborative changes in an occupational epidemiological study; although no MOA is available, some relevant mechanistic changes have been observed in well-conducted studies of the male reproductive organs of exposed rodents.

Lastly, while a number of studies reported evidence of potential neurotoxic effects, including developmental neurotoxicity, behavioral toxicity, and an increased incidence of, or

mortality from, the motor neuron disease amyotrophic lateral sclerosis (ALS), due to limitations in the database (e.g., poor methodology, lack of consistency), the integration of the evidence for each of these manifestations of potential neurotoxicity ultimately resulted in the determination that the **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation may pose a human health hazard, and additional study is warranted. The available data on potential nervous system effects were considered insufficient for developing quantitative toxicity estimates.

ES.2.2. Cancer

Formaldehyde is ***Carcinogenic to Humans by the Inhalation Route of Exposure***. This conclusion is independently supported by three evidence integration judgments:

- The **evidence demonstrates** that formaldehyde inhalation causes nasopharyngeal cancer (NPC) in humans. This is based primarily on observations of increased risk of NPC in groups exposed to occupational formaldehyde levels and nasal cancers in mice and several strains of rats, with strong, reliable, and consistent mechanistic evidence in both animals and humans (i.e., *robust* evidence for both the human and animal evidence, and strong mechanistic support for the human relevance of the animal data). The nasopharynx, although not typically specified in animal studies, is the region adjacent to the nasal cavity, where the animal evidence was predominantly observed (thus, the animal evidence is judged as *robust*). In addition, the evidence is sufficient to conclude that a mutagenic MOA of formaldehyde is operative in formaldehyde-induced nasopharyngeal carcinogenicity.

- The **evidence demonstrates** that formaldehyde inhalation causes sinonasal cancer (SNC) in humans. This is based primarily on observations of increased risk of SNC in groups exposed to occupational formaldehyde levels (i.e., *robust* human evidence) and supported by apical and mechanistic evidence for nasal cancers across multiple animal species. Some uncertainties remain in the interpretation of the animal nasal cavity data as wholly applicable to interpreting human sinonasal cancer (thus, the animal evidence is judged as *moderate*). In addition, while uncertainties remain, the evidence is sufficient to conclude that a mutagenic MOA of formaldehyde is operative in formaldehyde-induced sinonasal carcinogenicity.

- The **evidence demonstrates** that formaldehyde inhalation causes myeloid leukemia in humans. This is based primarily on observations of increased risk in groups exposed to occupational formaldehyde levels. This evidence integration judgment is further supported by other studies of human occupational exposure that provide strong and coherent mechanistic evidence identifying clear associations with additional endpoints relevant to LHP cancers, including an increased prevalence of multiple markers of mutagenicity and other genotoxicity in peripheral blood cells of exposed workers, other perturbations to immune cell populations in blood (primarily from human studies), and evidence of other systemic effects (i.e., developmental or reproductive toxicity). Generally, evidence supporting the development of LHP cancers after formaldehyde inhalation has not been observed in experimental animals (i.e., rodents), including a well-conducted, chronic cancer bioassay in two species, a similar lack of increased leukemias in a second rat bioassay, and multiple mechanistic evaluations of relevant biological changes, including genotoxicity (i.e., **inadequate evidence**). The exact mechanism(s) leading to cancer formation outside of the respiratory tract are unknown.

The hazard conclusion for cancer is consistent with those drawn by other expert review panels. Formaldehyde was classified as a known carcinogen by the NTP (2011) and a Group 1 carcinogen by IARC (2012, 2006) , both based on evidence for nasal cancers in humans and animals and myeloid leukemia in humans, with supporting data on mechanisms of carcinogenesis. In addition, an expert committee convened by the NAS confirmed the conclusions of the NTP 12th Report on Carcinogens (RoC) and conducted an independent review of the literature through 2013, concluding that formaldehyde is a known carcinogen. The European Union and Health Canada concluded that formaldehyde is a genotoxic carcinogen with a cytotoxic MOA (SCOEL, 2017; ECHA, 2012; Health Canada, 2006, 2001).

ES.3 DOSE-RESPONSE ASSESSMENT SUMMARY

ES.3.3. Inhalation Reference Concentration (RfC) for Noncancer Effects:

The reference concentration (the RfC) of 0.007 mg/m^3 is the concentration one can breathe every day for a lifetime that is not anticipated to cause any harmful noncancer health effects.

Organ- or system-specific reference concentrations (osRfCs)

In this assessment, the RfC is based on several osRfCs, which are themselves based on candidate reference concentrations (cRfCs). The cRfCs are estimates for a specific endpoint based on a single, specific study within an organ- or system-specific hazard domain. The osRfCs differ from the associated cRfCs only when there are multiple cRfCs for the same organ system.

The osRfCs that were used to calculate the overall RfC in this assessment were all based on epidemiological studies and were interpreted with either *high*- or *medium-confidence* based on (1) the study results (i.e., confidence in the individual studies used to derive the osRfC), (2) the point of departure (POD) and the cRfC derivation, and (3) the hazard determination (the strongest, highest confidence judgment of **evidence demonstrates** was preferred) (see Table ES-1). In general, the studies preferred as the basis for the derivation of the RfC were those human studies that best represented the general population, including sensitive subgroups. An osRfC was typically selected from those cRfCs that had a greater degree of certainty with regard to both reliability of study results and cRfC derivation (including POD selection). In addition, candidate RfCs with lower composite uncertainty factors (UF_Cs) were preferred.

The overall RfC is within the narrow range (0.006–0.009 mg/m^3) of the group of respiratory system-related osRfCs (sensory irritation, pulmonary function, allergy-related conditions, and current asthma prevalence or degree of control). The health effects generally were observed in the range of indoor formaldehyde concentrations in population studies (effects were observed in studies at approximately 35–40 µg/m^3), and these were used to arrive at the osRfCs associated with the lowest UF_Cs. Thus, the selected RfC is at the upper end of the range of outdoor formaldehyde levels recorded in some locations (average or median levels of formaldehyde in outdoor air typically range from 0.4 to 10 µg/m^3), and it would be expected that levels in indoor air would

exceed this concentration in many situations. However, as the RfC is interpreted to be without appreciable risk, even in sensitive subgroups, it is important to note that the potential for health effects in individuals at concentrations between the RfC (0.007 mg/m^3) and levels at which health effects have been observed in the available population studies (~35–40 μg/m^3) is unknown.

Although the RfC is designed to apply to exposures over a lifetime, the relevant window of exposure for some of the effects observed in the contributing studies may be less than a lifetime. Sensory irritation is an immediate response to reactive compounds like formaldehyde. The relevant window of exposure for effects on asthma outcomes is also less than lifetime, although the time frame for the control of asthma symptoms (i.e., a few weeks) is different than that for the prevalence of current asthma symptoms or a decrease in pulmonary function (i.e., the past 12 months). In addition, the relevant window of exposure for female reproductive or developmental outcomes is from conception to the end of the pregnancy.

Overall confidence in the RfC is **high**, based on *high* confidence in the composite set of studies used to derive the RfC, *high* confidence in the completeness of the literature database supporting the judgment that formaldehyde causes the adverse effects identified (although uncertainties remain for other potential health effects), and *medium*-to-*high* confidence in the derivation of the candidate RfC numerical values.

ES.3.4. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure:

The inhalation unit risk (IUR) is 1.1 × 10^{-5} per μg/m^3, which is an upper-bound estimate of the increased lifetime risk of cancer from inhaling 1 μg/m^3 of formaldehyde for 70 years. The estimate is based on an estimate of increased risk for NPC, for which **evidence demonstrates** that formaldehyde inhalation causes this type of cancer in humans. The IUR does not incorporate a unit risk estimate for myeloid leukemia (also for which the **evidence demonstrates** that formaldehyde inhalation causes this type of cancer in humans) presented in Section 2 of this assessment because the interpretation of the published exposure-response modelling results was deemed too uncertain.[6] This estimate also does not incorporate risk from sinonasal cancer for which the **evidence demonstrates** that formaldehyde inhalation exposure causes this type of cancer in humans given appropriate exposure circumstances, as amenable data were unavailable. The IUR is based on the modeling results of the association of cumulative formaldehyde exposure with NPC mortality in an occupational cohort followed by the National Cancer Institute (Beane Freeman et al., 2013). The regression coefficient from the dose-response model (log-linear models) was applied to age-specific cancer incidence rates from the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) database using life-table methods to estimate the upper

[6]A charge question is provided for external peer review asking for advice regarding the development of a unit risk estimate for myeloid leukemia and how, if at all, the unit risk estimate might inform the quantification of risk for cancer.

bound on the extra risk[7] expected at a formaldehyde concentration of 0.1 ppm. The IUR is expressed as the upper-bound number of extra cancer cases estimated for a lifetime inhalation exposure to 1 μg/m^3. This estimate, based on a human study, was found to be within the range of estimates derived using experimental animal data, including estimates that incorporate BBDR modeling approaches using available mechanistic evidence (see Section 2.2). The estimated IUR for total cancer prior to any age adjustments is 6.4×10^{-6} per μg/m^3 (see Table ES-2). EPA guidelines recommend that ADAFs be used when estimating the risk of NPC from childhood inhalation exposures to formaldehyde because the NPCs are judged to be due, at least in part, to a mutagenic MOA. In the absence of information to support a chemical-specific age adjustment factor, EPA's default ADAFs should be applied. Thus, the unit risk estimate was adjusted using age-dependent adjustment factors (ADAFs) to address expected increased susceptibility from early-life exposures (see Table ES-1).

Overall confidence in the IUR is **medium**. The availability of suitable human data from which to derive unit risk estimates eliminates one of the major sources of uncertainty inherent in most unit risk estimates—the uncertainty associated with interspecies extrapolation. The NCI longitudinal cohort study used as the basis for the preferred unit risk estimate is a well-conducted study for the purposes of deriving unit risk estimates and there is *high* confidence in the study's results. However, it was the only independent study with adequate exposure estimates for the derivation of unit risk estimates.

There are some uncertainties that could result in an underestimation of the IUR. An important uncertainty is the inability to derive unit risk estimates for all cancer sites with conclusions of **evidence demonstrates** that formaldehyde inhalation exposure causes these cancer types given appropriate exposure circumstances, resulting in an underestimate of the IUR, Since industrial workers are healthier than the general population overall, the unit risk estimates derived from the NCI worker cohort data could underestimate the cancer risk for the general population to an unknown, but likely small, extent. Given the high survival rates for NPC, cancer incidence risk estimates were calculated using the dose-response relationships from the NCI mortality study to reduce the potential to underestimate the unit risk. However, the calculation required certain assumptions, thus, the estimates may under- or overpredict the true risk by an amount expected to be relatively small.

Because a mutagenic MOA was established for NPC, the IUR was calculated using linear low-dose extrapolation from the 95% lower bound on the exposure level associated with the extra risk level serving as the benchmark response, which is considered to be a plausible upper bound on the risk at lower exposure levels. The low dose extrapolation is a source of uncertainty potentially

[7] Extra risk is defined as (Rx − Ro)/(1 − Ro), where Rx is the lifetime risk in the exposed population and Ro is the lifetime risk in an unexposed population; it is the added risk applied to the portion of the population that did not show background tumors.

resulting in overestimation of the IUR, possibly by a substantial (e.g., over an order of magnitude) extent.

ES.4 SUSCEPTIBLE POPULATIONS AND LIFESTAGES

Overall, the most extensive research on the health effects of inhaled formaldehyde and susceptible groups indicates a greater susceptibility among children to respiratory disease, manifested as reduced pulmonary function, increased prevalence of current asthma, and greater asthma severity (reduced asthma control). More research is needed to investigate the role of sex, race, nutrition, exercise, and coexposures that may modulate susceptibility to formaldehyde toxicity. Increased early-life susceptibility for cancer is assumed because of the mutagenic MOA for NPC carcinogenicity. Health status and disease, particularly related to the respiratory system, are likely to be modifying factors of formaldehyde toxicity. Studies suggest that asthmatics are more susceptible than nonasthmatics to declines in respiratory function following formaldehyde exposure. Based on multiple mechanistic studies of respiratory hypersensitivity, it also appears likely that persons with preexisting respiratory allergies would be more sensitive to the respiratory health effects of formaldehyde exposure, although the data informing potential associations between more generalized atopy and respiratory effects in the available human studies were inconsistent. Experimental animal studies and occupational studies indicate that nasal lesions are more severe among individuals with prior nasal damage which could result in heightened susceptibility to the development of nasal cancer following formaldehyde exposure.

In addition, epidemiological and toxicological studies identify female reproductive or developmental toxicity as a hazard of formaldehyde exposure. At this time, it is not clear whether increased time to pregnancy and spontaneous abortion rates seen in occupationally exposed women are due to reproductive system toxicity or to toxicity to the developing fetus. Finally, reproductive toxicity in males has been associated with formaldehyde inhalation, although this association has only been tested in well-conducted studies of rodents at very high formaldehyde concentrations.

1. HAZARD IDENTIFICATION

Potential health hazards from the inhalation of formaldehyde were evaluated across multiple health domains, including sensory irritation; reduced pulmonary function; immune system effects, focusing on allergies and asthma; respiratory tract pathology; nervous system effects; reproductive and developmental toxicity; and cancer. Research results for several cancer sites were evaluated, specifically cancers of the upper respiratory tract ([URT]; i.e., nasopharyngeal cancer, sinonasal cancer, cancers of the oropharynx and hypopharynx, laryngeal cancer) and of the lymphohematopoietic system (i.e., Hodgkin lymphoma, multiple myeloma, myeloid leukemia, lymphatic leukemia). The evidence regarding the potential for formaldehyde exposure to cause other cancer types (i.e., lung, non-Hodgkin lymphoma, brain, bladder, colon, pancreas, prostate, skin) were not systematically evaluated because only a few studies reported analyses for these cancer sites (see Appendix A.5.9 for detail). Multiple health endpoints were evaluated within each of these hazard domains using primary research studies in human populations and experimental animals and in supporting mechanistic studies. The mechanistic studies informing all potential respiratory effects were considered and analyzed together due to the potential interdependencies of the mechanisms involved (see Appendix A.5.6). The majority of studies evaluating the potential toxicity of formaldehyde inhalation exposure have focused on effects at the portal of entry (POE), primarily the URT, with less research available to inform potential systemic, or nonrespiratory, effects. Thus, the synthesis of the evidence for each identified health endpoint is provided in Section 1.2 for potential respiratory system-related effects (including cancer and noncancer endpoints) and in Section 1.3 for potential nonrespiratory health effects.

1.1. SUMMARY OF USES, HUMAN EXPOSURE, AND TOXICOKINETICS

1.1.1. Chemical Properties and Uses of Formaldehyde

Formaldehyde (CASRN 50-00-0) is an aliphatic aldehyde noted for its reactivity and versatility as a chemical intermediate. At room temperature, pure formaldehyde is a colorless gas with a strong, pungent, and irritating odor. Formaldehyde is readily soluble in water, alcohols, ether, and other polar solvents. Due to its chemical properties (see Appendix A.1 for additional details), formaldehyde is widely used in both commercial and industrial settings. Based on EPA's Chemical Data Reporting, the national production volume for formaldehyde was 3.9 billion lb/yr in 2011 and between 1 and 5 billion lbs/yr for 2012 through 2015 (https://chemview.epa.gov/chemview/#).

Products containing formaldehyde are widespread in industry and in the home. Approximately 55% of the consumption of formaldehyde is in the production of industrial resins (NTP, 2010). Formaldehyde is used in plywood adhesives, surface coatings, molding compounds, laminates, phenolic thermosetting, resin curing agents, and other products (WHO, 1989). Formaldehyde is used in smaller quantities for the preservation and embalming of biological specimens. It is also used as a germicide, an insecticide, and a fungicide in some products. Some industries with the greatest potential for exposure to the workforce include health services, business services, printing and publishing, chemical manufacturing, garment production, beauty salons, and furniture manufacturing (IARC, 1995).

1.1.2. Exposure to Formaldehyde

Generally, formaldehyde levels are higher in the indoor environment than in ambient air. Indoor sources of formaldehyde in air include building materials and household products (e.g., volatilization from pressed wood products, carpets, fabrics, insulation, permanent-press clothing, latex paint), as well as household sources of combustion (e.g., gas burners, kerosene heaters, cigarettes) (WHO, 2010). Median indoor air concentrations in some European countries in both commercial and residential buildings ranged from 10 to 50 μg/m^3 (Sarigiannis et al., 2011; Salthammer et al., 2010). Indoor average formaldehyde concentrations reported since 2000 in U.S. and Canadian conventional homes ranged from 12 to 39 μg/m^3 (see Appendix A.1.2). For example, a fairly large study of 398 homes in Los Angeles, CA, Houston, TX, and Elizabeth, NJ, between 1999 and 2001 reported formaldehyde levels of 22 ± 7.1 μg/m^3 (Weisel et al., 2005). Higher levels are found in mobile homes and trailers. In 2018, annual site averages of formaldehyde concentrations outdoors ranged from 0.25 – 11.06 μg/m^3 (0.20 – 9.01 ppb), with an overall annual site average concentration of 2.97 μg/m3 (2.42 ppb) (EPA's Ambient Monitoring Archive for HAPs, which includes data from the Air Quality System database and other data sources at https://www.epa.gov/amtic/amtic-air-toxics-data-ambient-monitoring-archive). A full summary of the information on formaldehyde exposure is included in Appendix A.1.2. Under the National-Scale Air Toxics Assessment (NATA) program, EPA has conducted an emissions inventory for a variety of hazardous air pollutants (HAPs), including formaldehyde. NATA uses the emissions inventory data to model nationwide air concentrations/exposures (https://www.epa.gov/national-air-toxics-assessment). The most recent NATA data are for 2014. The results of the 2014 ambient air concentration modeling for formaldehyde suggest that county mean air levels range from 0.1 to 2.78 μg/m^3 with a national mean of 1.3 μg/m^3 [personal communication to EPA (Palma, 2018)].

1.1.3. Toxicokinetics of Formaldehyde

Formaldehyde is a respiratory irritant for which the human body has developed several detoxification and removal processes, especially at the site(s) of first contact (i.e., nasal passages for inhalation). Thus, this discussion of the toxicokinetics of inhaled formaldehyde at the POE is organized according to the most likely sites of first contact between inhaled formaldehyde and

biological materials, in the context of the known anatomy and potential elimination processes of the respiratory tract tissues. A more comprehensive summary of what is known about the absorption, distribution, metabolism, and excretion of inhaled formaldehyde is provided in Appendix A.2. This section also includes a discussion of published analyses of the potential impact of endogenous levels of formaldehyde produced during normal cellular metabolism on the toxicokinetics of inhaled formaldehyde.

Distribution of Inhaled Formaldehyde

Much of what is known about the uptake and distribution of formaldehyde is based on experimental animal studies, primarily in monkeys and rats. Several of the key considerations for evaluating the toxicokinetics of inhaled formaldehyde at the POE in the rat nose are represented schematically in Figure 1-1. Species differences in the structure of the airways and breathing patterns, as well as the composition of the surface epithelium at various nasal locations, are important considerations when interpreting results in experimental animals and extrapolating observations to humans. While the nasal passages in humans are generally similar to those in other mammalian species, one key difference is that humans and nonhuman primates have nasal passages adapted for both oral and nasal (oronasal) breathing, as opposed to obligate nasal breathing in rodents. A second key difference regards the shape and complexity of the nasal turbinates, with relatively simple shapes in humans, and complex, folded patterns in rodents. In general, these differences provide better protection of the rodent lower respiratory tract against inhaled toxicants than is provided to the human lower respiratory tract (Harkema et al., 2006).

Uptake of formaldehyde (defined as retention within the respiratory tract tissue), based on rough estimates determined from the amount of formaldehyde removed from the air, indicates that the vast majority of formaldehyde is removed from inhaled air by the upper respiratory tract (URT) in monkeys (Casanova et al., 1991; Monticello et al., 1989), dogs (Egle, 1972) and rats (Kimbell et al., 2001b; Chang et al., 1983; Heck et al., 1983; Kerns et al., 1983). Further, dosimetric modeling studies in humans have shown close agreement with observations of exposed rodents, namely, that 90–95% of inhaled formaldehyde is deposited in the URT (Yang et al., 2020; Kimbell et al., 2001b; Overton et al., 2001; Subramaniam et al., 1998). Most recently, Yang et al. (2020) conducted inhalation studies in 120 (70 female and 50 male) healthy human volunteers and measured their absorption of formaldehyde and selected volatile organic compounds. The absorbed formaldehyde $C_{inh} - C_{exh}$ was seen to be linearly related to C_{inh}. The slope of this straight line, which expresses a mean deposition rate for the range of concentrations from 2 ppb to 18 ppb was determined to be 0.97, indicating that most of the inhaled formaldehyde is absorbed, on average, at these low concentrations. This is consistent with prior understanding regarding the extent of formaldehyde absorbed. A detailed description of dosimetry modeling efforts in humans, monkeys, and rats is provided in Appendix B.2.2. As demonstrated in monkeys and rats, and as modeled in humans, a concentration gradient of inhaled formaldehyde follows an anterior-to-posterior distribution, with high concentrations of formaldehyde distributed to squamous, transitional, and respiratory

epithelium, and less uptake by olfactory epithelium. Except under exercise conditions or with exposure to high formaldehyde concentrations, very little formaldehyde reaches more distal sites such as the lung. The possibility that more extensive distribution to the LRT may occur when people are regularly breathing through the mouth or when they have an upper respiratory tract infection has not been directly investigated (see Sections 1.2.2 and 1.2.3 for discussions of the available, indirect evidence). Likewise, no specific toxicokinetic studies focusing on the possibility of inhaled formaldehyde distributing to the developing fetus were identified; however, based on current understanding of its reactivity and distribution, it is unlikely that inhaled formaldehyde would reach the developing fetus.

Asgharian et al. (2012) developed a pharmacokinetic model for transport of formaldehyde and other gases in the human lung, across the air-tissue interface towards arterial blood, that explicitly incorporates information on partition coefficient, metabolism and tissue reactivities (considered as saturable and first-order clearance pathways). This was a substantial improvement over the approach in Overton et al. (2001) that was used for providing formaldehyde dose to the lung in the Conolly et al. (2004) model for extrapolating cancer risk to the human; Overton et al. (2001) did not model the tissue kinetics [and hence the systemic dose] but assumed a constant mass transfer coefficient. There are several noteworthy results from this paper:

- Surface flux rates of formaldehyde appeared to be predictive of local tissue concentrations.
- 97% of the inhaled formaldehyde was absorbed.
- Formaldehyde did not penetrate beyond 60 μm of tissue depth in any breathing scenario, thus predicting that systemic penetration is not likely to take place.
- This model predicted a 25% higher tracheal mass flux of formaldehyde, and correspondingly lesser flux to the deep lung, than Overton et al. (2001). It is important to note that this quantitative result is not relevant to the dose-response modeling in this assessment (see Sections 2.1.1 and 2.2.1). While the extrapolation model by Conolly et al. (2004) uses formaldehyde dose to the human lung as input, this model is not used in this assessment and lung cancer is not identified as a hazard (see Section 1.2.5).

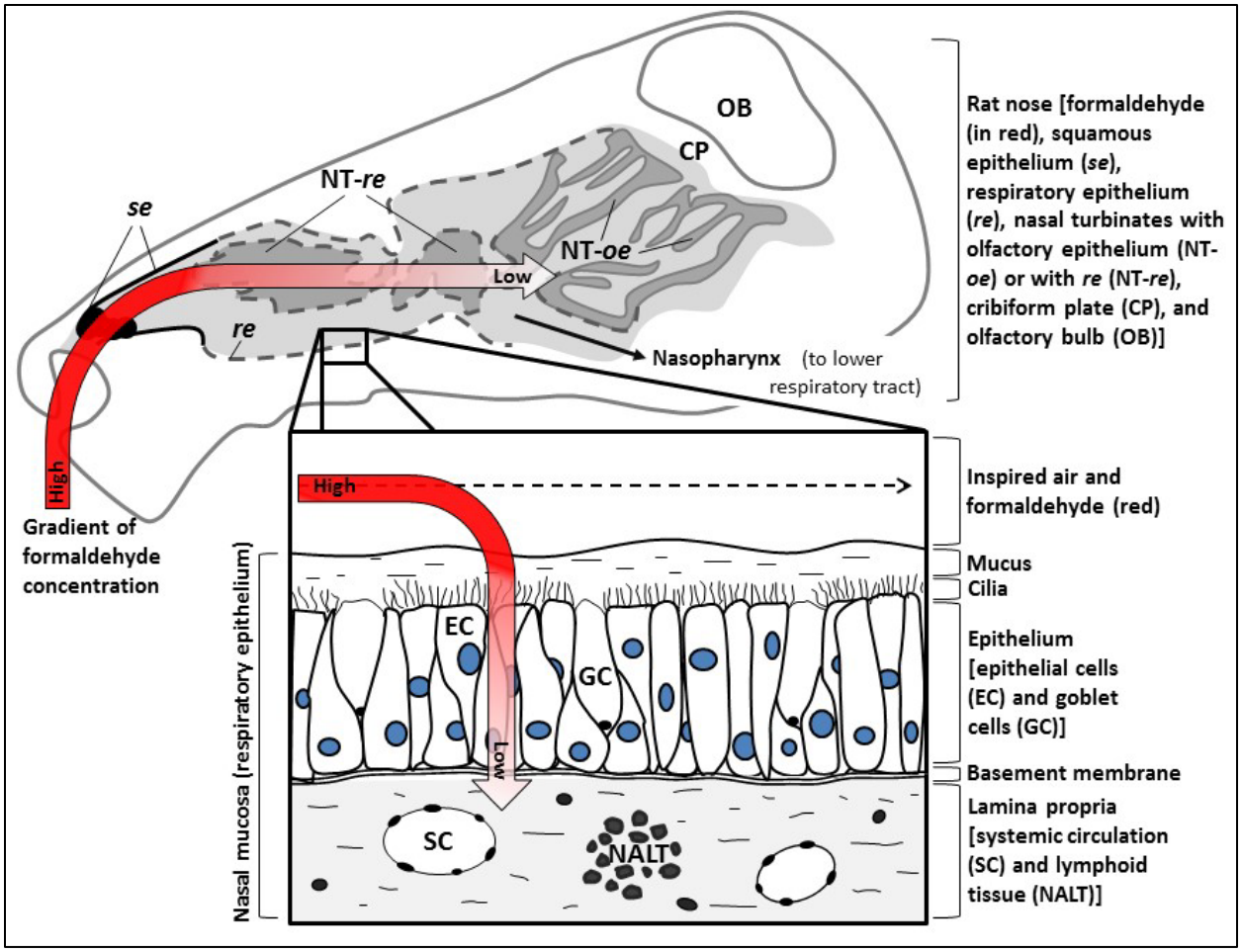


Figure 1-1. Schematic of the rat upper respiratory tract depicting the gradient of formaldehyde concentration formed following inhalation exposure, both from anterior to posterior locations, as well as across the tissue depth.

Modeling based on observations in rodents predicts a similar pattern of distribution in humans. Drawing is based in part on images by NRC (2011) and Harkema et al. (2006). Note: Other components (e.g., naris, transitional epithelium) have been omitted for clarity.

Corley et al. (2015) developed integrated air and tissue transport models for predicting airway region-specific tissue dose of tobacco smoke in the rat and human, upper and lower, respiratory tracts. Their approach coupled CFD models for gas transport in the airways with airway region-specific PBPK models for tissue transport, and included realistic, transient breathing patterns. Although the paper was aimed at tobacco smoke, results were separately provided for the acrolein, formaldehyde and acetaldehyde constituents. Metabolic interactions and reactions were described by clearance through a saturable enzymatic pathway, a first order pathway representing intrinsic tissue reactivity, and a first order binding to DNA to form DPX. Details on regional distribution of metabolic enzymes and local blood perfusion rates were incorporated and the simulations were carried out until breath-by-breath, steady-state kinetics was achieved in all

tissues. These calculations of regional tissue concentrations as a function of tissue depth are a substantial improvement over other dosimetry models that could model only airway wall flux rates of formaldehyde. The primary results relevant to this assessment were as follows:

- Formaldehyde does not penetrate deep into epithelial or subepithelial tissue even in the olfactory region where the penetration was greatest, and therefore does not transport directly to the systemic blood circulation at moderate exposure concentrations.

- As with prior formaldehyde rat dosimetry models, their model predicted greatest initial uptake rates of the gas in the anterior respiratory nasal region. However, the uptake was greater in the anterior dorsal olfactory epithelium when area under the curve (AUC) concentrations were calculated by integrating the concentration profile over time of exposure as well as depth normal to the air-tissue interface under more realistic transient breathing profiles.

- The simulation covered only oral inhalation in the human because the purpose of the research was to investigate uptake from cigarette smoke. In the human, oral and laryngeal tissues received the greatest local tissue dose. Overall formaldehyde absorbed was 97% at 2 and 6 ppm and about 94% at 15 ppm exposure concentrations.

- Formaldehyde surface fluxes did not correlate well with local time dependent tissue concentration AUCs for all nasal tissues in the rat; the AUCs were significantly higher in the olfactory region than would be predicted by surface flux alone. This finding was counter to the conclusion in Asgharian et al as detailed above.

The modeling approach in Corley et al. (2015) could potentially make a tangible difference in extrapolated dose over that computed by solely surface flux-based models in the case of reactive gases that result in adverse effects in the rat olfactory region. Because the findings of formaldehyde induced cancer or non-cancer effects in the URT of the rat are not observed in the olfactory region (see Section 1.2), this modeling approach by Corley et al. (2015) was not applied.

As inhaled formaldehyde enters the URT, it interacts with the mucociliary apparatus, the first line of defense against inhaled materials in the nose. In nasal mucus, most of the formaldehyde is rapidly converted to methanediol (~99.9%) and a minor fraction remains as free formaldehyde (~0.1%) (Bogdanffy et al., 1986). Inhaled formaldehyde induces mucostasis and ciliastasis in the rat that extends from anterior to posterior regions of the nasal cavity depending on the concentration and duration of exposure (Morgan et al., 1986a). Thus, inhalation of higher concentrations can potentially slow clearance mechanisms and increase the proportion of formaldehyde that is available to react with cellular components or that is distributed to epithelium and systemic circulation. Whether mucostasis or ciliastasis is induced with longer exposure duration to low levels of formaldehyde is not known. Methanediol is assumed to be better able to penetrate the tissues while free formaldehyde reacts with macromolecules. It is assumed that the equilibrium is rapid, hence that the methanediol:free formaldehyde equilibrium ratio is maintained (Fox, 1985). Formaldehyde levels are reduced through interactions with components of the mucus and through mucociliary clearance, through reactions with cellular materials at the plasma

membrane of the respiratory epithelium, via interactions with glutathione (GSH) and other macromolecules in the intracellular and extracellular space, through localized metabolism and conjugation reactions, and through reversible interactions with intracellular materials. These processes result in the formation of a gradient of formaldehyde across the tissue space, with the greatest formaldehyde concentration at the apical surface of the mucosa, and the lowest levels of formaldehyde at deeper components of the tissue, such as the nasal-associated lymphoid tissues (NALT) and blood vessels.

Several uncertainties exist regarding the transition of inhaled formaldehyde from the mucociliary layer to the underlying epithelium. Although direct experimental evidence is lacking, the biochemical properties of formaldehyde make it likely that inhaled formaldehyde (in the hydrated or anhydrated form) undergoes passive transport, via simple diffusion, across biological membranes. As a result, higher extracellular formaldehyde levels would be expected to result in increased diffusion into the cell owing to the concentration gradient formed. However, this concentration gradient may be affected by endogenous formaldehyde levels, since in humans, as in other animals, formaldehyde is an essential metabolic intermediate in all cells (Thompson et al., 2009).

Two groups of researchers, Schroeter et al. (2014) and Campbell Jr et al. (2020) developed toxicokinetic models of formaldehyde uptake that incorporate the production of endogenous formaldehyde in nasal tissue. Schroeter et al. (2014) revised the fluid dynamic modeling by Kimbell et al. (2001a; 2001b) to explicitly include tissue pharmacokinetics. The Campbell Jr et al. (2020) model simulates observed data for formaldehyde-induced DNA mono-adducts (N^2-hydroxymethyl-dG) using exogenous and endogenous formaldehyde adduct data published after 2010. This model was based on a modification of Andersen et al. (2010) which simulated formaldehyde-induced DNA-protein cross-links (DPX). Both models, Schroeter et al. (2014) and Campbell Jr et al. (2020), predicted the endogenous formaldehyde to reduce uptake of inhaled formaldehyde from the air phase to the tissue compartment.

In the first model, net desorption of the gas was predicted at exposure concentrations below 1ppb in humans. In the second model developed only for the rat, the model was calibrated with the restriction that formaldehyde absorption in the nose occurs only at exposure concentrations above 0.3 ppm based upon the available experimental DNA adduct data, and the model predicted that the inhalation rate must exceed the tissue clearance rate for formaldehyde to be absorbed by the tissue. The results from both these pioneering projects add to our characterization of uncertainties related to formaldehyde dose-response at low exposures; at sufficiently low levels of exogenous formaldehyde, the contribution of endogenous formaldehyde could become significant. Additionally, when including endogenous formaldehyde in an analysis it is important to incorporate considerations of the large variability in these levels. [The impact of this variability was apparent, for example, from the individual animal data on DNA adducts formed by formaldehyde in Swenberg et al. (2013), kindly made available to EPA by the authors. A number of animals in these data had

very high endogenous levels of these adducts; in these animals, the total (endogenous plus exogenous) internal dose even at a low inhaled exposure concentration of 2 ppm, as measured by the level of DNA adducts, was comparable to the mean total internal dose measured in the group of animals exposed at 10 ppm. At this dose, considerable carcinogenicity was observed in animal bioassays in other studies.] There are also crucial uncertainties in the measurements of free endogenous formaldehyde levels as highlighted by Campbell Jr et al. (2020) and discussed further in Appendix A.2.

EPA evaluated the Schroeter et al. (2014) model and determined that the model predicts *any* external exposure to cause some, albeit very small, increase in formaldehyde tissue concentration over background levels. EPA's evaluation, as detailed in Appendix A.2, pointed to critical uncertainties in model assumptions; therefore, this model was not directly used in EPA calculations. However, it was seen that EPA benchmark concentrations based on formaldehyde as a dose metric in Sections 2.1.1 and 2.2.1 do not change appreciably when results from Schroeter et al. (2014) are used.

Extrapolation of results in Campbell Jr et al. (2020) to humans is not possible because the data and the model are specific to rats. These models and a discussion of studies of formaldehyde distribution in the URT are discussed further in context of the toxicokinetics of inhaled formaldehyde in Appendix A.2.

Metabolism, Binding, and Removal of Inhaled Formaldehyde

In the URT, formaldehyde is predominantly metabolized by glutathione-dependent class III alcohol dehydrogenase (ADH3) and by a minor pathway involving aldehyde dehydrogenase 2 (ALDH2) to formate. Formate can either enter the one-carbon pool leading to protein and nucleic acid synthesis or is further metabolized to CO_2 and eliminated in expired air or excreted in urine unchanged. ADH3 and ALDH2 show region-specific differences in distribution in the respiratory and olfactory mucosa, and higher levels of ADH3 activity have been reported in the cytoplasm of the respiratory and olfactory epithelial cells of rats and in the nuclei of olfactory sensory cells, as compared to other regions of the nasal mucosa (Keller et al., 1990). The presence of areas of high enzyme activity highlights a significant barrier to the penetration of inhaled formaldehyde beyond the respiratory epithelium.

Formaldehyde can interact with macromolecules either by noncovalently binding to glutathione (GSH), tetrahydrofolate (THF), or albumin in nasal mucus or by covalently forming DNA-protein crosslinks (DPXs), DNA-DNA crosslinks (DDCs), hydroxymethyl-DNA (hm-DNA) adducts (see Appendix A.2), or protein adducts, such as N^6-formyllysine (Edrissi et al., 2013b; Edrissi et al., 2013a). In rats and monkeys, a concentration-dependent increase in DPX formation is observed in nasal passages. Metabolic incorporation studies with ^{14}C-formaldehyde have shown both covalent binding and metabolic incorporation in nasal tissues (Casanova and Heck, 1987; Casanova-Schmitz et al., 1984b). Inhaled formaldehyde induces a concentration-dependent

increase in N^2-hydroxymethyl deoxyguanosine (N^2-hm-dG) adducts, another form of formaldehyde-induced covalent DNA modification, in the nasal passages of monkeys and rats. Recently, analytical methods have been developed that can distinguish between N^2-hm-dG adducts from exogenous (inhaled) formaldehyde and N^2-hm-dG adducts from endogenous formaldehyde (Lu et al., 2012; Lu et al., 2011; Moeller et al., 2011; Lu et al., 2010a). For example, an increase in exogenous formaldehyde adducts has been observed in rat nasal tissue at 0.7–15 ppm (0.86–18.45 mg/m^3) formaldehyde without any significant increases in endogenous adducts following a single 6-hour exposure (Lu et al., 2011) or at 10 ppm (12.3 mg/m^3) after exposure to formaldehyde for 1 or 5 days (6 hrs/day) (Lu et al., 2010a). However, in a more recent study with a lower detection limit for adducts and testing lower formaldehyde exposure levels, Leng et al. (2019) did not observe an increase in exogenous hmDNA adducts or DPXs, including in nasal and respiratory tissues as well as at systemic sites (e.g., bone marrow), at formaldehyde levels of 0, 1, 30, or 300 ppb (up to 0.37 mg/m^3) after exposure for 28 days. The lack of detectable exogenous adducts in the URT at 0.3 ppm (0.37 mg/m^3) helps to inform the evolving understanding of formaldehyde-induced DPX at lower concentrations, which would benefit from additional study. DNA monoadducts (Yu et al., 2015a; Lu et al., 2011; Moeller et al., 2011; Lu et al., 2010a) and DPXs (Lai et al., 2016) derived from exogenous formaldehyde were detectable in nasal tissues, but not in distal tissues (including the bone marrow), of experimental animals exposed by inhalation, supporting that exogenous formaldehyde is not systemically distributed. Also, toxicokinetic studies showed that labeled carbon from inhaled formaldehyde measured in bone marrow of rats was the result of metabolic incorporation from the 1-Carbon (1C) pool, not covalent binding, further supporting the lack of transport of formaldehyde or metabolites of formaldehyde to the distal tissues (Casanova-Schmitz et al., 1984b). Finally, inhalation exposure to formaldehyde does not appear to alter blood formaldehyde levels (approximately 0.1 mM across different species), suggesting that inhaled formaldehyde is not significantly absorbed into blood (Kleinnijenhuis et al., 2013; Casanova et al., 1988; Heck et al., 1985).

The toxicokinetics of formaldehyde may be influenced by certain formaldehyde-related effects, such as mucociliary clearance (Morgan et al., 1983), reflex bradypnea (rodents only) and corresponding reductions in minute volume (Chang and Barrow, 1984; Chang et al., 1981), and dynamic changes in tissue structure (Kamata et al., 1997), all of which have the potential to modulate formaldehyde uptake and clearance. For example, during repeated inhalation exposure to formaldehyde, mice but not rats lower their minute volume thereby restricting the intake of the gas (Chang and Barrow, 1984; Chang et al., 1981), which may impact dosimetric adjustment if the dose-response results from these studies are extrapolated to humans. Exposure to formaldehyde can also cause a perturbation of ADH3-dependent pathways involved in cell proliferation (Nilsson et al., 2004; Hedberg et al., 2000), protein modification and cell signaling (Que et al., 2005), S-nitrosoglutathione (GSNO) metabolism, and deregulation of nitric oxide-dependent pathways (Thompson et al., 2010). In rats exposed by inhalation to high concentrations of formaldehyde, a

rapid GSH depletion can occur, which may result in more free formaldehyde available for covalent binding and a decrease in metabolic incorporation (Casanova and Heck, 1987).

Assumptions based on what is known about the distribution and metabolism of formaldehyde and its detoxification products allow inferences to be made about how inhaled formaldehyde is eliminated as CO_2 in expired air or in various forms in urine. Approximately one-third of inhaled formaldehyde is estimated to be removed in the URT mucus (Schlosser, 1999). It is expected that the majority of this formaldehyde would be removed from the URT via esophageal clearance and excreted in urine in various forms. A large amount of inhaled formaldehyde penetrating the mucociliary layer of the URT is metabolized in the nasal cavity, giving rise to formate, which can be excreted in urine. Part of this formate may also be further oxidized and eliminated in the exhaled breath as CO_2. Some formaldehyde is incorporated into the 1C pool and repurposed for protein and nucleic acid synthesis.

1.2. SYNTHESIS OF EVIDENCE FOR EFFECTS ON THE RESPIRATORY SYSTEM

Research on several noncancer respiratory health effects was synthesized for the following health domains: sensory irritation (see Section 1.2.1), pulmonary function (see Section 1.2.2), immune system effects focusing on allergies and asthma (see Section 1.2.3), and respiratory tract pathology (see Section 1.2.4). Synthesis of the evidence relevant to potential carcinogenicity at respiratory sites focused on cancers in the upper respiratory tract ([URT]; see Section 1.2.5), as less has been reported concerning cancer associations at other respiratory sites (see Appendix A.5.9 for details).

As previously described, inhaled formaldehyde is highly reactive at the portal of entry (POE), that is, nose and upper airways, which results in alterations to the local tissues that could give rise to respiratory system health effects. The potential noncancer effects, in particular, involve many of the same biological processes; thus, a high degree of overlap across the mechanistic changes underlying these responses is expected. Similarly, because the potential respiratory health effects are interrelated, effects on one outcome may affect others. Accordingly, an overarching evaluation of the mechanistic information pertinent to any or all potential noncancer respiratory system health effects (some of which is relevant to carcinogenicity) was performed (see Appendix A.5.6). The primary mechanistic conclusions drawn from this overarching evaluation are summarized in the MOA analyses in Sections 1.2.1-1.2.4. Section 1.2.3 includes a discussion expanded to include mechanistic changes in nonrespiratory tissues that might relate to respiratory system health effects, although these findings are also relevant to the nonrespiratory (systemic) health effects reviewed in Section 1.3.

Finally, an essential component of the analysis of potential carcinogenicity at respiratory sites involves evaluating whether inhaled formaldehyde causes genotoxicity or mutagenicity.

Because abundant information exists on this topic, the data are comprehensively described in Appendix A.4, with the primary conclusions summarized in Section 1.2.5. Some of the conclusions from the genotoxicity evidence analyzed in Appendix A.4 are also relevant to interpretations regarding potential cancers at nonrespiratory (distal) sites in Section 1.3.3).

1.2.1. Sensory Irritation

This section describes research on formaldehyde inhalation and sensory irritation in experimental and observational studies in humans. Although not formally evaluated for this review, formaldehyde inhalation-induced sensory irritation in animals is a well-established phenomenon (Nielsen et al., 1999; Barrow et al., 1983; Chang et al., 1981; Kane and Alarie, 1977).

Formaldehyde has been found to be a sensory irritant of the eyes and respiratory tract in several epidemiological studies causing mild to severe symptoms, including itching, stinging, and watering eyes; sneezing and rhinitis; sore throat; coughing; and bronchial constriction. Symptoms of eye irritation were reported at lower concentrations than symptoms of the nose or throat. Many epidemiology studies evaluated symptoms of irritation among residents exposed to formaldehyde in their homes, workers involved in the production or use of formaldehyde products, and anatomy students participating in the dissection of formaldehyde-preserved cadavers. In addition, data from several controlled human exposure studies are available that evaluated acute responses among healthy or asthmatic volunteers during rest or exercise (see Table 1-1). The controlled human exposure studies showed that the irritant response to formaldehyde is an immediate phenomenon apparent at concentrations of 0.1 mg/m^3, the lowest concentration evaluated, and higher. The irritation resolves when exposure is removed (Krakowiak et al., 1998; Sauder et al., 1986; Andersen and Molhave, 1983; Andersen, 1979). Concentration was related to both prevalence and severity of symptoms. In addition, a large variability in sensitivity to the irritant properties of formaldehyde at specific concentrations was observed (Mueller et al., 2013; Berglund et al., 2012). Because of the wide variability in responses, it has been difficult for experimental studies to characterize the exposure-response relationship in the lower range of concentrations experienced by the general population. Sensory irritation is understood to occur as a result of direct interactions of formaldehyde with cellular macromolecules in the nasal mucosa leading directly or indirectly to stimulation of trigeminal nerve endings located in the respiratory epithelium.

Studies in humans provide *robust* evidence of sensory irritation based on the controlled human exposure studies and observational epidemiology studies, and this effect also is well described and accepted across a range of experimental animal species (*robust*). Further, there is an established MOA for this well-studied health effect, based primarily on mechanistic evidence in experimental animals, and this MOA is interpreted to be operant in humans. Overall, a judgment was drawn that the **evidence demonstrates** that inhalation of formaldehyde causes sensory irritation in humans, given the appropriate exposure circumstances. The primary support for this conclusion is based on residential studies with mean formaldehyde concentrations >0.05 mg/m^3

(range 0.01 to approximately 1.0 mg/m^3) and controlled human exposure studies testing responses to concentrations 0.1 mg/m^3 and above.

Literature Search and Screening Strategy

The identification of relevant epidemiology studies (i.e., both observational and controlled exposure studies) on sensory irritation included systematic literature searches in PubMed and Web of Science through September 2016 (see Appendix A.5.2 for search details), and a systematic evidence map updating the literature through 2021 (see Appendix F). Based on the extensive database of research studies on relevant apical endpoints in humans after formaldehyde exposure, systematic searches for studies of sensory irritation in experimental animals were not conducted. However, mechanistic data informing this health effect were identified and evaluated as part of the overarching review of mechanistic data relevant to potential respiratory health effects (see Appendix A.5.6 for details). Epidemiological studies describing reports of sensory irritation based on questionnaire responses or objective measures, such as eye blink frequency or conjunctival redness, were included. Articles reporting on case reports, illness investigations, and surveillance studies were not included because the studies were not designed to derive an effect estimate of the association between measures of irritation and formaldehyde exposure. The bibliographic databases, search terms, and specific strategies used to search them are provided in Appendix A.5.2 and A.5.6, as are the specific PECO criteria. Literature flow diagrams summarize the results of the sorting process using these criteria and indicate the number of studies that were selected for consideration in the assessment through 2016 (see Appendix F for the identification of newer studies through 2021). The relevant health effect studies in humans, as well as the mechanistic data informative to sensory irritation, were evaluated to ascertain the level of confidence in the study results for hazard identification (see Appendix A.5.2 and A.5.6).

Methodological issues considered in evaluation of studies

This review focused on the results of controlled human exposure studies and observational studies of exposure to residential populations. The relevant period for the assessment of irritant responses was considered to be concurrent with the time period of the exposure assessment because the symptoms associated with irritation occur immediately (Krakowiak et al., 1998; Andersen and Molhave, 1983; Andersen, 1979). The controlled human exposure studies were able to evaluate symptoms in a controlled environment; therefore, the exposure-response relationship was more precise, and potential confounders were of less concern. However, the study groups were selected for age (younger adults) and were healthy enough to conform to study protocols. These studies evaluated formaldehyde concentrations above 0.1 mg/m^3, while exposure levels in the residential studies ranged from 0.01 (the limit of detection [LOD] in the available studies) to approximately 1 mg/m^3, with a large proportion of residences having levels less than 0.1 mg/m^3. The studies of residential formaldehyde exposure included a wider range of ages (adults and children) and potentially susceptible individuals, some of whom had existing respiratory issues and

other health conditions. Evaluations of individual mechanistic studies emphasized consideration of issues related to exposure conduct, as previously described (see Preface and Appendix A.5.6).

Sensory Irritation Studies in Humans

The following discussion is organized by exposure setting, starting first with evidence from controlled human exposure studies, followed by studies of residential exposure, and then laboratory and occupational studies. Evidence tables for each exposure setting (see Tables 1-1 and 1-2) are organized by level of confidence in the study's results and then by publication year.

Controlled human exposure studies (short-term exposures)

Controlled human exposure studies testing exposures from less than 1 hour to 5 hours reported slight-to-moderate irritation of the eyes, nose, and throat detected by subjects at formaldehyde concentrations beginning at around 0.3–0.4 mg/m^3 (see Table 1-1), although the data do not clearly identify the concentration at which symptoms of irritation begin. Eye irritation was reported at lower concentrations than nasal or throat irritation, and symptoms increased in frequency and severity with exposure level.

Both prevalence and severity of symptoms were associated with increasing concentration between 0.12 and 2.5 mg/m^3 (Mueller et al., 2013; Berglund et al., 2012; Lang et al., 2008; Kulle et al., 1987; Andersen and Molhave, 1983; Bender et al., 1983). Overall, the prevalence of eye irritation increased from <10 to >80% across several studies with formaldehyde concentrations of 0–4 mg/m^3 (see Figure 1-2). The prevalence of mild-to-moderate irritation varied among individuals at specific concentration levels. For example, at concentrations above 2 mg/m^3, prevalence ranged from 53 to 100% (Kulle et al., 1987; Schachter et al., 1987; Witek et al., 1987; Schachter et al., 1986a; Andersen and Molhave, 1983). Possible reasons for the variation may include differences in exposure duration or differences in the characteristics of the volunteers (e.g., interindividual variation due to smoking status, prior exposure history, or respiratory health). Participants in all of the studies were 18 to 35 years old. Two studies by one research group reported a much lower symptom prevalence (27%) among healthy and asthmatic subjects exposed to 3.7 mg/m^3 formaldehyde for 60 minutes (Green et al., 1987). This response is not directly comparable to the other studies, however, because the authors only presented irritation prevalence for more severe symptoms (moderate severity or greater).

Only a few studies evaluated whether symptom prevalence or severity changed over the course of the exposure period. One research group recruited university volunteers and compared their responses to controlled formaldehyde exposure against responses in hospital laboratory workers with routine exposure to formaldehyde; responses were similar between the two groups during the 40-minute period at 2 ppm (Schachter et al., 1987; Schachter et al., 1986a). The study of the laboratory workers was concluded to have *medium* confidence because some study aspects may have reduced the study's sensitivity, including that the previous formaldehyde exposure was not characterized, and other characteristics, such as being a smoker, were not controlled. The

university volunteers reported the highest symptom scores when subjects first entered the exposure chamber with declines over the 40-minute exposure period. Andersen and Molhave (1983) also found that eye irritation was experienced earlier in the exposure period among subjects exposed to higher concentrations (1 and 2 mg/m^3) and that symptom severity increased and then plateaued or decreased after 3 hours. However, the initiation of symptoms was delayed at lower concentrations (0.3 and 0.5 mg/m^3), and symptom severity continued to increase over the rest of the exposure period. Other studies involving exposures from a few minutes to 1 hour also reported irritation responses that slightly decreased or plateaued (Green et al., 1987; Bender et al., 1983). Note that Bender et al. (1983) used a protocol involving exposure to the eyes only, which may involve a different type of response compared to inhalation. Therefore, these few studies suggest that some acclimatization may occur over a few hours at higher concentrations; however, this phenomenon may not be apparent when concentrations are lower (<1 mg/m^3). Further, based on the few studies available, individuals with long-term occupational exposure to formaldehyde do not appear to respond differently than individuals with no previous known exposure.

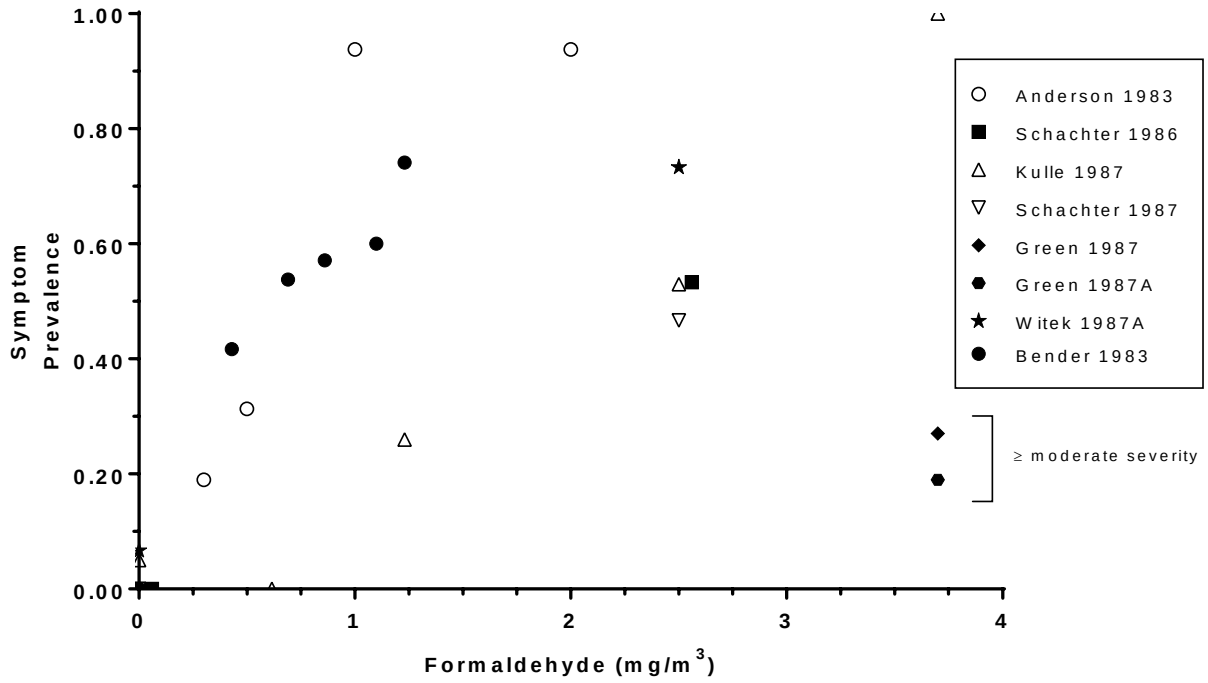


Figure 1-2. Prevalence of eye irritation in controlled human exposure studies of formaldehyde.

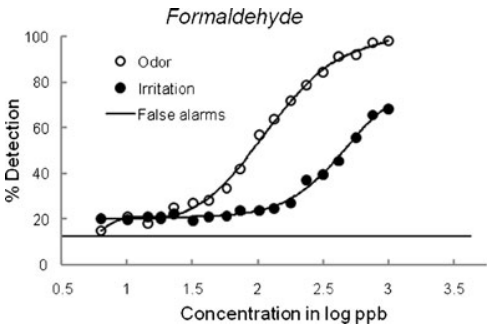
Studies that randomly assigned the order of exposure levels are graphed in relation to formaldehyde concentration. Three studies limited by reporting deficiencies regarding randomization (Bender et al., 1983) or blinding (Kulle et al., 1987; Andersen and Molhave, 1983) are graphed with open symbols. The results from Schachter et al. (1987) also are graphed in open symbols because subjects were also exposed to formaldehyde through their occupations or cigarette smoke. Two studies reported increases in symptom intensity or scores for eye irritation but did not report prevalence and are not graphed (Mueller

et al., 2013; Lang et al., 2008; Yang et al., 2001). Note that the figure does not convey differences in severity scores, which also increased with formaldehyde level.

In addition to subjective reports, some investigators evaluated objective measures, including eye blink frequency, conjunctival redness, and nasal flow and resistance (Mueller et al., 2013; Lang et al., 2008; Andersen and Molhave, 1983; Andersen, 1979). Eye blink frequency was increased at exposure levels above those where subjective symptoms were reported. For example, two studies evaluated responses to a combination of concentration peaks superimposed on a constant formaldehyde exposure (Mueller et al., 2013; Lang et al., 2008). Lang et al. (2008) found that increased eye blink frequency and conjunctival redness occurred at 0.62–1.2 mg/m^3 among subjects who also reported symptoms of eye irritation at 0.37 mg/m^3. Mueller et al. (2013) found no exposure-related effect on blinking frequency and conjunctival redness, although total symptom scores increased beginning at 0.37 mg/m^3 with peaks of 0.7 mg/m^3 in a group with nasal hypersensitivity. Studies using objective measures of nasal irritation reported variable results including no change in nasal flow and resistance between 0.19 and 0.62 mg/m^3 (Lang et al., 2008), a decrease in nasal mucus flow at a concentration of 0.37 mg/m^3 and higher (Andersen and Molhave, 1983), and an increase in nasal flow rate among hypersensitive participants at 0.86 mg/m^3 (Mueller et al., 2013). Subjects exhibited a large degree of individual variability in sensitivity for both objective and subjective responses (Mueller et al., 2013; Berglund et al., 2012; Lang et al., 2008).

Table 1-1. Summary of controlled human exposure studies of formaldehyde and human sensory irritation

Study and design	Results
Mueller et al. (2013) **Design:** *N* = 41, age 32 years, nonsmoking, healthy male volunteers; categorized into hyposensitive and hypersensitive based on CO_2 sensitivity measurements in nasal mucosa (cutpoint median 80.3 mm on visual analogue scale [VAS]). Exposure order randomly assigned; repeated measures cross-over design; blinding not described. Five 4-hour exposure conditions, 1 per day, over 5 days. Four 15-minute cycle exercise segments during exposure period. **Outcome:** Irritation assessed by conjunctival redness (digital photographs), blinking frequency (blinks counted in 60-second segments from 5-minute video, two counters blind to concentration), tear film break-up time (time to first close of eyelid while staring at mark on wall), nasal flow and resistance (rhinomanometry), and validated symptom questionnaire (SPES German translation) measured before and 15 minutes before end of exposure. Severity rated using VAS with 100-mm scale. **Exposure:** 4 hours in groups of 2. Clean air, 0.3 + 4 peaks of 0.6 ppm, 0.4 + 4 peaks of 0.8 ppm, 0.5 ppm and 0.7 ppm (0.0, 0.37 + 0.74, 0.49 + 0.98, 0.62, and 0.86 mg/m^3).[a] Formaldehyde generation via thermal depolymerization of paraformaldehyde, dynamic chamber, analytical concentrations reported. Confidence: ***High***	Results presented in graphs of difference between pre- and end of test values. Large variability in scores between subjects for all measures. Blinking frequency and conjunctival redness—no exposure-related effect, tear film break-up time—increased in 0.4/0.8 ppm and 0.5 ppm ($p < 0.05$), nasal flow rate increased in hypersensitive 0.7 ppm ($p < 0.01$); total symptom score increased in hypersensitive at 0.3/0.6 ppm ($p < 0.001$) and 0.4/0.8 ppm ($p < 0.01$), perception of impure air increased in hypersensitive at all exposure levels (including clean air, 0.01 ppm). Control for "negative affectivity" did not alter associations. Combined eye symptom score reported to be increased with higher scores among hypersensitives at all exposures except 0.7 ppm (0.86 mg/m^3). Changes in scores were not statistically significant and no exposure-response was observed (results in online supplemental resource 10 in Mueller et al. (Mueller et al., 2013)). Severity measured using VAS ranged between −0.2 and 2.1 mm). **SPES Symptom Score (SD)—Eye Irritation** mg/m^3 Average/peak | Hypo-sensitive[a] | Hyper-sensitive[a] 0 | −0.17 (2.02) | 1.96 (7.59) 0.37/0.74 | 0.23 (2.65) | 2.13 (4.71) 0.49/0.98 | 0.62 (5.71) | 1.43 (5.31) 0.62 | −0.09 (2.14) | 1.24 (2.84) 0.86 | 0.94 (4.56) | 0.52 (4.14) [a]Sensitivity categorized as above or below median for nasal sensitivity to CO_2 irritation.

Study and design	Results
Berglund et al. (2012) **Design:** *N* = 31 healthy volunteers, 52% male, age 24.5 years, nonsmokers. Exposure concentrations randomly presented; blinding not described. **Outcome:** Participants evaluated detection of odor and nasal irritation for each "sniff" with forced-choice responses (yes-yes, yes-no, no-yes and no-no). Goal was to identify the concentration at which a participant detected nasal irritation in all (100%) of the 12 presentations. **Exposure:** Series of 18 concentrations; 6.36−1,000 ppb (0.0078−1.23 mg/m^3).[a] 12 presentations at each concentration plus 72 blanks; 1 sniff in exposure hood (<3 seconds) followed by clean air, 3 sniffs per minute; 36 exposures per each of eight 12-minute sessions over 4 hours. Formaldehyde generation via thermal depolymerization of paraformaldehyde, dynamic chamber, analytical concentrations reported. **Confidence:** *High*	None of the 31 participants detected nasal irritation in 100% of 12 presentations at any formaldehyde concentration. 13% false alarms (reports of detection of odor or irritation for blanks). Large variation in individual distributions of percentage detections for nasal irritation vs. log concentration. Authors could not calculate threshold distributions for irritation. See pooled data below (see Figure 5 in paper). 

Study and design	Results
Lang et al. (2008) **Design:** *N* = 21, age 19–39 years, nonsmoking, healthy volunteers. Exposure order randomly assigned; double blinded. Ten 4-hour exposure conditions, 1 per day, over 10 days. Three 15-minute cycle exercise segments during exposure period. **Outcome:** Irritation assessed by conjunctival redness (digital slit lamp photographs, two scorers), blinking frequency (90-second count from 6-minute video), nasal flow and resistance (rhinomanometry), and symptom questionnaire (SPES German translation) measured before, three times during, and after exposure, and after last exposure day. Rated on 5 levels (0–5). **Exposure:** 4 hours in groups of 4. Clean air, 0.15, 0.3, and 0.5 ppm (0.0, 0.19, 0.37, and 0.62 mg/m^3); additional 0.3 and 0.5 ppm with peaks up to 1.0 ppm (1.23 mg/m^3).[a] Additional 0.0, 0.3, and 0.5 ppm with ethyl acetate (EA) introduced as a "mask" for formaldehyde odor. Formaldehyde generation via thermal depolymerization of paraformaldehyde, dynamic chamber, analytical concentrations not reported. **Confidence:** *High*	Blinking frequency, conjunctival redness significantly increased at 0.5 ppm with peaks of 1.0 ppm. Symptoms: Maximum scores at 195 minutes; eye and olfactory symptom scores were elevated at 0.3 ppm ($p < 0.05$). With control for "negative affectivity," eye irritation symptoms significantly associated with 0.5 ppm with EA or 0.5 ppm with peaks. Severity: Average severity scores were less than 2 ("somewhat"). Nasal irritation: no significant increase in objective measures; symptoms significantly increased at 0.5 ppm and 0.3 ppm with coexposure to EA (also an irritant; $p < 0.05$).
Green et al. (1989) **Design:** *N* = 24, 10 male, mean age 24 ± 0.7 yr, nonsmoking, no history of allergies or hay fever. Random assignment to order of exposure; double blinded. Four 15-min exercise segments in the 2-hr exposure period. **Outcome:** Symptoms questionnaire (presence and severity, scored none = 0 to severe = 5) before, and four times during exposure. Testing pre- and during exposure period (approximate 15-min intervals). **Exposure:** 2 h, four exposures over 4 weeks, clean air, 3 ppm (3.69 mg/m^3)[a], 0.5 mg/m^3 activated carbon aerosol (ACA), HCHO + ACA. Formaldehyde generation via thermal depolymerization of paraformaldehyde, dynamic chamber, analytical concentrations reported. **Confidence:** *High*	Symptom scores presented graphically for 80-min time point. Formaldehyde treatment elevated symptom scores ($p < 0.05$) at all time points for eye, nasal and throat irritation, odor, chest discomfort. No effect modification by ACA exposure. Average eye irritation scores <1.5 at 80 minutes; similar response at all measurements (20, 50, 80, and 110 minutes). No separate effect on cough by formaldehyde, but combined formaldehyde and ACA exposure resulted in elevated score for cough at 20 minutes ($p < 0.02$) and 80 minutes ($p < 0.05$).

<table>
<tr><th>Study and design</th><th>Results</th></tr>
<tr><td>Green et al. (1987)

Design: n = 22, mean age 26.9 ± 3.6 years, nonsmoking, no history of allergies or hay fever. Random assignment to order of exposure; single blinded. Two 15-min exercise segments in the 60-min exposure period.

Outcome: Symptoms questionnaire (presence and severity, scored none = 0 to severe = 5) before, and four times during exposure. Testing pre- and during exposure period (approximate 15-min intervals).

Exposure: 60 minute, clean air and 3 ppm (3.69 mg/m^3).[a]

Formaldehyde generation via thermal depolymerization of paraformaldehyde, dynamic chamber, analytical concentrations reported.

Confidence: High</td><td>Mean symptom scores associated with 3-ppm exposure at all time points, difference from clean air statistically significant for odor, nose or throat irritation, and eye irritation. Individual severity scores ranged from none to severe.

Prevalence of scores ≥ moderate severity at 3 ppm (p < 0.01)
<table><tr><th></th><th>Healthy (%)</th><th>Asthmatic (%)</th></tr><tr><td>Odor</td><td>23</td><td>31</td></tr><tr><td>Nose/throat</td><td>32</td><td>31</td></tr><tr><td>Eye</td><td>27</td><td>19</td></tr></table></td></tr>
<tr><td>Kulle (1993); Kulle et al. (1987)

Design: Group 1 (N = 10), Group 2 (N = 9), nonsmoking healthy, age 26.3 ± 4.7 years, 53% male. Exposure order randomly assigned; Blinding not reported. 3-hour exposures each week, at same time on five occasions. 8-minute exercise segment every half hour during 2-ppm exposure.

Outcome: Symptom questionnaires before and after each exposure, and 24-hours postexposure. Severity was scored none, mild, moderate, severe (0−5).

Exposure: 3 hour, Group 1: 0.0, 0.5, 1.0, or 2.0 ppm (0.0, 0.62, 1.23, 2.46 mg/m^3)[a] at rest, and an additional 2.0 ppm with exercise; Group 2: 0.0, 1.0, or 3.0 ppm (0.0, 1.23, or 3.69 mg/m^3) at rest, and an additional 2.0 ppm with exercise.

Formaldehyde generation via thermal depolymerization of paraformaldehyde, dynamic chamber, analytical concentrations reported.

Confidence: Medium

Deficiencies in reporting detail regarding blinding and quantitative results</td><td>Mean difference in scores before and after exposure period: Linear dose-response (N = 19) for odor and eye irritation, 0, 1, and 2 ppm (p < 0.0001); and nose/throat (Group 2, p = 0.054). Log-linear dose-response for odor and eye irritation, 0, 0.5, 1.0 and 2.0 ppm (Group 1, p < 0.05). Test for nonlinearity not significant. Data presented graphically, prevalence reported in Kulle et al. (1993), Table 3 in the paper.

<table><tr><th>Concentration</th><th>#</th><th>Prevalence (mild/moderate)</th></tr><tr><td>0</td><td>19</td><td>0.05</td></tr><tr><td>0.62</td><td>10</td><td>0</td></tr><tr><td>1.23</td><td>19</td><td>0.26</td></tr><tr><td>2.46</td><td>19</td><td>0.53</td></tr><tr><td>3.69</td><td>9</td><td>1.0</td></tr></table></td></tr>
</table>

<table>
<tr><th>Study and design</th><th>Results</th></tr>
<tr><td>Witek et al. (1987); Witek et al. (1986)

Design: n = 15 with asthma, ages 18–35 years, nonsmoking. Random assignment to order of exposure; double blinded. Two protocols (at rest and during exercise).

Outcome: Symptoms questionnaire, severity scores (0–4). Testing at beginning and at 30 min during and 4- to 8-hr and 24-hr postexposure.

Exposure: 40 minutes, 0 and 2 ppm (2.46 mg/m^3).[a]

Formaldehyde generation via thermal depolymerization of paraformaldehyde over boiling 2-propanol, dynamic chamber, analytical concentrations reported.

Confidence: Medium</td><td>Symptoms during exercise not different from rest.

Prevalence (%) and severity scores during rest
<table><tr><th></th><th>0 ppm</th><th></th><th>2 ppm</th><th></th></tr><tr><th></th><th># (%)</th><th>S[a]</th><th># (%)</th><th>S[a]</th></tr><tr><td>Odor</td><td>5 (33.3)</td><td>7</td><td>15 (100)</td><td>30</td></tr><tr><td>Eye</td><td>1 (7)</td><td>2</td><td>11 (73.3)</td><td>16</td></tr><tr><td>Nose</td><td>3 (20)</td><td>4</td><td>7 (46.7)</td><td>10</td></tr><tr><td>Throat</td><td>4 (26.7)</td><td>4</td><td>5 (33.3)</td><td>6</td></tr></table>[a]Total severity score across all subjects

Symptoms reported to have disappeared postexposure.</td></tr>
<tr><td>Schachter et al. (1986a); Witek et al. (1986)

Design: N = 15 healthy, age 18–35 yr, nonsmokers. Random assignment to order of exposure, double blinded. Two protocols (at rest and during exercise), separated by 4 days.

Outcome: Symptoms questionnaire at beginning and at 30 min during exposure and at 8 and 24 hr after exposure, severity scores (0–4).

Exposure: 40 min; clean air and 2 ppm (2.46 mg/m^3).[a]

Formaldehyde generation via thermal depolymerization of paraformaldehyde over boiling 2-propanol, dynamic chamber, analytical concentrations reported.

Confidence: Medium

Co-exposure to 2-propanol</td><td>Symptoms during exercise not different from rest; highest symptom scores at beginning of exposure with decrease by 30 minutes.

Prevalence (%) and severity scores during rest
<table><tr><th></th><th>0 ppm</th><th></th><th>2 ppm</th><th></th></tr><tr><th></th><th># (%)</th><th>S[a]</th><th># (%)</th><th>S[a]</th></tr><tr><td>Odor</td><td>7 (46.7)</td><td>7</td><td>12 (80.0)</td><td>18</td></tr><tr><td>Eye</td><td>0</td><td>0</td><td>8 (53.3)</td><td>12</td></tr><tr><td>Nose</td><td>4 (26.7)</td><td>4</td><td>6 (40.0)</td><td>7</td></tr><tr><td>Throat</td><td>2 (13.3)</td><td>2</td><td>4 (26.7)</td><td>4</td></tr></table>[a]Total severity score across all subjects

Eye Irritation Severity by Exposure, n (%)
<table><tr><th></th><th>0 ppm</th><th>2 ppm</th></tr><tr><td>Mild</td><td>0</td><td>5 (33.3)</td></tr><tr><td>Moderate</td><td>0</td><td>2 (13.3)</td></tr><tr><td>Severe</td><td>0</td><td>1 (7)</td></tr></table></td></tr>
</table>

<table>
<tr><th>Study and design</th><th>Results</th></tr>
<tr><td>Andersen and Molhave (1983); Andersen (1979)

Design: N = 16 healthy students, age 30–33, 68.8 % male, 31.2% smokers, groups of four over 4 days. Exposure order determined by Latin square design, blinding not described. Testing before (during 2-hour clean air) and two times during exposure.

Outcome: Subjects used a pointer to express the degree of airway irritation (scale 1 to 100) while being exposed.

Exposure: 5 hours; 0.3, 0.5, 1.0 and 2.0 mg/m^3 (0.24, 0.40, 0.81 and 1.61 ppm respectively).

Formaldehyde generation via thermal depolymerization of paraformaldehyde, dynamic chamber, analytical concentrations reported.

Confidence: Medium

Variation exposure concentrations, reporting deficiencies regarding blinding, potential confounding by smoking</td><td>Irritation prevalence with clean air was not reported. At end of exposure to 0.3, 0.5, 1.0, and 2.0 mg/m^3 of formaldehyde; 3, 5, 15 and 15 subjects respectively of the 16 who participated reported conjunctival irritation, dryness in the nose and throat. Smokers were found to be less sensitive than nonsmokers.

Severity: Maximum individual scores ranged from 30 (slight discomfort) at 0.3 mg/m^3 to 50 (discomfort) at 3 mg/m^3. After the first 2 hours, discomfort increased during the exposure period at 0.3 and 0.5 mg/m^3. In two highest concentrations, discomfort reported during first hour, increased to hour 3, then plateaued or decreased.

Eye blinking increased at 2.0 mg/m^3 (1.70 ppm).
Subjects reported no symptoms the next morning.</td></tr>
<tr><td>Schachter et al. (1987)

Design: N = 15 healthy hospital laboratory workers routinely exposed to formaldehyde as part of their job, age 32 ± 11.3 years, 33.3% male, N = 2 smokers. Random assignment to order of exposure, double blinded. Two dose levels, four exposure conditions, 2 days at rest and 2 days with exercise. One 10-minute exercise segment at 5 minutes in the 40-minute exposure period.

Outcome: Symptoms diary, scores 0–4, at t = 0, t = 30 minutes, and 4–8 hours and 24 hours postexposure.

Exposure: 40 minutes; clean air and 2.0 ppm (2.46 mg/m^3).[a]

Formaldehyde generation via thermal depolymerization of paraformaldehyde over boiling 2-propanol, dynamic chamber, analytical concentrations reported.

Confidence: Medium

Co-exposure to 2-propanol, potential confounding by smoking</td><td>Symptoms during exercise not different from rest.

Prevalence and scores during rest

<table>
<tr><th></th><th colspan="4">Concentration (ppm)</th></tr>
<tr><th></th><th colspan="2">0</th><th colspan="2">2</th></tr>
<tr><th></th><th># (%)</th><th>S[a]</th><th># (%)</th><th>S[a]</th></tr>
<tr><td>Odor</td><td>7 (46.7)</td><td>10</td><td>12 (80.0)</td><td>22</td></tr>
<tr><td>Eye</td><td>0</td><td>0</td><td>7 (46.7)</td><td>9</td></tr>
<tr><td>Nose</td><td>1 (0.07)</td><td>2</td><td>0</td><td>0</td></tr>
<tr><td>Throat</td><td>1 (0.07)</td><td>2</td><td>0</td><td>0</td></tr>
</table>
[a]Total Score Across all Subjects

Eye Irritation Severity by Exposure, # (%)

<table>
<tr><th></th><th>0 ppm</th><th>2 ppm</th></tr>
<tr><td>Mild</td><td>0</td><td>5 (33.3)</td></tr>
<tr><td>Moderate</td><td>0</td><td>2 (13.3)</td></tr>
<tr><td>Severe</td><td>0</td><td>0</td></tr>
</table></td></tr>
</table>

Study and design	Results
Bender et al. (1983) **Design:** Panels of seven volunteers from Battelle Memorial Institute (age, health status, smoking status, and gender not reported) exposed to clean air and formaldehyde. Individuals who responded to 1.3 and 2.2 ppm formaldehyde were tested. Order of exposure assignment not reported, blinding not described. Eye-only exposures for 6 minutes. **Outcome:** Response time (seconds); proportion of subjects with shorter response time to formaldehyde than to clean air. Subjective score (0–3) when first detected and after 6 minutes. **Exposure:** 6 minutes, eye only, 0, 0.35, 0.56, 0.7, 0.9 and 1.0 ppm (0.0, 0.43, 0.69, 0.86, 1.11, and 1.23 mg/m^3).[a] Formaldehyde generation via thermal depolymerization of paraformaldehyde, dynamic chamber, analytical concentrations not reported. **Confidence:** *Low* Reporting deficiencies regarding analytical concentrations, random allocation and blinding. Sample size <10.	Median time to first irritant response decreased with increasing concentration (Cochran's χ^2 test for trend). Severity index increased with increasing concentration. **Proportion with shorter response to formaldehyde compared to clean air** **Respondents** PPM | Total | # | % 0 | 28 | – | – 0.35 | 12 | 5 | 41.7 0.56 | 26 | 14 | 53.8 0.7 | 7 | 4 | 57.1 0.9 | 5 | 3 | 60.0 1.0 | 27 | 20 | 74.1* *$p < 0.05$, compared to control

Abbreviations: ACA = activated carbon aerosol; ATS = American Thoracic Society; EA = ethyl acetate; HCHO = formaldehyde; NASA = National Aeronautics and Space Administration; S = Symptom score; SPES = symptom questionnaire; UFFI = urea foam insulation.

[a]Concentrations reported by authors as ppm or ppb converted to mg/m^3.

Studies in residential settings

Two studies investigated the prevalence of irritation symptoms in relation to residential formaldehyde exposure during the 1980s (Liu et al., 1991; Sexton et al., 1986; Hanrahan et al., 1984). These studies met the criteria for a *high* confidence study but did not describe or provide a reference for the questionnaire used to assess symptoms. Two studies of occupational exposure in mobile trailers (Main and Hogan, 1983; Olsen and Dossing, 1982) are included with this group because the exposure settings (mobile homes with particle board paneling) are similar. Formaldehyde exposure was associated with an increasing prevalence of eye irritation in all of these studies (see Table 1-2 and Figure 1-3). One study, Olsen et al. (1982), assessed the severity of symptoms as well as their presence within the previous month using a linear analogue scale. Among those reporting symptoms of eye irritation, a severity at approximately the midpoint of the scale was reported, which is consistent with the mild or moderate severity reported by the controlled human exposure studies. Two studies in residential populations analyzed exposure-response relationships and observed a statistically significant relationship between increasing formaldehyde concentration (from approximately 0.01 to >0.60 mg/m^3) and symptoms of irritation using logistic regression models with adjustment for age, gender, smoking behavior and other potential confounders (Liu et al., 1991; Sexton et al., 1986; Hanrahan et al., 1984). Data were

collected on current symptoms occurring after participants had moved into their homes (Hanrahan et al., 1984) or those that occurred during the 2 weeks prior to the end of the one-week formaldehyde sampling period (Liu et al., 1991). Although the sampling period used by Hanrahan et al. (1984) was shorter (1 hour), the presence of smokers or gas appliances in the home, sources that might contribute to variability in concentrations, were not associated with indoor formaldehyde concentrations. Therefore, the formaldehyde concentrations measured by both studies were considered to be relevant to the time frame of the symptom reports. Other emissions released from the same sources as formaldehyde that also can contribute to eye irritation, such as phenols from resins in floor or wall coverings or pinene and terpenes from wood products, were not analyzed. However, a strong exposure-response relationship with formaldehyde, as a cumulative measure (ppm-hr) or a 1-hour concentration, was reported by two *medium* confidence studies, which is unlikely to be explained to a great extent by unmeasured confounding. Although limited by low participation rates, participants were randomly selected for recruitment, and the investigators noted that the characteristics of the respondents and nonrespondents, such as age of housing stock, demographics, and formaldehyde concentrations, were comparable.

Figure 1-3 graphs prevalence of eye irritation (or burning eyes) by formaldehyde concentration reported by controlled human exposure studies and residential studies that evaluated concentrations below 1 mg/m^3. These results are complementary for the most part and indicate a consistent pattern in response to formaldehyde concentrations between 0 and 1 mg/m^3. As seen in Figures 1-2 and 1-3, the concentration-response curve for eye irritation in the Kulle et al. (1987) study was shifted to the right compared to other studies that evaluated multiple concentration levels. The study by Bender et al. (1983) used a protocol that involved exposure to the eyes only, although the concentration-response pattern was similar to the studies that evaluated exposure via inhalation. Two controlled human exposure studies that also evaluated concentrations below 1 mg/m^3 used a different metric to measure symptoms, a subjective symptom score using a validated questionnaire (Mueller et al., 2013; Lang et al., 2008). The results of the two studies differed; Lang et al. (2008) reported an increase in symptom scores for eye irritation at 0.3 mg/m^3, although with control for responses to questions that assessed "negative affectivity," the association was not observed until 0.5 mg/m^3, and Mueller et al. (2013) reported no effect related to formaldehyde exposure.

Other URT symptoms were reported by these studies as well, including irritation of the nose and throat. A recent study of formaldehyde levels in redecorated homes in China and respiratory symptoms among residents exposed from 1 month to 3 years, reported a higher prevalence of nasal irritation, and throat irritation among adults and children at concentrations above 0.08 mg/m^3 (Zhai et al., 2013). The association was independent of other factors including age, gender, smoking in the family, occupation, education, presence of domestic animals, family history of allergy, and ventilation frequency.

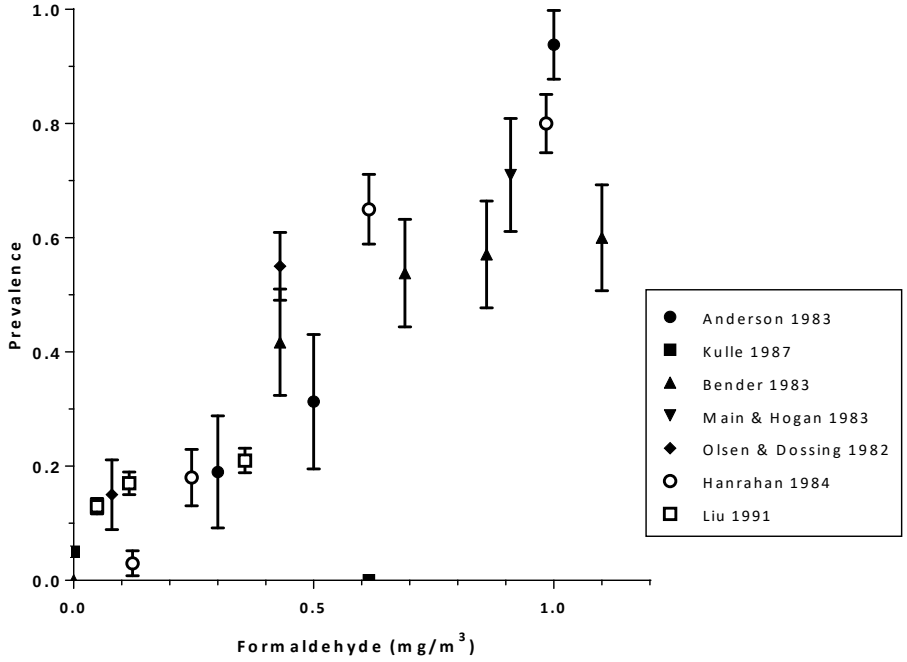
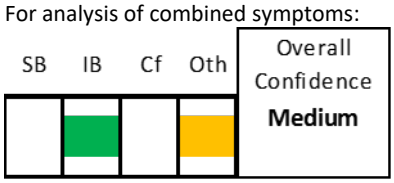
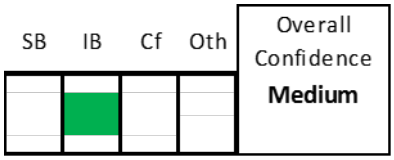
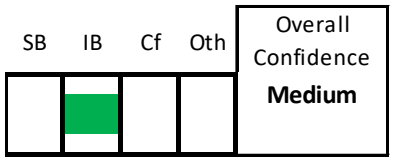


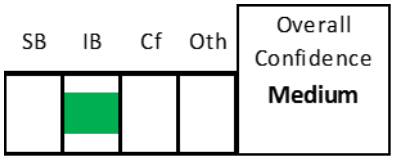
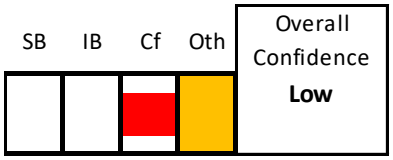
Figure 1-3. Prevalence of eye irritation among study groups exposed to formaldehyde in residential settings and controlled human exposure studies.

Different symbols are used for each study. Olsen and Dossing (1982) and Main and Hogan (1983) are occupational studies with exposure in mobile trailer offices and are presented with the residential mobile home studies. Prevalence at formaldehyde concentrations measured among comparison groups is graphed if reported (Holness and Nethercott, 1989; Holmström and Wilhelmsson, 1988; Horvath et al., 1988; Olsen and Dossing, 1982). Error bars are standard error (SE) calculated by EPA. Average weekly concentrations in three categories for Liu et al. (1991) were estimated from the midpoint of each category of reported weekly cumulative exposure (ppm-hour) and an assumption that individuals spent 60% of a 24-hour period at home.

Table 1-2. Summary of epidemiological studies of residential exposures to formaldehyde and human sensory irritation

Study and design	Results
Zhai et al. (2013) Jan 2008–Dec 2009 (China) (prevalence) **Population:** 186 homes in Shenyang surveyed, homes were decorated in past 4 years and occupied within the past 3 years; randomly selected one adult from each house, plus 82 children (assisted by parents); characteristics of participants were not described. **Outcome:** Reported symptoms and disorders via questionnaire Ferris (1978). **Exposure:** Cited code for indoor environmental pollution control of civil building engineering (GB50325-2001); sampling period not reported. Samplers in breathing zone in bedroom, living room, and kitchen; *N* = 558 in 186 homes; exposure groups "polluted" homes: >0.08 mg/m^3, mean 0.09–0.13 mg/m^3, range 0.01–0.55 mg/m^3, in three rooms; nonpolluted ≤0.08 mg/m^3, mean 0.04–0.047 mg/m^3. **Analysis:** Compared symptom prevalence for children and adults by exposure category (reported *p*-values); multivariate logistic regression of respiratory system symptoms (all) in children and adults, adjusting for age, gender, smoking in family, occupation, education, ventilation frequency, domestic pets, house facing, family history of allergy, height, weight. **Evaluation:**[a] For analysis of combined symptoms:  Combined analysis does not distinguish URT irritation symptoms from asthma-related symptoms; sampling period not reported.	**Respiratory system symptoms and disorders by exposure group (*N* = 186 adults, 82 children)** Symptom / >0.08 mg/m^3 (%) / ≤0.08 mg/m^3 (%) Cough, adults: 16.0* / 4.5 Cough, children: 25 / 8.1 Phlegm, adults: 6.7 / 3.0 Phlegm, children: 15 / 6.7 Wheeze, adults: 5.0 / 3.0 Wheeze, children: 10 / 6.6 Nasal irritation, adults: 52.1** / 16.4 Odor disorder, adults: 21** / 3.0 Throat irritation, adults: 31.9* / 13.4 *p < 0.05, **p < 0.01 **Association of formaldehyde exposure with respiratory system symptoms in adults and children (*N* = 186 adults, 82 children)** Odds Ratio / 95% CI Adults[a]: 2.6 / 1.8, 3.8 Children[b]: 4.3 / 2.1, 8.8 [a]Other statistically significant covariates were ventilation frequency (OR = 1.6) and domestic pets (OR = 1.5) [b]Other statistically significant covariates were ventilation frequency (OR = 1.8) and family history of allergy (OR = 1.9)
Liu et al. (1991); Sexton et al. (1986) (California) Prevalence survey, 1984–1985. 2,203 randomly selected mobile home occupants recruited, 44% response (836 of 1,895 contacted). 1,394 residents in 663 mobile homes in summer and 1,096 residents in 523 mobile homes in winter. 20–64 years of age. **Outcome:** Symptoms (occurrence during 1 week prior to end of sampling period) from mailed questionnaire, questionnaire not described. **Exposure:** Formaldehyde sampling using passive monitors mailed to participants, 7-day samples, two rooms. Average concentration: 0.091 (SD 0.069, range <0.01 (LOD)–0.464) ppm in summer and 0.091 (SD 0.052, range 0.017–0.314) in winter. (0.11 (SD 0.095), range <0.012–0.57 mg/m^3) Cumulative formaldehyde: formaldehyde concentration × hours spent in the residence (ppm-hr).	Significant associations with burning/tearing eyes, stinging/burning skin in summer, and burning/tearing eyes, chest pain, sore throat in winter (effect estimates from logistic regression model were not presented). **Prevalence Burning/Tearing Eyes** ppm-hr / Summer (%) / Winter (%) <7.0: 13.3 / 10.8 7.0–12: 17.1 / 14.7 >12.0: 21.4 / 20.6 Burning/tearing eyes higher among females in regression models.

Study and design	Results
Analysis: Logistic regression adjusting for age, gender, smoking status, time spent at home, and chronic respiratory/allergy status. **Evaluation:**[a]  Reporting deficiencies regarding type of questionnaire and quantitative results	
Hanrahan et al. (1984) (Wisconsin) Prevalence survey, 1979 61 teenage and adult occupants from 65 of 208 randomly selected mobile homes. Mean age 48 yrs, 61% female. Participants blinded to exposure status. **Outcome:** Current symptoms with occurrence since moving into home from self-administered questionnaire, questionnaire not described. **Exposure:** Formaldehyde measurements: 1-hour samples, average of measurements in two rooms. Median: 0.16 ppm. Range: <0.1 ppm to 0.80 ppm. Outdoor mean (SD) = 0.04 (0.03) ppm. Windows closed, smoking banned, gas appliances turned off for 30 minutes prior to measurements. **Analysis:** Logistic regression adjusting for age, gender, and smoking. **Evaluation:**[a]  Limited sampling period for formaldehyde measurements; Questionnaire not described	A statistically significant concentration-response relationship was reported individually for burning eyes and eye irritation; no regression coefficients provided. **Burning Eyes** Concentration (ppm) / Prevalence (%)[a] 0.1 — <5 0.2 — 17.5 0.5 — 65 0.8 — 80 [a]Predicted response estimated by EPA from graphical presentation of logistic regression results normalized to mean age. Formaldehyde concentration not associated with presence of smoker in home or gas appliances. Regression model showed higher prevalence of eye irritation in younger persons.
Olsen and Dossing (1982) (Denmark) Prevalence survey, 1979. Exposed: 66 of 70 employees of seven mobile day care centers (average of 6 months old) paneled indoors with urea formaldehyde glued particle board; mean age 29 years, 10/90 percentiles 19/40 years. Referent: 26 of 34 employees randomly selected from three control (nonmobile home) centers with no materials containing formaldehyde. Mean age 32 years, 10/90 percentiles 25/38 years. All worked in day care centers for >3 months. **Outcome:** Prevalence (yes/no), Severity of symptoms experienced within 1 month measured in centimeters on scale from 0 to 10, "linear" analogue self-assessment method." **Exposure:** Formaldehyde measurements taken after questionnaire study: 2-hour samples in 2–4 locations in the homes. Mean mobile units = 0.43 mg/m^3 (range 0.24–0.55 mg/m^3). Mean referent = 0.08 mg/m^3 (range 0.05–0.11 mg/m^3).	The average frequency of mucous membrane irritation of eyes, nose, and throat was 3× higher among staff of mobile units vs. stationary institutions ($p < 0.01$). Symptoms disappeared after end of work. **Percentage with affirmative answer**[a] Exposed (%) / Referent (%) Eye — 56 — 14.6 Nose/throat — 74 — 25 [a]Estimated by EPA from bar chart in Figure 1 in the paper.

Study and design	Results
Analysis: Prevalence and average impact scores compared. **Evaluation:**[a]  Some uncertainties regarding temporal concordance of exposure and symptom assessments	
Main and Hogan (1983) Prevalence survey 21 exposed individuals working in two mobile trailers for 34 months (mean [SD] age 38 [9] years, 76% male) 18 referent staff members who did not work in the trailers (mean [SD] age 30 [6] years, 50% male) **Outcome:** Modified ATS questionnaire **Exposure:** Three 1-hour area samples taken on four occasions (August, September, December, April) always on a Monday. At least one sample was taken from each office in both trailers. Concentration range 0.12–1.6 ppm (0.15–1.97 mg/m^3)[a] **Analysis:** Group comparisons, χ^2 statistic **Evaluation:**[a]  Potential dissimilarity between comparison groups; more exposure to ETS among referent; small sample size	**Symptom Prevalence While at Work** Symptom / Exposed (n = 21) / Referent (n = 18) / χ^2 (p-value) Eye irritation: 0.71 / 0.0 / 20.9 (<0.001) Nasal symptoms: 0.33 / 0.0 / 7.3 (0.01) Throat irritation: 0.48 / 0.0 / 11.5 (0.001)

LOD = limit of detection; RD50 = concentration resulting in a 50% reduction in the respiratory rate; RIL = recommended indoor limit; VOC = volatile organic compound.

[a]Evaluation of sources of bias or study limitations (see details in Appendix A.5.1 and A.5.2). SB = selection bias; IB = information bias; Cf = confounding; Oth = other feature of design or analysis. Extent of column shading reflects degree of limitation. Direction of anticipated bias indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact would be likely to be away from the null (i.e., spurious or inflated effect estimate).

Laboratory and occupational exposure

The studies of anatomy students and formaldehyde-exposed workers provide further evidence that formaldehyde exposure is associated with symptoms of eye, nose, and throat irritation. These studies are summarized in tables in the appendix for sensory irritation (Appendix A.5.2). Exposure levels experienced during anatomy laboratory courses and in occupational settings were high and variable. Formaldehyde levels during anatomy courses generally averaged 0.9 mg/m^3 and above during the lab, with short-term peaks above 5 mg/m^3 (Takahashi et al., 2007; Kriebel et al., 2001; Wantke et al., 2000; Kriebel et al., 1993; Uba et al.,

1989). These exposures were episodic, one to two sessions per week, for 1–4 hours. Study designs that analyzed reported symptoms and formaldehyde levels measured in close temporal proximity were considered less subject to information bias. The intensity of symptoms (Kriebel et al., 2001) and prevalence or frequency of occurrence (Takigawa et al., 2005; Wantke et al., 2000) of symptoms was related to exposure during the lab. Over time, the magnitude of the increase in symptoms during a laboratory session was reported to decline over the succeeding weeks of the course (Kriebel et al., 2001; Kriebel et al., 1993). Kriebel et al. (2001) modeled average formaldehyde concentration during each lab session in relation to irritation symptoms (separate models for eye, nose, and throat irritation) and reported that intensity of eye irritation symptoms increased by 1.22% per unit increase in ppm, and the magnitude of the increase in intensity declined with each successive week during the course.

Formaldehyde concentrations in the workplace varied by industry. Examples of industrial formaldehyde levels include mean levels of 0.26 mg/m^3 in a formaldehyde-producing plant in Sweden (Holmström and Wilhelmsson, 1988), 0.96 mg/m^3 in a melamine-formaldehyde resin-producing plant (Neghab et al., 2011) in Iran, and 1.04 mg/m^3 in a particleboard plant (Horvath et al., 1988). Excursions above 2 mg/m^3 were measured in some industries. Most of the studies compared responses in exposed groups to those in a referent group, and symptoms of URT and eye irritation were associated with exposure status in these studies. One study also reported a strong exposure-related trend for burning nose, stuffy nose, burning eyes, itchy nose, sore throat, and itchy eyes in multiple regression models, although quantitative results were not reported (Horvath et al., 1988).

Evidence on Mode of Action for Sensory Irritation

Sensory irritation is understood to occur as a result of direct interactions of formaldehyde with cellular macromolecules in the nasal mucosa leading directly or indirectly to stimulation of trigeminal nerve endings located in the respiratory epithelium. While other mechanistic changes (e.g., oxidative stress; airway inflammation; damage or dysfunction of the respiratory epithelium) and biological differences (e.g., nasal morphology; underlying allergy, infection, or other respiratory conditions) are expected to be strong modifiers of this sequence of events, this pathway is interpreted as likely to be the dominant mechanism by which formaldehyde exposure causes sensory irritation. The primary evidence for this conclusion includes mechanistic changes in the URT, which are supported by robust or moderate formaldehyde-specific data (see summary interpretations in Figure 1-4 and Table 1-3; Appendix A.5.6 includes additional details and evidence supporting other relevant mechanistic changes, some of which are discussed briefly below), and the relationships described are largely well understood biological phenomena, or they have been demonstrated following formaldehyde exposure. This mechanistic understanding provides strong support for the biological plausibility of this effect. Although the primary support for an MOA reliant on stimulation of receptors on nasal trigeminal nerve endings is from studies in

experimental animal models, the mechanistic events presumed to be driving sensory irritation after formaldehyde exposure are expected to be conserved in humans.

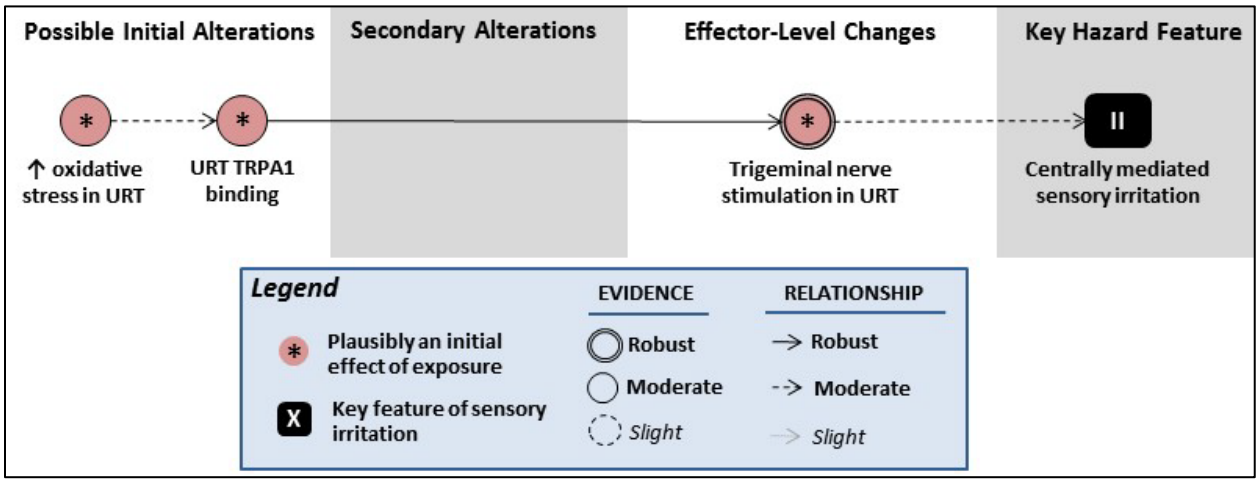


Figure 1-4. Possible mechanistic associations between formaldehyde exposure and sensory irritation.

An evaluation of the formaldehyde exposure-specific mechanistic evidence informing the potential for formaldehyde exposure to cause respiratory health effects (see Appendix A.5.6 for clarifying details) identified this sequence of mechanistic events as likely to be the dominant mechanism by which formaldehyde inhalation could cause sensory irritation.

As illustrated in Figure 1-4, formaldehyde exposure appears to result in activation of chemosensory afferents, likely C fibers, in the URT, presumably in the anterior third of the nasal cavity, based on the pattern of chemosensory activation and consistent with the distribution of inhaled formaldehyde (see Appendix A.5.6). This activation initiates central signals that result in the burning sensation characteristic of sensory irritation. The rapid detection of these sensations in exposed individuals, as well as insights from other irritants, suggest a receptor-mediated event that is dependent on formaldehyde penetration to the nerve endings, which may not have an exposure duration threshold. In vitro and ex vivo studies suggest that activation of the trigeminal nerve by formaldehyde is mediated, at least in large part, through cation channels, primarily the Transient Receptor Potential A1 channel (TRPA1). Alongside the centrally mediated physiological response, the initial activation of the trigeminal nerve is also known to cause a localized release of neuropeptides, such as substance P, from nerve terminals (not shown in Figure 1-4), which can affect local inflammatory and immune responses. Observations of these local neuropeptide changes have been reported at slightly higher formaldehyde levels than those shown to activate the trigeminal nerve, generally at >1 mg/m^3, although the data suggest that they too may be dependent on TRPA1 activation. All of these direct and indirect interactions could act independently or together in a concentration- and duration-dependent manner.

While the response to some irritant chemicals exhibits desensitization or fading of the irritant response over time (e.g., through receptor downregulation) (Nielsen, 1991), it is not clear this is the case with formaldehyde. As previously discussed, results from acute, controlled human exposure studies indicate that some acclimatization may occur over exposures of a few hours at higher concentrations; however, this reduction in symptoms is less apparent (or may be absent) when concentrations are lower (<1 mg/m^3), and changes to this response pattern in humans over time, particularly with exposure longer than 1 day, remain poorly tested. Studies of reflex bradypnea in rodents (see Appendix A.3), a phenomenon dependent on the activation of the trigeminal nerve, show that repeated exposure for up to a month elicits a similar level of activation of this pathway. However, uncertainties with the rodent data include a nonconstant exposure (i.e., there is at least partial recovery from the reflex effects in rodents with continued exposure in acute studies of minutes to hours, while the available short-term studies employed work hour-like exposure periodicity) and testing only at reflex bradypnea-inducing levels (e.g., >1 mg/m^3). It is unclear whether the results based on acute or episodic exposures apply to long-term responses to constant oronasal exposure in humans (who do not exhibit reflex bradypnea) at lower formaldehyde levels.

Sensitivity (i.e., activation of this pathway) is expected to vary between individuals due to differences in TRPA1 channel sensitivity or access of formaldehyde to TRPA1 channels, as might occur due to differences in airway structure, mucus production, or TRPA1 channel density. Thus, enhanced irritation could plausibly occur directly as a result of sensitization of the receptors to formaldehyde with prolonged exposure or due to the accumulation of other factors that could reduce the threshold for TRPA1 activation by formaldehyde, or indirectly by increased access of formaldehyde to trigeminal nerve endings following damage to juxtaposed epithelial cells or reduced mucociliary function. Airway inflammation has been shown to reduce the threshold for activation of afferent fibers, through an unknown mechanism (Carr and Undem, 2001), and lipid peroxidation byproducts can independently stimulate sensory nerve activation. These latter possibilities are of particular relevance, as exposure to formaldehyde (possibly even at lower levels, e.g., <1 mg/m^3) appears to result in airway inflammation and increased oxidative stress. Conversely, other modifications to the respiratory epithelium following formaldehyde exposure (e.g., at levels causing effects such as squamous metaplasia, which is generally observed in animals at ≥2.5 mg/m^3; see Section 1.2.4) could plausibly result in a decreased access of formaldehyde to trigeminal nerve receptors. However, while the structure and function of the URT across species is similar, interpretation of compensatory or adaptive changes within the human URT following long-term exposure based on findings in experimental animals is difficult to infer, and modification of sensory nerve signaling in the context of these important scenarios has, for the most part, not been directly tested. In addition, studies of related chemicals suggest that human sensitivity may also be dependent on demographic factors such as age, gender (women are generally more sensitive), and allergy status (Shusterman, 2007; Hummel et al., 2003), complicating an understanding of changes

in sensitivity. While additional studies clarifying modifications to the sensitivity of this pathway with longer-term exposure or under different exposure scenarios would be useful, it is likely that rodents acutely exposed to ~0.2 mg/m^3 formaldehyde under normal conditions would exhibit this effect, and exposed humans are expected to be more sensitive.

Table 1-3. Mechanistic evidence most informative to the occurrence of sensory irritation after formaldehyde inhalation

Endpoint	Endpoint-specific findings and confidence		Summary of evidence	Conclusion
↑ URT Oxidative Stress	*High or Medium*	*Human*: Increased nasal epithelial M1dG adducts (oxidative stress and lipid peroxidation marker) (Bono et al., 2016): unknown duration (but likely years) at >0.066 mg/m^3	Direct and indirect evidence of elevated reactive oxygen species (ROS), possibly at low concentrations (e.g., at >0.066 mg/m^3; maximum of 0.444 mg/m^3) with prolonged human exposure	Moderate
		Animal: mRNA changes indicating increased stress-response proteins (Andersen et al., 2008): short-term exposure at ≥2.46 mg/m^3		
	Low	*Human*: Increased nasal lavage nitrites (Priha et al., 2004): acute (8-hr shift) exposure at 0.19 mg/m^3	Data suggest elevated oxidative stress at very low formaldehyde concentrations with acute and short-term exposure.	
		Animal: Increased glutathione peroxidase and/or nonprotein sulfhydryl groups (Cassee et al., 1996; Cassee and Feron, 1994): short-term (3 d) duration at 3.94 and 4.43 mg/m^3, respectively		
Trigeminal Nerve Stimulation	*High or Medium*	*Human*: None	Increased activity of trigeminal nerve afferents at <0.5 mg/m^3 following acute exposure in anesthetized rats	Robust (data are primarily from acute exposure)
		Animal: Increased afferent nerve activity (Tsubone and Kawata, 1991): acute duration exposure resulted in ~20% at 0.62 mg/m^3 and ~50% at 2.21 mg/m^3; (Kulle and Cooper, 1975): acute exposure (threshold detection at 25 seconds) at 0.31 mg/m^3		
	Low	*Human*: None	Supportive indirect evidence from ex vivo and in vitro experiments	
		Animal: Indirect evidence: with acute exposure, dose-dependent increase in nerve currents and Cl—release in intact rat trachea (Luo et al., 2013), and stimulation using in vitro neuronal preparations (Kunkler et al., 2011; Mcnamara et al., 2007)		
TRPA1 Stimulation	*High or Medium*	*Human*: None	Indirect data identify TRPA1 as a molecular target for formaldehyde exposure-induced sensory effects	Moderate (data are primarily from acute or short-term exposure)
		Animal: Formaldehyde and related chemicals such as acrolein activate the trigeminal system in wild-type mice, but not TRPA1 knockout mice following acute exposure, at least at high exposure levels (Yonemitsu et al., 2013); taken together with the established role for TRPA1 in acrolein-induced sensory effects (e.g., (Bautista et al., 2006)), these data indirectly support a role for TRPA1 in sensory nerve-related changes following formaldehyde exposure		
	Low	*Human*: None	Indirect data identify TRPA1 as a molecular target of formaldehyde exposure with acute or short-term exposure; inhibitor studies demonstrate that downstream	
		Animal: Formaldehyde activates TRPA1 in in vitro and ex vivo models relevant to acute inhalation exposure of the URT and upper LRT (Luo et al., 2013; Mcnamara et al.,		

		2007), and is well established in in vivo models using formalin as a pain stimulus (not a focus of this review); inhibition of TRPA1 channels localized to sensory nerve endings reduce formaldehyde exposure-induced nerve currents in rat trachea (Luo et al., 2013) and immune-related responses in mice (Wu et al., 2013; Lu et al., 2005) with short-term (2- or 4-wk) exposure at 1 or 3 mg/m^3	effects of sensory nerve stimulation depend on TRPA1 stimulation	

Integrated Summary of Evidence on Sensory Irritation

Symptoms of sensory irritation were consistently reported by studies of formaldehyde exposure in multiple settings, and both prevalence and severity of symptoms increased with the level of exposure. Sensory irritation is an acute phenomenon, and symptoms resolve when exposure is removed (Sauder et al., 1986; Andersen and Molhave, 1983; Andersen, 1979). The irritant effects of formaldehyde on the eyes and URT were reported by several controlled human exposure studies that evaluated responses among healthy or asthmatic volunteers using relatively high formaldehyde concentrations (0.12 and 3.7 mg/m^3) during rest or exercise. In addition to subjective reports, some investigators evaluated objective measures, including eye blink frequency, conjunctival redness, and nasal flow and resistance (Mueller et al., 2013; Lang et al., 2008; Andersen and Molhave, 1983; Andersen, 1979). Eye blink frequency was increased at exposure levels above those where subjective symptoms were reported. Symptoms of sensory irritation also were documented in the epidemiological literature among residential and occupational populations, and students exposed in anatomy classes. Exposed groups described eye, nose, and throat symptoms with formaldehyde exposure, including itching, stinging, and watering eyes; sneezing and rhinitis; sore or dry throat; and coughing. Average formaldehyde concentrations for exposed populations were 0.9 mg/m^3 (median) among anatomy students (Kriebel et al., 1993) and 0.2 mg/m^3 and lower among residential populations (Zhai et al., 2013; Liu et al., 1991; Hanrahan et al., 1984). A statistical exposure-response relationship for the prevalence of eye irritation or burning eyes was described using regression models in some studies (Kriebel et al., 2001; Kriebel et al., 1993; Liu et al., 1991; Horvath et al., 1988; Kulle et al., 1987; Hanrahan et al., 1984). Alternative explanations for these symptoms can be ruled out since there is strong evidence from controlled human exposure studies and residential studies, with exposure-response trends that were adjusted for potential confounders, including age, gender, and smoking. Coexposures in homes, such as that from terpenes, phenol, and acetaldehyde, which are emitted from wood products, carpets and wall coverings, and combustion, were present at lower levels compared to formaldehyde. Sensory irritation also was reported among groups in exposure settings without those coexposures (e.g., controlled human exposure studies, anatomy labs). NO_2, which is emitted from gas stoves, has not been correlated with formaldehyde levels in homes (Mullen et al., 2015).

The magnitude or severity of symptoms does not appear to worsen over periods of prolonged exposure, and some studies have observed decreases over observation periods lasting a few weeks. However, change in responses over time has been examined in only a few studies. Notably, controlled human exposure studies involving occupationally exposed individuals did not observe responses that were less sensitive than those among subjects with no occupational exposure, suggesting that the response persists even with prolonged exposure. Controlled human exposure studies that examined change in response during exposures at relatively high levels (>1 mg/m^3) reported higher symptom scores initially with subsequent declines suggestive of acclimation during exposure (Green et al., 1987; Schachter et al., 1986a; Andersen and Molhave, 1983). However, at lower concentrations (0.3 and 0.5 mg/m^3), the initiation of symptoms was delayed, and symptom severity continued to increase during the exposure period (Andersen and Molhave, 1983). Overall, these few studies suggest that some acclimatization may occur over a few hours at higher concentrations; however, this phenomenon may not be apparent when concentrations are lower (<1mg/m^3).

Stimulation by formaldehyde of sensory nerve endings in the URT, presumably involving activation of TRPA1 ion channels on C fibers of the trigeminal nerve, is likely to be the dominant MOA for the observed effects on sensory irritation. It is expected that differences in nasal anatomy and respiratory health status would be strong modifiers of this MOA.

In conclusion, studies in humans provide *robust* evidence based on the controlled human exposure studies and observational epidemiology studies, *robust* evidence exists supporting an effect in animals (this phenomenon is well described and accepted across a range of experimental species), and there is an established MOA based on mechanistic evidence in animals (the identified MOA is interpreted to be operant in humans). Overall, the **evidence demonstrates** that inhalation of formaldehyde causes sensory irritation in humans, given appropriate exposure circumstances. The primary support for this conclusion is based on well-conducted residential studies with mean formaldehyde concentrations >0.05 mg/m^3 (range 0.01 to approximately 1.0 mg/m^3) and controlled human exposure studies testing responses to concentrations 0.1 mg/m^3 and above (Table 1-4).

Table 1-4. Evidence integration summary for effects on sensory irritation

Evidence	Evidence judgment	Hazard determination
Human	*Robust*, based on: *Human health effect studies*: • Four *high* and *medium* confidence studies of symptom prevalence (eye, nose, throat) among adults and children in residential settings (mean >0.05 mg/m^3 formaldehyde, range 0.01 to approximately 1.0 mg/m^3) • Numerous *high* and *medium* confidence studies involving acute exposure (controlled human exposure studies) • Numerous *high* and *medium* confidence studies with longitudinal designs (occupational, panel studies of medical school pathology/ anatomy lab courses)	The **evidence demonstrates** that formaldehyde inhalation causes sensory irritation in humans given appropriate exposure circumstances[a] Primarily based on well-conducted residential studies with mean formaldehyde concentrations >0.05 mg/m^3

	• Consistent observations of irritation symptoms in all studies; clear exposure-response trends *Biological Plausibility*: No directly relevant human mechanistic studies were found	and controlled human exposure studies testing ≥0.1 mg/m^3 *Potential susceptibilities*: Potentially large variations in sensitivity are expected, depending primarily on differences in nasal health (including allergy or inflammatory status) and physiology
Animal	*Robust*, based on: *Animal health effect studies*: Although animal studies were not formally evaluated, formaldehyde inhalation-induced sensory irritation in rodents is a well-documented phenomenon (e.g., reflex bradypnea in mice and rats; see Appendix A.3). *Biological Plausibility*: Robust and moderate evidence for mechanistic events from animal studies identifies stimulation of the trigeminal nerve as the dominant MOA	
Other inferences	• *Relevance to humans*: Assumed, based on similarities in systems mediating the identified MOA across species • *MOA*: Trigeminal nerve stimulation is likely to be the dominant mechanism • *Other*: This effect does not appear to worsen with longer exposure durations, although uncertainties remain	

[a]The "appropriate exposure circumstances" are more fully evaluated and defined through dose-response analysis in Section 2.

1.2.2. Pulmonary Function

This section describes research on formaldehyde inhalation and pulmonary function effects in experimental and observational studies in humans. The systematic review process assigned controlled human exposure studies of acute exposure involving healthy individuals to the review of pulmonary function and the studies involving asthmatic volunteers to the review of effects on immune-mediated conditions and their results are summarized there (see section 1.2.3). However, since all of these studies involved measurements of pulmonary function, the results of the studies involving participants with asthma have been integrated with the evidence from studies of acute exposure in healthy individuals in this section. Animal studies of analogous endpoints were not included in the hazard evaluation because there were few directly relevant studies in the peer-reviewed literature and the extensive literature on these endpoints in humans was considered adequate to draw a hazard conclusion.

While studies involving acute exposures (<24 hours) reported either no change or inconsistent responses, more consistent effects were available from studies of occupational populations exposed over long periods and children exposed in residential settings. The acute, controlled human exposure studies involving healthy or asthmatic volunteers consistently did not observe changes, even at high concentrations, although two studies by one research team observed small decrements (<5%) when longer exercise components (15 minutes) were included. Studies using shorter exercise components (8–10 minutes) reported no changes. Two studies of asthmatic volunteers included an allergen challenge (dust mites, pollen), which resulted in a hyperreactive bronchial response at a lower challenge dose associated with formaldehyde exposure compared to clean air in one study that imposed mouth breathing (nose clips). Many of the studies of

occupational groups or dissection labs observed pulmonary function declines over the course of the workday or lab; however, most did not account for diurnal changes, limiting the interpretation of these results.

The review of the epidemiological literature provides evidence that long-term formaldehyde exposure is associated with declines in pulmonary function, including forced expiratory volume (FEV_1), forced vital capacity (FVC), FEV_1/FVC, and expiratory flow rates. Pulmonary function was lower in highly exposed occupational groups employed at exposed jobs for long durations compared to their nonexposed or lesser-exposed comparison groups. The few longitudinal studies found some evidence of declines in some measures in excess of that expected from aging, although the duration of follow-up and individual variation combined with small group sizes may have resulted in lack of associations with other measures. There are few studies of residential exposure; however, a clear exposure-response relationship in children was reported by a well-conducted residential study with most household concentrations <0.045 mg/m^3 (Krzyzanowski et al., 1990).

There is mechanistic support, primarily from studies in animals, for the biological plausibility of formaldehyde exposure-induced effects on decreased pulmonary function, although a definitive MOA(s) has not been fully defined. Overall, the most relevant mechanistic evidence (predominantly evidence interpreted as moderate or robust) included inflammatory structural alterations and eosinophil increases in the lower airways that appear to be at least partially related to indirect activation of sensory nerve endings. However, the initial cellular or tissue modifications that ultimately lead to these later events are not understood, and given the limitations of the available studies, it is unclear whether and to what extent certain events would be triggered with chronic, low-level exposure. Although there is an expectation that other important mechanistic events would be identified with additional study, the available data were interpreted to provide reasonable support for the biological plausibility of the observed associations and to identify what is likely to be an incomplete mechanism by which formaldehyde inhalation could cause decreased pulmonary function.

Spirometric measures are used along with other diagnostic criteria in the evaluation of asthma and chronic obstructive pulmonary disease in individuals. While a group mean decrement in any pulmonary function measure does not indicate that the prevalence of these respiratory diseases has increased, EPA considered a decrease in mean values to suggest a shift toward a decline in the respiratory health status of the population. Poor pulmonary function, as well as a decrease in pulmonary function, is an important health endpoint associated with the development of chronic respiratory disease, coronary heart disease, and mortality (Clayton et al., 2014; Menezes et al., 2014; Young et al., 2007; Sin et al., 2005; Schroeder et al., 2003; Schunemann et al., 2000; Sorlie et al., 1989). The American Thoracic Society evaluated the clinical significance of small average declines in pulmonary function observed in a population in response to air pollutants and concluded that although the magnitude of the observed declines may not be clinically relevant to an

individual, a shift in the population distribution toward lower pulmonary function, assuming the association is causal, may have a large impact on public health (ATS, 2000).

Overall, based on *moderate* human evidence from observational epidemiology studies, with corresponding *slight* evidence for an effect in animals based on mechanistic studies supporting biological plausibility, the **evidence indicates** that long-term inhalation of formaldehyde likely causes decreased pulmonary function in humans given the appropriate exposure circumstances. The primary support for this conclusion includes a study of children and adults in a residential setting (mean, 0.03 mg/m^3, maximum 0.17 mg/m^3) and numerous studies of workers with long-term exposure to >0.2 mg/m^3. The **evidence** is **inadequate** to interpret whether acute or intermediate-term (hour-weeks) formaldehyde exposure might cause this effect.

Literature Search and Screening Strategy

The identification of human health effect studies of formaldehyde exposure and effects on pulmonary function involved literature searches in PubMed and Web of Science through September 2016 (see Appendix A.5.3 for details), and a systematic evidence map updating the literature through 2021 (see Appendix F). Studies were included if the exposure to formaldehyde was quantified and if analyses compared outcomes in relation to exposure for one or more of a standard set of pulmonary function measures (see Table 1-5). Studies that evaluated both short-term as well as long-term exposure to formaldehyde were reviewed. Observational studies of human populations evaluated exposures in residential communities, school classrooms and university lab courses, and industrial and other workplace settings. Controlled human exposure studies, which exposed subjects for minutes or hours, also were included. The mechanistic evidence informing this health effect was identified and evaluated as part of the overarching review of mechanistic data relevant to potential respiratory health effects (see Appendix A.5.6 for details). The bibliographic databases, search terms, and specific strategies used to search them are provided in Appendix A.5.3 and A.5.6, as are the specific PECO criteria. Literature flow diagrams summarize the results of the sorting process through 2016 using these criteria and indicate the number of studies that were selected for consideration in the assessment (see Appendix F for the identification of newer studies through 2021). The relevant health effect studies in humans, and the mechanistic data informative to changes in pulmonary function, were evaluated to ascertain the level of confidence in the study results for hazard identification (see Appendices A.5.3 and A.5.6).

Methodological issues considered in evaluation of studies

Pulmonary function is assessed using spirometry, which measures the volume and speed of air that is exhaled or inhaled. Several parameters can be measured during spirometric testing to characterize an individual's respiratory health. Some common measures evaluated in the studies of formaldehyde exposure are defined in Table 1-5. It was preferred if the measurement of pulmonary function outcomes used by the studies followed the guidelines published by the American Thoracic Society (Tepper et al., 2012; Miller et al., 2005a; Miller et al., 2005b; Pellegrino

et al., 2005) or provided a description of the protocols and reference equations that were used. In addition to the use of conventional spirometric equipment, peak expiratory flow has been measured in research settings using portable flow meters operated by study participants trained in their use. Although it requires careful training and monitoring, this method has the advantage that it can be used in large epidemiological studies and multiple measurements can be obtained over time (Tepper et al., 2012). Studies of residential exposure to formaldehyde were conducted in this way (Kriebel et al., 2001; Krzyzanowski et al., 1990).

Table 1-5. Common measures of pulmonary function reported in studies of formaldehyde inhalation

Measure	Definition
Vital Capacity (VC) (Liters at BTPS)	The volume of air between a full inspiration and maximal expiration (an unforced maneuver)
Forced Vital Capacity (FVC) (Liters at BTPS)	The maximum volume of air forcibly exhaled after a maximal inspiration
Forced Expiratory Volume, 1 second (FEV_1) (Liters at BTPS)	The volume of air that is exhaled with maximal force in the first second
Forced Expiratory Flow 25–75% (FEF_{25-75}) (L/sec)	The mean forced expiratory flow in the 25th and 75th percentiles of FVC (also called maximum mid-expiratory flow [MMEF, MEF])
Ratio of FEV_1 to FVC (FEV_1/FVC)	Proportion of vital capacity exhaled in the first second of forced expiration
Peak Expiratory Flow Rate (PEF or PEFR) (L/sec at BTPS or L/min)	The maximum flow obtained from a person's maximum forced expiration starting from the point of a maximal lung inflation

BTPS: Body temperature and ambient pressure saturated with water vapor.
Source: Miller et al. (2005a).

Pulmonary function varies by race or ethnic origin, gender, age, and height and is best compared when normalized to expected pulmonary function based on these variables (Tepper et al., 2012; Pellegrino et al., 2005; Hankinson et al., 1999). Studies that did not adjust or otherwise account for these variables when comparing results between exposure groups were not considered. Pulmonary function also is associated with smoking status (Becklake and White, 1993), which was considered in the evaluation of potential confounding. FEV_1 and PEFR exhibit diurnal variation and this complicates the interpretation of changes across a work shift or during a laboratory session if no comparisons were made with an unexposed group (Chan-Yeung, 2000; Lebowitz et al., 1997).

Pulmonary Function Studies in Humans

The synthesis of pulmonary function first discusses responses to acute exposures including experimental study designs (controlled human exposure studies) or analyses of changes across a work shift or lab session in occupational groups or medical school anatomy students. Controlled human exposure studies of pulmonary function change among asthmatic volunteers are summarized in Section 1.2.3 (Immune-mediated Conditions, Focusing on Allergies and Asthma), but

their results are most informative to the pulmonary function outcome and are included in the integration of evidence in this section. Then, panel studies of students in anatomy labs with intermediate-duration exposure over a period of weeks or months are discussed. Subsequently, studies of long-term exposures are synthesized involving occupational groups or residential populations of adults and children. Evidence tables for each exposure setting (see Tables 1-6 through 1-10) are organized by level of confidence in the study's results and then descending publication year. The table summarizing the studies of occupational exposure are organized first by study design (cross-sectional, longitudinal), then by confidence in study results and descending publication year.

Generally, in the included studies of formaldehyde exposure and effects on pulmonary function, groups exposed to formaldehyde during the course of their jobs experienced TWA concentrations above 0.2 mg/m^3 with intermittent peaks above 1 mg/m^3. Students meeting once or twice a week in anatomy labs experienced fluctuating concentrations during dissections averaging between 0.1 and >1.0 mg/m^3. Formaldehyde concentrations in residential or primary school settings are much lower and less variable (<0.1 mg/m^3). EPA included both the higher exposure and the lower exposure studies in its evaluation of pulmonary function effects.

Acute and intermediate-duration formaldehyde exposure

Controlled human exposure studies

Formaldehyde exposures (0.62–3.7 mg/m^3), lasting from minutes to up to 5 hours, have not induced pulmonary function deficits in healthy, nonexercising volunteers in controlled human exposure studies (see Appendix A.5.3 for study summaries). The studies exposed small numbers (<25) of diverse individuals, often including males and females of varying age, and two included current smokers [31% of participants in the study described in Andersen (1979) and Andersen and Molhave (1983), and 13% of the participants in Schachter et al. (1987)]. In some studies, the variation around the mean change in lung function was quite large suggesting that the response to exposure was large in some individuals, and in others, the response was small (Schachter et al., 1987; Schachter et al., 1986b; Witek et al., 1986).

In contrast to the studies of exposure without exercise, small but statistically significant deficits in pulmonary function (e.g., decreased FEV_1, FVC, FEV_3, FEF_{25-75}, specific airways conductance) during formaldehyde exposures of 2.5 or 3.7 mg/m^3 were reported in two studies from one research group that included two or more 15-minute exercise regimens within the study protocol (Green et al., 1989; Green et al., 1987). These effects were not seen, however, in studies with shorter exercise segments [8–10 minutes; (Kulle et al., 1987; Schachter et al., 1987; Schachter et al., 1986b)]. Although the average change in lung function was generally small, some individuals exhibited clinically significant deficits, even after only 2 hours of exposure, suggesting that individual susceptibility may be an important consideration (Green et al., 1987).

Changes in pulmonary function across a work shift or anatomy course lab session

Daily changes in pulmonary function measures (e.g., across a work shift or during a lab session lasting a few hours) were assessed in studies among workers employed for several years in exposed jobs or among students enrolled in an anatomy lab. Most of the studies measured changes only among exposed individuals; measurements in a comparison group would have allowed adjustment for diurnal effects. One study using repeated peak expiratory flow measures taken by students trained in the procedure at multiple points during dissection lab sessions found that PEF declined over the course of a lab and these daily declines became attenuated over successive weeks (Kriebel et al., 2001). Kriebel et al. (2001) also measured overall changes after a few weeks' duration (see next section, Exposure durations <1 year).

Several studies reported daily cross-shift change in pulmonary function, although the same measures were not evaluated by all of the studies (see Appendix A.5.3).The interpretation of responses in the occupational groups is complicated because workers had significant previous exposure to formaldehyde (>0.2 mg/m^3) and few studies included an unexposed comparison group. Occupational studies in the wood products or chemical industries reported declines across a shift in one or more of FEV_1, FVC and FEV_1/FVC (Neghab et al., 2011; Herbert et al., 1994; Alexandersson and Hedenstierna, 1989; Horvath et al., 1988; Alexandersson et al., 1982). However, declines in these measures were not observed among other cohorts of plywood workers (Malaka and Kodama, 1990), industrial workers (Löfstedt et al., 2009), workers using acid hardening lacquers (Alexandersson and Hedenstierna, 1988), nor among funeral workers during an embalming session (Holness and Nethercott, 1989). The magnitude and direction of changes also were varied among anatomy students who were assumed to have no prior significant exposure to formaldehyde (Binawara et al., 2010; Khaliq and Tripathi, 2009; Akbar-Khanzadeh and Mlynek, 1997; Akbar-Khanzadeh et al., 1994; Chia et al., 1992; Uba et al., 1989). The heterogeneity in results cannot be explained by the study evaluation conclusions indicating confidence in a study's results (*high*, *medium*, *low*). Studies of exposure in dissection labs that evaluated an unexposed referent group or measured change in pulmonary function prior to the first lab generally reported that referent groups also experienced a change (either an increase or decrease) in pulmonary function, further complicating interpretations.

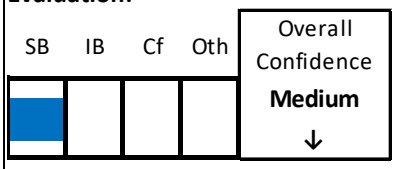
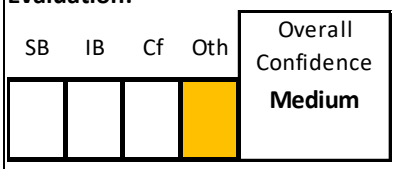
Daily declines in $FEF_{25–75}$ were more consistently reported by the occupational studies of wood products employees (Neghab et al., 2011; Malaka and Kodama, 1990; Horvath et al., 1988; Alexandersson et al., 1982), and exposed groups had larger decrements compared to the referent groups among the two studies that reported cross-shift changes in both groups (Malaka and Kodama, 1990; Horvath et al., 1988). Further, although $FEF_{25–75}$ was not reported by Holness et al. (1985), 2.3 and 8.5% decreases in FEF_{50} and FEF_{75}, respectively, were observed during embalming sessions among 22 embalmers, in contrast to a 1.2 and 1.9% increase, respectively, among 13 referent individuals assessed over a 2- to 3-hour period.

Exposure durations <1 year—changes among anatomy/pathology students

Three panel studies examined pulmonary function changes over the course of 10 weeks, 12 weeks, and 7 months among anatomy students exposed to formaldehyde, with average concentrations ranging from 0.12 to 6.2 mg/m^3 intermittently (once or twice a week: Kriebel et al., 2001; Kriebel et al., 1993; Uba et al., 1989); see Table 1-6]. The primary source of formaldehyde exposure in the laboratory air was formalin, a preservative composed of a mixture of formaldehyde (37%) and methanol (14%). Methanol is not expected to be associated with pulmonary function deficits and would not be a strong confounder in these studies (U.S. EPA, 2013). One study that measured pulmonary function using spirometry did not observe statistically significant declines over 7 months (FVC, FEV1, FEV1/FVC, FEF25−75), Uba et al., 1989). Two studies by the same research group using repeated peak expiratory flow measures taken by students trained in the procedure at multiple points during the lab sessions suggested an average decline in PEF over 2 to several weeks related to concentration averaged over the entire duration, as well as reductions during dissections that decreased in magnitude over time (Kriebel et al., 2001; Kriebel et al., 1993). Cumulative exposure (ppm-minutes) summed over all previous weeks was not a significant predictor of changes in pulmonary function. The measurement of multiple measures of PEF per student in the studies by Kriebel et al. (2001; 1993) increased the precision of the mean value and, consequently, the statistical power to detect a significant change. Interpretation of the analyses by both Kriebel et al. and Uba et al. is complicated by the consideration that class attendance as well as formaldehyde concentrations decreased over the semester in the studies (Kriebel et al., 2001; Uba et al., 1989).

Table 1-6. Formaldehyde effects on pulmonary function in laboratory settings (changes over <1 year)

Study and design	Results
Reference: Uba et al. (1989) Panel study, California **Population:** 96 medical students (72.5% participation) during a 7-month anatomy class meeting twice a week for 4 hours. Mean age: 24.3 years, 88% white, 73.8% male, nonsmokers, 12 asthmatics. **Exposure:** Personal sampling monitors (impingers) in the breathing zone, 32 samples during different class periods in 7-month period. Short-term samples (*N* = 16) for peak concentrations during dissection. Range of TWA formaldehyde: below LOD (0.05 ppm) to 0.93 ppm (0.06 to 1.14 mg/m^3).[a] Monthly averages in September, October, and May: 0.6, 0.8, and 0.1 ppm (0.74, 0.98, and 0.12 mg/m^3),[a] respectively. Peak concentrations: During dissection: mean 1.9 ppm (2.3 mg/m^3),[a] range 0.1 to 5.0 ppm (0.12 to 6.1 mg/m^3),[a] observing dissection: mean 1.2 ppm (1.5 mg/m^3)[a] range 0.2 to 2.0 ppm (0.25 to 2.5 mg/m^3).[a] **Methods:** Pre- (noon) and postlab spirometric measures (ATS methods) taken before the class began, after the first 2 weeks, and after 7 months. Analyzed using repeated measures ANOVA, adjusted for sex. **Evaluation:**[a] SB: ; IB: ; Cf: ; Oth: ; Overall Confidence: **High**	**Pulmonary function by test day (mean ± SD) (*N* = 96)** Before exposure (Day 1): FVC (L) 5.246 ± 1.025; FEV_1 (L) 4.379 ± 0.846; $FEF_{25–75}$ (L/sec) 4.492 ± 1.216; FEV_1/FVC 0.835 2 Weeks: FVC (L) 5.277 ± 1.027; FEV_1 (L) 4.409 ± 0.824; $FEF_{25–75}$ (L/sec) 4.484 ± 1.151; FEV_1/FVC 0.836 7 months: FVC (L) 5.308 ± 1.027; FEV_1 (L) 4.399 ± 0.823; $FEF_{25–75}$ (L/sec) 4.392 ± 1.198; FEV_1/FVC 0.829
Reference: Kriebel et al. (2001) Panel study, USA **Population:** 51 gross anatomy students (out of 54 total) during a 12-week class meeting once per week for 2.5 hours. Mean age: 24.9 years, 23.7% male, two current smokers, four with history of asthma. **Exposure:** Continuous monitoring in six homogenous sampling zones (LOD = 0.05 ppm). 12-minute work-zone concentrations calculated per student using sampling data and recorded work locations. Geometric mean concentration: 0.7 ppm (0.9 mg/m^3)[a] (GSD: 2.13 ppm). Peak 12-min concentration: 10.91 ppm (13.4 mg/m^3).[a] Average concentration: 1.1 ppm (1.35 mg/m^3)[a] (SD = 0.56 ppm). Concentrations decreased over 12-week semester. **Methods:** Spirometry (FEV_1, FVC) using ATS criteria before 1st exposure and during 10th week. Pre- and postlab PEF measurements obtained for at least 1 week for 38 students. PEF as fraction of value before 1st lab session; individual pre-lab and cross-lab change data analyzed together in relation to recent, average, and cumulative formaldehyde in single generalized estimating equations model. Generalized estimating equations regression	Exposure metrics: Recent exposure = mean concentration during 2.5-hour lab; cumulative exposure = ppm-minutes for all previous weeks; past average exposure: Cumulative exposure divided by total number of minutes of exposure. **PEF as fraction of baseline (before 1st lab) (L/s per ppm)** Recent exposure: ß (SE) −1.05 (0.33); *p*-value 0.002 Recent exposure *ln(wk): ß (SE) 0.69 (0.24); *p*-value 0.004 Past average exposure: ß (SE) −0.52 (0.30); *p*-value 0.08 Cold on lab day: ß (SE) −1.67 (0.41); *p*-value 0.001 No association with cumulative exposure. Pulmonary function among asthmatics not

Study and design	Results
adjusted for cold on lab day. **Evaluation:**[a]  Attrition and declining concentration over course—bias to healthy individuals and toward null	different.
Reference: Kriebel et al. (1993) Panel study, USA **Population:** 24 clinical anatomy students (out of 25 total) during a 10-week anatomy class meeting once a week for 3 hours. Mean age 26, 42% male, 1 current smoker, five reported history of asthma. **Exposure:** Personal samples in the breathing zone, 1−1.5 hours sampling periods. Formaldehyde concentration geometric mean: 0.73 ppm (0.9 mg/m^3),[a] GSD 1.22; range: 0.49−0.93 ppm (0.6−1.14 mg/m^3); 8 samples. No trend in concentrations over semester. Pentachlorophenol: ND (LOD = 83 µg/m^3. **Methods:** PEF measured by trained students pre- and postlab and 1−3 times during lab using Mini-Wright peak flowmeters. Mean absolute value (SD) pre- and cross-lab change in pulmonary function analyzed in separate models using multivariate linear models, including asthma, asthma × week, eye and nose or throat symptoms. **Evaluation:**[a]  **Limited sample size**	**PEF (L/min) during course (mean ± SD) (*n* = 20)** Weeks 1−2 PEF (L/min) 538.9 (86.9) Weeks 9−10[a] PEF (L/min) 529.4 (88.4) Weeks 24−25 PEF (L/min) 536.6 (86.2) [a]End of course. Decrement over 10-week course, β = −2.7 ± 1.1 L/min per week; *p* = 0.01, Model included asthma, asthma × week, eye symptoms, nose symptoms.

[a]Evaluation of sources of bias or study limitations (see details in Appendix A.5.1 and A.5.3). SB = selection bias; IB = information bias; Cf = confounding; Oth = other feature of design or analysis. Extent of column shading reflects degree of limitation. Direction of anticipated bias indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact would be likely to be away from the null (i.e., spurious or inflated effect estimate).

Long-term formaldehyde exposure

Occupational exposure

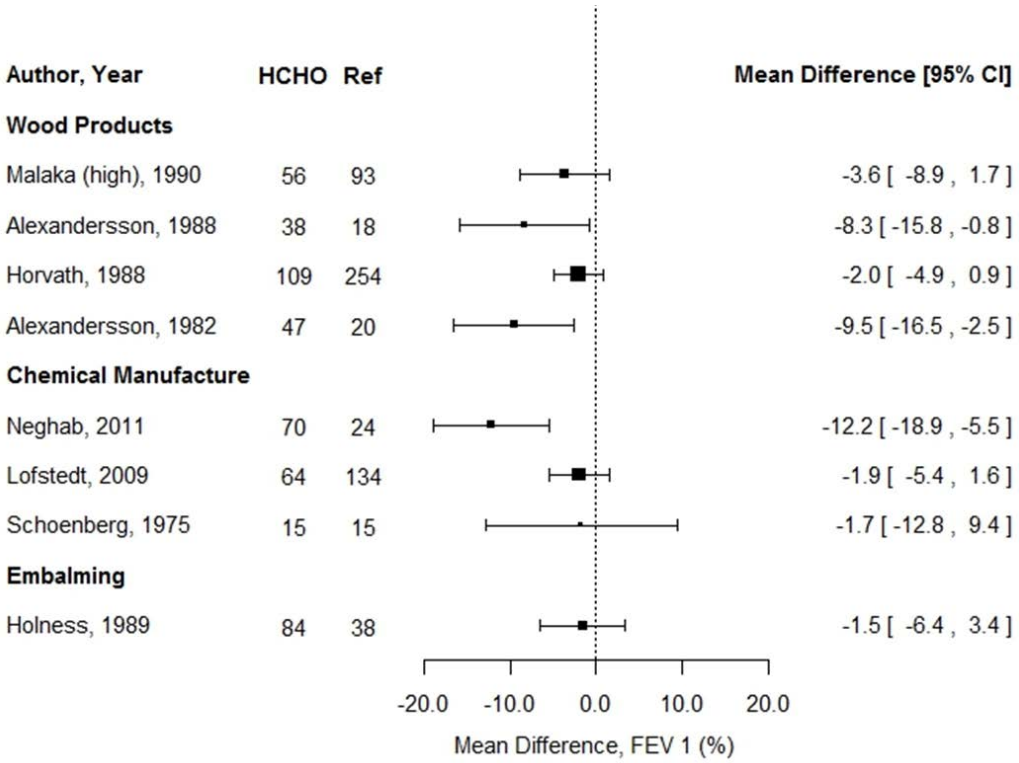
Overall, the set of occupational studies indicates that inhalation of formaldehyde over long periods at work is associated with declines in measures of pulmonary function. With only a few exceptions, average values for FEV_1, FVC, and FEF measured before a work shift at the beginning of the work week were lower among exposed workers than average values in their referent groups (see Table 1-7). However, the differences were relatively small and some were imprecise. The occupational groups under study were exposed to high average formaldehyde concentrations

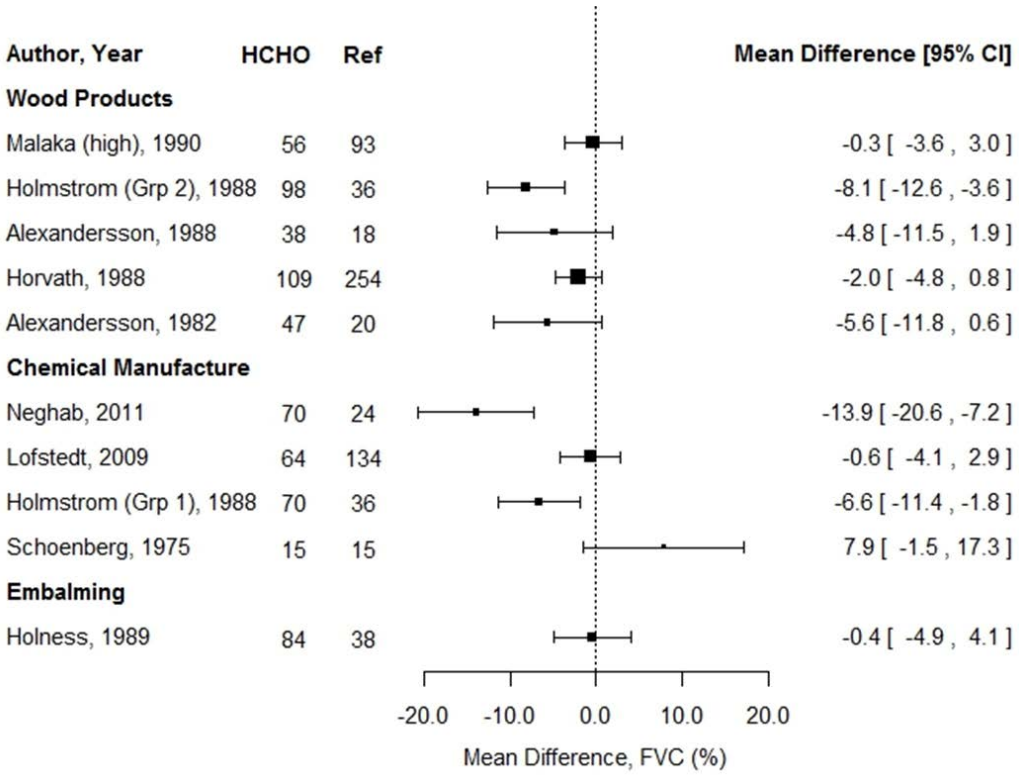
(≥0.2 mg/m^3) in a variety of industries, including funeral homes (embalming), wood products (plywood, cabinetry), chemical products (formaldehyde resins), and manufacturing. Employees had worked at these jobs for at least 5 years, and in a few studies, for more than 10 years. While a few studies conducted longitudinal analyses, most of the occupational studies were cross-sectional in design, recruiting only current employees, and likely were limited by lead time bias, a selection bias that results in attenuated effect estimates. In general, when only current employees are recruited for a cross-sectional study of an exposure that causes symptoms, there is a possibility that former workers may have left their jobs to reduce their exposure (lead time bias, healthy worker survival effect). Further, for studies that recruited from among those present on the day of the study, if employees were not present because of symptoms related to their formaldehyde exposure, attenuated effect estimates may have been observed (Alexandersson and Hedenstierna, 1988; Alexandersson et al., 1982).

The healthy worker effect and survivor (lead time) bias raised a concern for selection bias for several cross-sectional occupational studies, some of which had no other notable limitations (Löfstedt et al., 2011a; Neghab et al., 2011; Löfstedt et al., 2009; Milton et al., 1996; Malaka and Kodama, 1990; Nunn et al., 1990; Alexandersson and Hedenstierna, 1989, 1988; Holmström and Wilhelmsson, 1988; Alexandersson et al., 1982; Schoenberg and Mitchell, 1975). In addition, one study compared pulmonary function values in individuals exposed occupationally to individuals in a community population, raising a concern about the healthy worker effect and a possible bias toward a null association (Holness and Nethercott, 1989). Community populations include employed individuals, as well as people who are unemployed, ill or disabled, or retired, with a spectrum of health conditions. Among the prospective studies, loss to follow-up of exposed participants with symptoms because they moved to jobs with less or no exposure, also was evident (Löfstedt et al., 2011a; Nunn et al., 1990; Alexandersson and Hedenstierna, 1989). This type of selection bias also could result in an attenuated effect estimate. For other studies, exposure to other substances that affect pulmonary function, such as dust or environmental tobacco smoke, appeared to be more prevalent in the referent group, and was not adjusted for in the analysis, also resulting in a potential bias toward the null (Herbert et al., 1994; Main and Hogan, 1983). Despite the bias toward the null, most studies observed associations of measures of pulmonary function with formaldehyde exposure, which increased EPA's confidence in their findings.

Figure 1-5 presents forest plots of the difference in mean FEV_1, FVC, and FEF_{25-75} between exposed and referent groups for 10 study results. Overall, while no difference in means was found by a few of the 10 studies for one or more of the measures, most of the comparisons indicate that exposed groups had lower mean values compared to their respective referent group. Studies that reported only the absolute values or used a different analysis could not be plotted. One study of laboratory technicians found differences, even though the referent group had relatively high average formaldehyde exposure [0.125 mg/m^3; (Khamgaonkar and Fulare, 1991)]. Another study

among workers in the wood products industry reported a decrease in FEV_1/FVC but not other measures (Herbert et al., 1994).


Author, Year
HCHO
Ref
Mean Difference [95% CI]
Wood Products
Malaka (high), 1990 56 93 -3.6 [-8.9 , 1.7]
Alexandersson, 1988 38 18 -8.3 [-15.8 , -0.8]
Horvath, 1988 109 254 -2.0 [-4.9 , 0.9]
Alexandersson, 1982 47 20 -9.5 [-16.5 , -2.5]
Chemical Manufacture
Neghab, 2011 70 24 -12.2 [-18.9 , -5.5]
Lofstedt, 2009 64 134 -1.9 [-5.4 , 1.6]
Schoenberg, 1975 15 15 -1.7 [-12.8 , 9.4]
Embalming
Holness, 1989 84 38 -1.5 [-6.4 , 3.4]
-20.0 -10.0 0.0 10.0 20.0
Mean Difference, FEV 1 (%)


Author, Year
HCHO
Ref
Mean Difference [95% CI]
Wood Products
Malaka (high), 1990 56 93 -0.3 [-3.6 , 3.0]
Holmstrom (Grp 2), 1988 98 36 -8.1 [-12.6 , -3.6]
Alexandersson, 1988 38 18 -4.8 [-11.5 , 1.9]
Horvath, 1988 109 254 -2.0 [-4.8 , 0.8]
Alexandersson, 1982 47 20 -5.6 [-11.8 , 0.6]
Chemical Manufacture
Neghab, 2011 70 24 -13.9 [-20.6 , -7.2]
Lofstedt, 2009 64 134 -0.6 [-4.1 , 2.9]
Holmstrom (Grp 1), 1988 70 36 -6.6 [-11.4 , -1.8]
Schoenberg, 1975 15 15 7.9 [-1.5 , 17.3]
Embalming
Holness, 1989 84 38 -0.4 [-4.9 , 4.1]
-20.0 -10.0 0.0 10.0 20.0
Mean Difference, FVC (%)

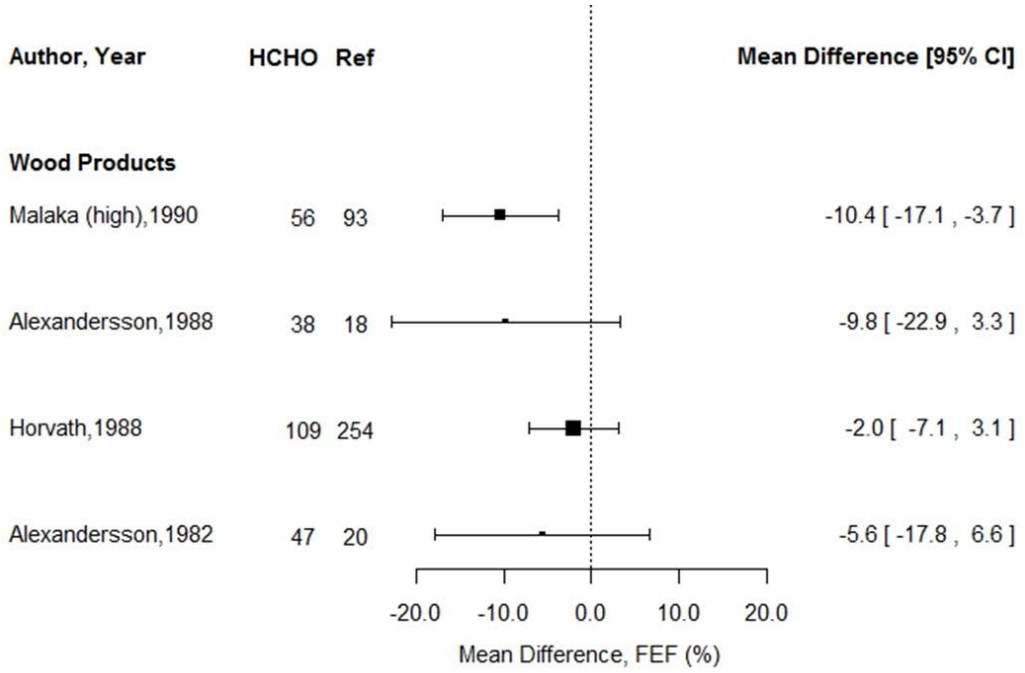


Figure 1-5. Forest plots depicting mean difference in pulmonary function (percentage predicted) between exposed and comparison groups for FEV_1, FVC, and FEF.

The plots include results from eight studies that reported the percentage of predicted normal function accounting for age, gender, and height, and three studies that reported mean absolute values and mean reference values for exposed and referent groups from which the percentage of the reference group could be calculated. The forest plot compares the mean difference between all exposed and referent groups when available, although one study reported appropriate data only for subgroups [e.g., low and high exposure categories; (Malaka and Kodama, 1990)]. The average of the standard deviations for a spirometric parameter specific to an exposure group, weighted by the size of the referent group, was used when no statistics from the individual study were available (Alexandersson and Hedenstierna, 1988; Holmström and Wilhelmsson, 1988; Alexandersson et al., 1982).

In addition to accounting for age, gender, and height, most of the studies adjusted for smoking in their statistical analyses or otherwise addressed potential confounding by smoking.

The studies evaluated three types of occupational settings—wood products industries, chemical production, and mortuaries—and employees in these industries were exposed to other chemical and physical agents that may co-occur with formaldehyde. Other common exposures in the wood products industry can include phenols and other solvents contained in resins and glues, terpenes, and dust, while embalming fluids include methanol. Phenol and terpenes are not expected to have strong effects on pulmonary function, particularly at the concentrations reported by the studies. However, occupational exposure to high concentrations of wood dust (>2 mg/m^3) has been associated with reductions in pulmonary function (Mandryk et al., 2000). Many of the studies of wood products workers reported measurements for dust, terpenes, and phenol, stating that levels were a fraction of occupational exposure limits. Studies that either adjusted for dust

levels or compared effects in formaldehyde-exposed groups with and without dust exposure did not find an independent effect by dust (Malaka and Kodama, 1990; Holmström and Wilhelmsson, 1988). The chemical industries included manufacture of formaldehyde products such as formaldehyde-phenol or formaldehyde-melamine resins and may involve exposures to phenols, other alcohols, VOCs, and other compounds, some of which may affect pulmonary function. However, since a pattern of reduction in pulmonary function was observed across several different exposure settings, all involving high formaldehyde exposure, confounding by a coexposure becomes less likely to be an alternative explanation for the observed associations. Three studies conducted longitudinal analyses of small groups of workers with continued exposure over 4–6 years (Löfstedt et al., 2011a; Nunn et al., 1990; Alexandersson and Hedenstierna, 1989). All three longitudinal studies measured FEV_1 and reported no change in the cohorts over the study period. However, one study of workers at a formaldehyde-urea resin manufacturing factory reported that among exposed nonsmokers, the annual decline was −45 mL/year (95% CI −28, −62 mL/year), which is 50% greater than the expected rate of age-related decline in FEV_1 in nonsmokers (29 mL/year Redlich et al., 2014; Lee and Fry, 2010). The annual decline among unexposed nonsmokers in this study was −29 mL/year, consistent with the expected rate of decline with age. In addition, Alexandersson and Hedenstierna (1989) reported a decline in FEF_{25-75} at a TWA concentration of 0.42–0.5 mg/m^3. FEF_{25-75} percentage among the carpentry workers declined by −168 ± 46 mL/second (10.1 L/minute) for each year of exposure over a 5-year period ($p < 0.001$). There was a larger decrease among nonsmokers compared to smokers, which might not be surprising since decreased pulmonary function is associated with smoking (−212 mL/sec/yr and −60 mL/sec/yr, respectively). The annual decrease was corrected for normal aging and reference pulmonary function spirometry values. The number of years that participants were followed by the three studies, 4–6 years, is the minimum length of time considered adequate to observe changes with time (Redlich et al., 2014), and the size of the exposure groups was quite small. Given the large amount of within-person variability in these measures when assessed over time, these studies would have had limited sensitivity to detect a small longitudinal change. Further, the studies were limited by potential differential loss to follow-up of exposed individuals who may have changed jobs or left the industry because of the irritation effect of formaldehyde. Despite the low sensitivity of these studies, some declines in FEV_1 and FEF_{25-75} were reported.

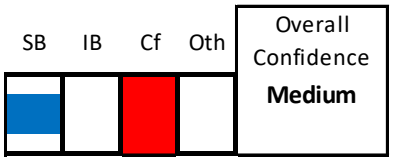
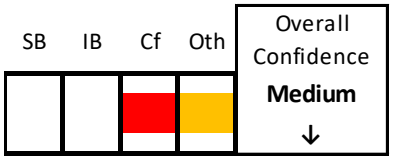
Duration of work in an exposed job was associated with decreased pulmonary function values in two studies (Neghab et al., 2011; Schoenberg and Mitchell, 1975), but not others (Holmström and Wilhelmsson, 1988; Horvath et al., 1988; Alexandersson et al., 1982). These analyses controlled for age, height, gender, and cigarette smoking. One study examined associations with cumulative exposure (ppm-years) and observed reductions in pulmonary function measures (FEV_1, FEV_1/FVC, and FEF_{25-75}) among male employees at a plywood company who had worked an average of 6–7 years (Malaka and Kodama, 1990). In addition to other relevant covariates, this analysis controlled for cigarette smoking and dust levels in the regression model.

Another study among wood products employees reported no association with a cumulative exposure measure, but did not present the results quantitatively (Holmström and Wilhelmsson, 1988).

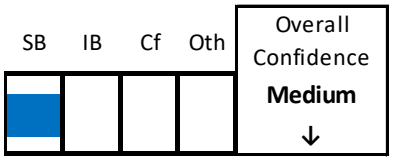
Table 1-7. Formaldehyde effects on pulmonary function in occupational settings (long-term effects)

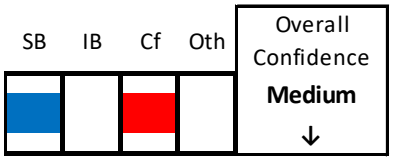
Study and design	Results
Prevalence studies	
Reference: Horvath et al. (1988) Cross-sectional study, Wisconsin. **Population:** 109 exposed (workers at a particleboard and molded products operation, 68.6% of all exposed), average age 37.4 ± 11.7 years, 57% males; average work duration in exposed: 10.3 years (1–20 years). 254 unexposed (workers from nearby food processing facilities; average age 34.2 ± 12.1 years, 44% male). 53% current and former smokers. **Exposure:** 8-hour TWA measured using personal passive monitors on the day of the exam (LOD 0.15 mg/m^3). Area levels measured with an active sampling train (impingers). TWA 0.69 ppm, range 0.17–2.93 ppm (0.85 mg/m^3, range 0.21–3.60 mg/m^3),[a] and 0.05 ppm, range 0.03–0.12 ppm (0.062 mg/m^3, range 0.037–0.15 mg/m^3)[b] in the exposed and unexposed industries, respectively. Other exposures in exposed: Respirable particulates (PEL 5 mg/m^3): median 0.11 mg/m^3; phenol (PEL 5 ppm): mean 0.15 ppm; carbon monoxide (PEL 50 ppm): mean 7.35 ppm; sodium hydroxide (PEL 2 mg/m^3): 0.4–0.21 mg/m^3; nitrogen dioxide: ND; acrolein: ND. **Methods:** Spirometry (volumetric) before and after the work shift. Pulmonary function (ATS methods) as percentage of predicted normal compared between exposed and unexposed (unpaired *t*-test); multiple linear regression of baseline absolute values by exposure group, adjusting for age, height, sex, and smoking. **Evaluation:**[a] SB: ☐ IB: ☐ Cf: ☐ Oth: ☐ Overall Confidence: **High**	**Comparison of mean preshift pulmonary function (percentage predicted (SD))** Exposed / Referent FEV_1 (L): 103 (13) / 105 (13) FVC (L): 105 (12) / 107 (13) FEV_1/FVC: 96 (8) / 95 (8) PEFR (L/sec): 100 (23) / 103 (22) FEF_{25-75} (L/sec): 83 (22) / 85 (25) FEF_{25} (L/sec): 6.91 (2.12) / 6.73 (1.98) FEF_{50} (L/sec): 4.5 (1.46) / 4.38 (1.43) FEF_{75} (L/sec): 1.63 (0.8) / 1.66 (0.77) $p > 0.05$ Exposure group was not associated with baseline absolute values in multiple linear regression models. Work duration was not associated with preshift pulmonary function.

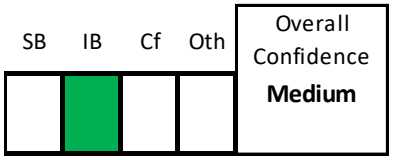
Study and design	Results
Reference: Neghab et al. (2011) Cross-sectional study, Iran. **Population:** 70 male workers at a local melamine-formaldehyde resin-producing factory with current exposure to formaldehyde and ≥2 years work history (mean age 38.2 ± 8.4 years, work duration 13.2 ± 7.8 years, 24.3% smokers). 24 healthy males from the same industry and comparable socioeconomic and demographic status, and no present or former formaldehyde or other exposure to respiratory irritants. 100% participation (mean age 40.0 ± 8.2 years, work duration 14.5 ± 8.1 years, 25% smokers). **Exposure:** Area samples (*N* = 7) in seven workshops with exposure and one area sample in office area (sampling in different time points and shifts). Sampling time 40 minutes. Exposed mean formaldehyde: 0.78 ± 0.4 ppm (0.96 ± 0.49 mg/m^3)[b]; referent: not detected. **Methods:** Pulmonary function tests (Vitalograph COMPACT), ATS methods) before and at the end of the work shift on the first working day of week, percentage predicted. Group comparisons and cross-shift difference among exposed, and multiple linear regression analysis of pulmonary function comparing exposed and referent adjusting for smoking, age, weight, height. **Evaluation:**[a] SB: ■ IB: □ Cf: □ Oth: □ Overall Confidence: **Medium** ↓ Healthy worker survivor bias	**Percentage predicted pulmonary function (mean (SD))** Exposed Preshift (*N* = 70) / Referent (*N* = 24) VC: 77.9 (12.0)[a] / 99.3 (21.0) FVC: 86.6 (14.5)[a] / 100.5 (14.5) FEV_1: 86.6 (14.4)[a] / 98.8 (14.6) FEV_1/FVC: 100.2 (8.8) / 98.8 (5.3) PEF: 90.9 (15.9) / 89.8 (31.2) [a]Difference between exposed and referent, $p < 0.025$ **Difference in pulmonary function between exposure groups** Regression coefficients (percentage difference; SD provided by author; *p*-value): VC −21.43 (3.48) ($p = 0.001$) FVC −13.88 (3.44) ($p = 0.001$) FEV_1 −12.23 (3.42) ($p = 0.001$) **Change in pulmonary function per year work duration** Regression coefficients (unit change/year): VC −0.1 ($p = 0.315$) FVC −0.43 ($p = 0.02$) FEV_1 −0.375 ($p = 0.035$) FEV_1/FVC −0.1 ($p = 0.225$) PEF −0.28 ($p = 0.2$)
Reference: (Herbert et al., 1994) Cross-sectional study, Canada. **Population:** 99 oriented strand board workers (exposed, 98% participation), mean age 35.4 years, 51.5% smokers; work duration 5.1 years; 165 oil/gas field plant workers (not exposed to formaldehyde or oil and gas vapors) from same geographic area (82% participation), mean age 34.9 years, 27.9% smokers, work duration 10 years. Excluded 14 workers in referent with hydrogen sulfide exposure. **Exposure:** TWA formaldehyde and dust concentrations at OSB plant based on 21 hours of continuous sampling in the breathing zone at five work sites on 2 separate days. Formaldehyde range: 0.07–0.27 ppm (0.09–0.33 mg/m^3),[b] dust mean: 0.27 mg/m^3, 2.5 µm diameter. **Methods:** Spirometric testing (volumetric, best of five satisfactory maneuvers) at start of work shift and after 6 hours (ATS guidelines). Analysis ANCOVA controlling for age, height, and smoking.	**Preshift pulmonary function (mean) by exposure group** OSB / Oilfield FEV_1 (mL): 4.203 / 4.223 FVC (mL): 5.364 / 5.257 FEV_1/FVC (%): 78.6[a] / 80.3[a] [a]$p = 0.028$ **Risk of airway obstruction (FEV_1/FVC < 75%) by smoking category (*N* = number below criteria)** Odds Ratio / 95% CI Nonsmokers (17): 1.68 / 0.54, 5.25 Exsmokers (15): 1.08 / 0.32, 3.64 Current (25): 2.98 / 1.10, 8.07

Study and design	Results
Evaluation:[a]  Healthy worker survivor bias; possible irritant exposure in referent, coexposure to dust.	
Reference: Khamgaonkar and Fulare (1991) Cross-sectional study, India. **Population:** 74 individuals working in anatomy and histopathology departments at three colleges and exposed to formaldehyde. Selected every 2nd person from occupational list. Comparison group matched by age and sex (*N* = 74) (individuals not working in laboratories with formaldehyde). Comparable for mean height and weight. Excluded persons with a history of pulmonary disease before their present occupation. **Exposure:** Multiple 30-minute area samples collected in the breathing zone in both the exposed (*N* = 43) and unexposed (*N* = 18) areas. Mean (SD) exposed 1.00 ppm (0.556), range 0.036–2.27 ppm (1.23 mg/m^3 (0.68), range 0.044–2.79 mg/m^3).[b] Referent 0.102 ppm (0.115), range 0–0.52 ppm (0.125 mg/m^3 (0.141) range ND–0.64 mg/m^3).[b] **Methods:** Pulmonary function tests on a subset of 37 exposed and 37 comparison individuals on a Monday morning after days of no exposure. **Evaluation:**[a]  Possible exposures in referent that affect pulmonary function; exposure to formaldehyde in referent labs.	**Mean pulmonary function values by exposure group** Exposed (*N* = 37) / Referent (*N* = 37) FVC (L): 2.18 / 2.63[a] MMEFR (L/sec): 1.55 / 2.71[b] FEV_1 (%): 60.68 / 78.74[a] [a]$p < 0.01$, [b]$p < 0.05$
Reference: Malaka and Kodama (1990) Cross-sectional study, Indonesia. **Population:** Male employees at plywood company. Exposed workers (*N* = 93) randomly selected with stratification by smoking status and work duration (<5 and ≥5 years; 93% participation), mean age 26.6 years, work duration 6.2 ± 2.4 years; unexposed group (*N* = 93) matched for age, ethnicity, and smoking status (53%), mean age 28.8 years, similar in height, work duration 6.7 ± 2.3 years, worked in areas where formaldehyde was not used, and had no previous or current exposure to formaldehyde based on occupational histories; 93% participation rate. **Exposure:** Area sampling and personal monitoring. Average exposed 0.9 ppm (1.1 mg/m^3),[b] range 0.22–3.48 ppm	**Mean baseline spirometric values (adjusted for dust) (SD)** Exposed / Referent FEV_1/FVC (%): 84.7 (6.5) / 86.9 (4.9)[a] FEV_1 (L): 2.78 (0.41) / 2.82 (0.30)[a] FVC (L): 3.28 (0.44) / 3.37 (0.36) $FEF_{25-75\%}$ (L/sec): 3.04 (0.76) / 3.44 (0.78)[a] [a]$p < 0.005$

Study and design	Results
(0.27–4.28 mg/m^3)[b]; calculated by EPA from weighted average of area specific averages in Table 2 in the paper; referent 0.003–0.07 ppm (0.0037–0.09 mg/m^3).[b] Cumulative exposure measure developed using area concentrations and duration in current job (mean 6.29 ppm-year, SD 2.72). Categorized into none (*N* = 93), low (<5 ppm-yr) (*N* = 37), and high (≥5 ppm-yr) (*N* = 56). Other exposures: average total dust 1.35 mg/m^3, average respirable dust 0.6 mg/m^3. **Methods:** Baseline (Monday) and cross-shift spirometric measurements (volumetric) followed ATS methods. Pulmonary function (percentage of expected function) by category of cumulative exposure analyzed using analysis of covariance. Stepwise regression of pulmonary function on cumulative formaldehyde (continuous) adjusted for age, height, weight, cigarettes/day, and dust. **Evaluation:**[a] SB IB Cf Oth — Overall Confidence **Medium** ↓ Healthy worker survivor bias	**Multiple regression model of pulmonary function**[a] β(per ppm-yr FA) FEV_1/FVC (%) −0.347[b] FEV_1 (L) −0.015[b] FVC (L) NS $FEF_{25–75}$ (L/sec) −0.043[b] [a]adjusted for age, height, weight, cigarettes/day, and dust. [b]$p < 0.05$ **Mean pulmonary function (percentage predicted) (SD) by Categories of Cumulative Exposure** None / Low / High FEV_1 94.4 (20.0) / 87.4 (10.2) / 90.8 (12.7) FVC 92.0 (9.2) / 87.1 (8.4) / 91.7 (10.4) FEV_1/FVC 86.9 (4.9) / 85.3 (6.4) / 84.4 (6.5) $FEF_{25–75}$ 90.4 (20.0) / 79.5 (18.2) / 80.0 (20.1) Dust was not associated with any pulmonary function measures.
Reference: Holness and Nethercott (1989) Cross-sectional study of funeral workers, Canada. **Population:** 67 currently active embalmers and 17 formerly active, recruited through a list of funeral homes from a district funeral directors association (86.6% participation). Average work duration 10 years. Unexposed group (*N* = 38) recruited from large service organization and paid student volunteers. **Exposure:** Average concentration from two area samples (impingers), measured during embalming procedures lasting from 30 to 180 minutes, 0.36 ± 0.19 ppm, range 0.08–0.81 ppm (0.44 ± 0.23 mg/m^3, range 0.10–1.0 mg/m^3).[b] Unexposed average concentration: 0.02 ppm (0.025 mg/m^3).[b] **Methods:** Information on symptoms, past and family medical history, and work practices by questionnaire. Spirometry (volumetric) tests on 22 embalmers before and after embalming procedure and on 13 referents 2–3 hours after first test. Pulmonary function (percentage predicted) compared using multiple regression, correcting for age, height, and pack-years smoked. **Evaluation:**[a] SB IB Cf Oth — Overall Confidence **Medium**	**Comparisons of baseline pulmonary function (percentage predicted) (SD)** Exposed (*N* = 84) / Unexposed (*N* = 38) FVC 100.5 (12.3) / 100.9 (11.5) FEV_1 99.2 (12.9) / 100.7 (12.9) FEV_1/FVC 98.4 (7.9) / 99.4 (8.7) FEF_{50} 104.8 (29.7) / 110.3 (34.5) FEF_{75} 76.2 (32.9) / 86.6 (36.0) Active (*N* = 67 / Inactive (*N* = 17) FVC 100.7 (12.2) / 95.8 (12.0)[a] FEV_1 100.8 (12.19) / 93.1 (14.1)[b] FEV_1/FVC 98.9 (7.8) / 96.6 (8.0) FEF_{50} 107.5 (28.7) / 94.1 (32.3) FEF_{75} 80.8 (33.1) / 57.1 (24.7) [a]$p = 0.0385$, [b]$p = 0.0652$

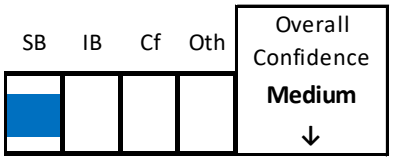
Study and design	Results
Comparison groups selected from different source populations.	
Reference: Alexandersson and Hedenstierna (1988) Cross-sectional study, carpentry shop, Sweden. **Population:** 38 exposed employees working with acid-hardening lacquers for the previous 12 months [mean age (SD): 34 (10) years, mean duration employment 7.8 years] and at work on the study day. 18 referent employees at the same company (mean age [SD] 37 [9] years). Asthmatics excluded. **Exposure:** Personal exposure monitored during three to four 15-minute periods during the workday. No formaldehyde measurements reported for referent group. TWA 0.40 mg/m^3, range: 0.12−1.32 mg/m^3. Peak concentration (15 minute) 0.70 mg/m^3, range 0.14−2.6 mg/m^3. Additional measurements of solvents and dust (4 hr)—considered very low compared to Swedish threshold limit values. **Methods:** Spirometry (volumetric) on Monday after 2 days unexposed and again at end of shift on second day. Half of referent employees tested before and half tested after shift. Compared difference from sex, age, and height matched reference values. **Evaluation:**[a]  Healthy worker survivor bias; small samples.	**Pulmonary function before work on Monday (Mean difference from reference values)** Exposed (*N* = 38) / Referent (*N* = 18) Difference (SD) / Difference (SD) FVC (L): −0.24 (0.64)* / 0.03 (0.65) FEV_1 (L): −0.21 (0.51)** / 0.15 (0.42) FEV%: −0.7 (6.7) / 1.8 (5.3) FEV_{25-75} (L/sec): −0.10 (0.98) / 0.31 (0.76) *p < 0.05; **p < 0.01 Difference from reference values greater among nonsmokers than smokers.
Reference: Holmström and Wilhelmsson (1988) Cross-sectional study, Sweden. **Population:** 3 study groups: 70 individuals (87% male) in formaldehyde products group (mean age 36.9 years); 100 furniture workers exposed to formaldehyde and wood dust (93% males, mean age 40.5 years). Comparison group, 36 persons (56% male, mean age 39.9 years), primarily local government clerks. 100% participation. Mean duration of employment 10.4 years for exposed and 11.4 years for referent group. **Exposure:** Mean formaldehyde in 1985. Group 1: mean 0.26 ± 0.17 mg/m^3, range 0.05−0.5 mg/m^3, Dust ≤1 mg/m^3. Group 2: mean 0.25 ± 0.05 mg/m^3, range 0.2−0.3 mg/m^3, dust 1.65 ± 1.06 mg/m^3. Referent: mean 0.09 mg/m^3. Data on formaldehyde concentrations available 1979−1984 and from 1 to 2 hours personal sampling in breathing zone at different workstations in 1985. Mean annual exposure estimated for each participant from start of employment; dose-years.	**Pulmonary function values compared to expected by exposure group** FA exposed (*N* = 70) / FA-dust exposed (*N* = 98) / Referent (*N* = 36) **FVC** Observed: 4.979[a] / 4.929[a] / 4.539 Expected: 5.556 / 5.593 / 4.718 **FEV%** Observed: 80.8 / 78.3 / 81.4 Expected: 80.6 / 79.5 / 80.7 [a]paired *t*-test comparing observed to expected, p < 0.001. No correlation of FVC with cumulative formaldehyde dose or years of service >5 years.

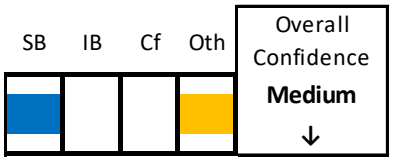
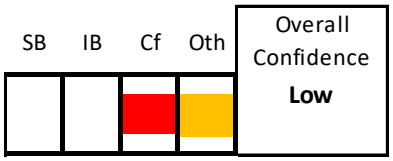
<table>
<tr><th>Study and design</th><th>Results</th></tr>
<tr><td>Other exposures (phenol, ammonia, epichlorhydrin, methanol, ethanol) <1% of occupational exposure limit.
Methods: Spirometric measures analyzed as percentage of expected normal based on age, sex, smoking, height, and weight.
Evaluation:[a]
 

Healthy workers; comparison groups selected from different source populations.</td><td></td></tr>
<tr><td>**Reference:** Levine et al. (1984b)
Cross-sectional study, USA, 1978.
Population: 105 white, male morticians attending postgraduate course (94% participation).
Exposure: # embalmings.
Exposure index: rank ordering of the total # embalmings; divided into categories of low and high exposure based on # bodies embalmed, matched on age (within 3 years).
Methods: Completed self-reported respiratory disease questionnaire (ATS) and detailed occupational history; pulmonary function testing (volumetric spirometer) (*N* = 99), analysis of 90 with complete data after excluding pipe and cigar smokers.
Evaluation:[a]
 

Uncertainty regarding assignment of exposure rank.</td><td>**Change in pulmonary function per unit exposure rank (*N* = 90)**
<table><tr><th>Variable</th><th>Exposure Rank</th></tr><tr><td>FVC (L)</td><td>+0.0003</td></tr><tr><td>FEV_1 (L)</td><td>−0.0001</td></tr><tr><td>FEV_1/FVC</td><td>+0.0019</td></tr><tr><td>$FEF_{25–75}$ (L/s)</td><td>−0.0016</td></tr><tr><td>$FEF_{25–75}$/FVC</td><td>−0.0002</td></tr><tr><td>Rank FVC/predicted</td><td>−0.0547</td></tr><tr><td>Rank FEV_1/predicted</td><td>+0.0229</td></tr><tr><td>$FEF_{25–75}$/predicted</td><td>−0.0676</td></tr></table>Coefficients were not statistically significant ($p > 0.05$).
Multiple regression equations adjusted for age, height, number of pack-years, and exposure index.

Comparison of pulmonary function by exposure group (low, high) in nonsmokers (*N* = 24); mean (SE)
<table><tr><th>Measure</th><th>Low</th><th>High</th></tr><tr><td>FVC (L)</td><td>4.69 (0.22)</td><td>4.56 (0.32)</td></tr><tr><td>FVC % predicted</td><td>100.5 (3.1)</td><td>98.9 (3.4)</td></tr><tr><td>FEV_1 (L)</td><td>3.80 (0.22)</td><td>3.64 (0.27)</td></tr><tr><td>FEV_1 % predicted</td><td>108.9 (3.3)</td><td>105.5 (4.1)</td></tr><tr><td>FEV_1/FVC</td><td>0.807 (0.02)</td><td>0.797 (0.02)</td></tr><tr><td>$FEF_{25–75}$ (L/sec)</td><td>4.28 (0.48)</td><td>3.88 (0.49)</td></tr><tr><td>$FEF_{25–75}$ % predicted</td><td>117.9 (8.8)</td><td>110.5 (11.7)</td></tr></table>Groups matched on age, similar in height
Group comparisons, $p > 0.05$</td></tr>
</table>

Study and design	Results
Reference: Alexandersson et al. (1982) Cross-sectional study, Sweden. **Population:** 47 exposed carpentry workers employed at the plant for >1 year and at work on study day (mean age 35 years, mean duration 5.9 years) and 20 unexposed employees. No asthmatics were included. **Exposure:** TWA concentration, measured using personal sampling over a working day, 0.47 mg/m^3 (range 0.05–1.62 mg/m^3). Other exposures: Terpenes: range ND–9 mg/m^3; dust (all particle sizes) mean 0.5 mg/m^3 (range 0.3–0.7 mg/m^3). **Methods:** Spirometric measurements (volumetric, ATS methods) Monday morning preshift and after work for exposed. Pulmonary function was measured in the unexposed in the morning or the afternoon. Statistical analysis of preshift values and cross-shift change, two-tailed Student's *t*-test. Linear regression of association with duration of employment. **Evaluation:**[a]  Healthy worker survivor bias.	**Comparisons of pre-shift mean pulmonary function (SD)** Exposed (*N* = 47) / Referent (*N* = 20) FVC (L): 5.73 (0.14) / 6.0 (0.2) FEV_1 (L): 4.52 (0.12)[a] / 4.86 (0.15) FEV%: 79.2 (1.0) / 80.7 (1.32) MMF (L/sec): 4.94 (0.2) / 5.08 (0.31) CV%: 16.7 (1.07) / 17.1 (1.5) [a]Difference from reference value, $p = 0.08$ No association with duration of employment (quantitative results not presented).
Reference: Schoenberg and Mitchell (1975) Cross-sectional study, USA. **Population:** Employees using formaldehyde-phenol resin in the filter acrylic wool filter department of a filter manufacturing plant. Exposed production line workers and supervisors, *N* = 63 (94% of recruited); younger age and cigarette smoking (packs/yr) less among present line group compared to never on-line. **Exposure:** Measurements taken by insurance company during same month; 0.5–1 mg/m^3. 3 breathing zone samples, 10.6–16.3 mg/m^3. Exposure groups Present line, *N* = 40 Previous line, *N* = 8 Never-on-line, *N* = 15 Some in never-on-line had some exposure. Other exposures: Phenol, four breathing zone samples, 7–10 mg/m^3. **Methods:** Standardized questionnaire, pulmonary function measured before and after shift on Monday and Friday (pneumotachometer); 5 maneuvers, average of best two used to calculate values; compared to predicted based on age, height, and gender.	**Monday preshift pulmonary function by exposure duration (mean, SEM)** Never (*N* = 15) / <1 year (*N* = 15) / 1–4 years (*N* = 10) / >5 years (*N* = 15) FVC[a]: 104.3 (2.9) / 103.7 (2.9) / 108.8 (2.7) / 112.2 (3.8) FEV_1[a]: 98.9 (3.6) / 100.7 (3.1) / 99.6 (3.5) / 97.2 (4.4) FEV_1/FVC, %[b]: 79.4 (1.3) / 79.9 (1.4) / 74.1 (2.2) / 71.2 (2.6)[c] $MEF_{50\%}$/FVC, %[b]: 90.3 (4.0) / 87.1 (6.1) / 73.6 (8.4) / 64.0 (6.2)[d] [a]percentage predicted [b]standardized to cigarette consumption of 15 pack-years [c]Different from never-on-line group ($p < 0.05$) [d]Different from never-on-line group ($p < 0.005$)

Study and design	Results
Evaluation:[a]  Healthy survival effect. Multiple exposures: formaldehyde, phenol. Phenol is an irritant but is not expected to be associated with pulmonary function at these levels.	
Reference: Main and Hogan (1983) Cross-sectional study, USA. **Population:** 21 exposed individuals working in two mobile trailers for 34 months (mean age 38 ± 9 years, 76% male, 19% nonsmokers). 18 referent individuals who did not work in the trailers (mean age 30 ± 6 years, 50% male, 22% nonsmokers). **Exposure:** Three 1-hour area samples using impingers taken on four occasions (August, September, December, April) always on a Monday. At least one sample from each office in both trailers. Concentration range 0.12 to 1.6 ppm (0.15–1.97 mg/m^3).[b] **Methods:** Volumetric spirometer, percentage predicted FEV_1 and FVC stratified by smoking status (unadjusted group means compared using t-tests). **Evaluation:**[a]  Comparison groups selected from different sources (possible unmeasured confounding), ETS in referent; small sample size (low sensitivity).	**Mean pulmonary function (percentage predicted)** Exposed (N = 14) / Unexposed (N = 17) FEV_1: 98 / 99 FVC: 94 / 97 FEF_{50}: 93 / 90 FEF_{75}: 69 / 70 %Δ FEF_{50}: 55 / 43
Longitudinal studies	
Reference: Nunn et al. (1990) Prospective study at chemical factory manufacturing urea formaldehyde resin, Duxford, England. **Population:** Exposed: 164 workers, aged 25 or older, exposed to free formaldehyde in 1980; 29% <35 years, 46% current smokers, 22% employed >22 years; referent: 129 workers from bonded structures division at same factory in 1980; 39% <35 years, 45% current smokers, 4% employed >22 years. Followed over 6 years (1980–1985). **Exposure:** Area samples (1–6 hours) periodically, 1979 and 1985, and personal sampling for representative exposed workers, 1985 to 1987. Exposure prior to 1976 based on subjective determinations and knowledge of process changes and industrial hygiene measures. Pre-1979 levels estimated as low, medium, and high, corresponding to an 8-hour day.	**Decline in FEV_1 with age by smoking history (mean slope, mL/year (95% CI)** Never: −45 (−28, −62), N = 26; −29 (−7, −51), N = 13 Ex-smoker: −33 (−20, −46), N = 34; −40 (−26, −54), N = 31 Current: −46 (−33, −59), N = 57; −46 (−32, −61), N = 36 Total: −42 (−34, −51), N = 117; −41 (−32, −50), N = 80 Among those lost to follow-up, FEV_1 was less than predicted among 75% of 12 exposed and 33% of 27 referent compared to 36% of 117 exposed and

Study and design	Results
TWA of 0.1–0.5 ppm (0.12–0.62 mg/m^3),[b] 0.6–2.0 ppm (0.74–2.46 mg/m^3),[b] and >2 ppm, respectively. Other exposures: Records examined for random sample of 20 per group; more exposure to asbestos, carbon and glass fibers, siliceous fillers, aliphatic amines in referent group; both groups exposed to phenol and urea formaldehyde resin (not free formaldehyde). **Methods:** Data on FEV_1 and FVC (volumetric spirometer) highest of two readings within 5% of each other) obtained from routine annual health screenings conducted by the same nurse throughout the study period. Follow-up complete for 76% of exposed and 74% of unexposed. FEV_1 values adjusted for height (FEV_1/height^3), regressed on time of screening visit for each worker, adjusted for age in 1980, smoking status in 1980, and at final assessment, maximum and mean exposure, assessment level, and total duration of exposure. **Evaluation:**[a] SB IB Cf Oth | Overall Confidence **Medium** ↓ Concern for selection bias: loss to follow-up higher among exposed with low pulmonary function compared to referent; referent exposed to other potential irritants.	45% of 80 referent followed.
Reference: Alexandersson and Hedenstierna (1989) Prospective occupational study, follow-up of Alexandersson et al. (1982), Sweden. **Population:** 47 exposed cabinetry workers and 20 unexposed workers examined in 1980, 34 exposed and 18 unexposed were examined again in 1984. Of the 34 originally exposed, 13 had been reassigned to other unexposed jobs. Average exposure duration among exposed and transferred workers: 11 years. **Exposure:** Personal monitoring during 3 or 4 15-minute periods during workday. TWA 0.42 ± 0.27 mg/m^3 in 1980 and 0.50 ± 0.12 mg/m^3 in 1984. Other exposures: terpenes ND; respirable dust: mean 0.1 ± 0.2 mg/m^3. **Methods:** Spirometric measures (volumetric, ATS methods) compared with reference values for sex, age, height, and weight. 5-year change corrected for age-dependent change. Results presented by smoking status. **Evaluation:**[a] SB IB Cf Oth | Overall Confidence **Medium** ↓ Healthy worker survivor bias; small sample.	**Annual change (1980–1984) in exposed, mean (SD)** Smokers (N = 10) / Nonsmokers (N = 11) / All (N = 21) FVC (mL/yr): −15 (24) / −10 (26) / −12 (16) FEV_1 (mL/yr): −15 (21) / −31 (20) / −24 (20) FEV_1/FVC (%/yr): −0.1 (0.4) / −0.4 (0.2)[a] / −0.3 (0.3) FEF_{25-75} (mL/s/yr): −60 (69) / −212 (66)[a] / −168 (46)[a] CV% (%/yr): −0.6 (0.3) / 0.2 (0.4) / −0.2 (0.3) [a]p < 0.001, compared to predicted normal Pulmonary function was unchanged among referent group. Pulmonary function was correlated with formaldehyde concentration in unadjusted regression analysis. Pulmonary function improved after a 4-week holiday.

Study and design	Results
Reference: Löfstedt et al. (2011b) Prospective study; follow-up of Löfstedt et al. (2011a), Sweden. **Population:** One of four foundries opted out of follow-up, plus 39 were lost to follow-up. 25 of 64 workers from 2009 study involved with Hot Box method; 55 of 134 referents from 2009 study working outside core-production and die-casting halls; not exposed to chemicals. Prevalence of childhood allergy lower in exposed than in referent in 2005 (4 vs. 31%, $p < 0.05$); higher prevalence of nasal symptoms among referent in 2005. **Exposure:** Formaldehyde, isocyanic acid, and methyl isocyanate measurements on same day as spirometry. Monoisocyanates: Mean of 4 to 5 15-minute samples Formaldehyde: sampling over entire shift Individual exposure estimated for 2001 and 2005 (mg/m^3); levels 50% lower in 2005 (mean, range). 2001 0.098 (0.094) 0.014–0.44 2005 0.045 (0.043) 0.01–0.19 Correlation low between formaldehyde and either methyl isocyanate ($r = -0.20$) or isocyanic acid ($r = 0.09$); 61% of exposed were coremakers where formaldehyde levels were highest and isocyanate levels were lower. **Methods:** Pulmonary function by spirometry (volumetric) using ATS guidelines. Pre- and postshift after 2 days with no exposure. Percentage predicted using Swedish reference. Regression analysis of formaldehyde adjusted for MIC, smoking, and childhood allergy. **Evaluation:**[a] SB IB Cf Oth Overall Confidence **Low** Limited sample size to detect small changes between 2001 and 2005; concern for survivor bias; coexposure to methyl isocyanate and isocyanic acid in exposed—unable to differentiate for comparisons of change from 2001 to 2005.	Decreased across shift pulmonary function reported in 2001 was correlated with decreased preshift pulmonary function in 2005. VC $r = 0.51$, FEV $r = 0.57$, $p < 0.05$ **Preshift value and change in pulmonary function (percentage predicted), 2001–2005** **2001** / **2001–2005** Mean (SD) / Mean (SD) / Range **VC** Exposed 93.3 (12.1) −0.8 (4.2) −11.2–6.5 Referent 93.9 (10.8) −0.4 (3.8) −11.0–5.9 **FEV_1** Exposed 94.4 (11.6) −1.3 (5.5) −14.0–8.8 Referent 96.3 (11.6) 0.3 (5.3) −13.8–10.3 Across shift change was not different between exposure groups (data not provided). No association of formaldehyde with change in pulmonary function at follow-up in regression analysis (data not provided).

[a]Evaluation of sources of bias or study limitations (see details in Appendix A.5.1 and A.5.3). SB = selection bias; IB = information bias; Cf = confounding; Oth = other feature of design or analysis. Extent of column shading reflects degree of limitation. Direction of anticipated bias indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact would be likely to be away from the null (i.e., spurious or inflated effect estimate).
[b]Concentrations reported by authors as ppm or ppb converted to mg/m^3.

Exposure in residences or school

Adults

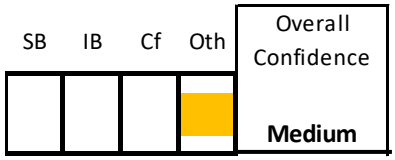
Results among four studies of residential exposure among adults are difficult to compare because different methods were used to assess pulmonary function and two of the studies did not report results quantitatively (Norback et al., 1995; Broder et al., 1988c) (see Table 1-8). A cross-sectional study of residential formaldehyde exposure in a large, representative sample in Arizona observed an association with declines in PEFR among adult smokers at formaldehyde concentrations between 0.049 and 0.172 mg/m^3, but not among the group as a whole (Krzyzanowski et al., 1990). Another study among elderly nursing home residents observed an elevated risk of low pulmonary function (defined as values falling in the lower 20% of the distribution) in association with formaldehyde concentrations above the median level measured in each nursing home (Bentayeb et al., 2015). The overall median and range of formaldehyde concentrations was 0.007 mg/m^3 and 0.001−0.021 mg/m^3, respectively, but the concentrations associated with elevated risks varied according to the median in each nursing home. Two additional studies that assessed effects of formaldehyde exposure on pulmonary function in primarily adult residential populations exposed to concentrations between 0.009 and 0.279 mg/m^3 reported no associations, although the outcomes evaluated by each study were not directly comparable (Norback et al., 1995; Broder et al., 1988c).

The study by Krzyzanowski et al. (1990), which used the most thorough exposure-assessment protocol and included repeated measurements of PEF (thus enhancing the ability to detect an association at the lower concentrations found in the homes) was interpreted with *high* confidence. Of the residential studies, only Krzyzanowski et al. (1990) examined effect modification by smoking status. Confidence in the regression results by Norbäck et al. (1995) is *low* because most of the measured formaldehyde concentrations were less than the LOD and the sensitivity of the study was low. Overall, results from the small set of studies suggest that adults in general did not experience declines in pulmonary function at average formaldehyde levels less than 0.05 mg/m^3; however, declines may be experienced at lower concentrations among susceptible subsets (e.g., elderly, smokers).

Table 1-8. Formaldehyde effects on pulmonary function among adults in residential settings

Study and Design	Results	
Reference: Krzyzanowski et al. (1990);Quackenboss et al. (1989c) Cross-sectional study, Arizona, USA. **Population:** A stratified random sample of 202 households of municipal employees, selected based on information about potential exposure (age of housing) and potential susceptibility obtained from an initial screening questionnaire. Households with children aged 5−15 years (613 adults and 298 children) were eligible for inclusion.	**Change in PEFR (L/min) in relation to indoor formaldehyde, ages >15 yrs. (*N* = 526; 8,463 observations)**	
	Formaldehyde (household mean)	0.09 (0.27)
	Morning formaldehyde (vs. bedtime)	−5.9 (1.1) [a]
	Bedroom formaldehyde	−0.07 (0.04) [b]

Study and Design	Results
Mean age: >15: 37 years, percentage male: >15: 43.4%, percentage white: >15: 70.4%, 24.4% current smokers. Asthma prevalence: >15: 12.9%. **Exposure:** Sampling: two one-week samples from each individual's kitchen, living area, and bedroom using passive sampling tubes (sensitivity 12 µg/m^3 for 1 week, 15% accuracy). Average formaldehyde concentration, 26 ppb [0.032 mg/m^3],[b] maximum 140 ppb, [0.172 mg/m^3].[b] The majority of subjects (83%) lived in homes with 2-week average concentrations below 40 ppb [0.049 mg/m^3].[b] **Methods:** Trained subjects measured peak expiratory flow rates (PEFRs) using Mini-Wright peak flow meters four times daily, in the morning, at noon, in the early evening, and before bed, for 2 weeks. The largest of three test results was recorded for each test period. Analysis of PEFR in relation to indoor formaldehyde concentration, random effects model adjusting for asthma status, smoking status, SES, NO_2 levels, episodes of acute respiratory illness, and time of day. Analysis performed separately for ages younger and older than 15 years. **Evaluation:**[a] SB: ; IB: ; Cf: ; Oth: ; Overall Confidence: **High**	× morning Morning × smoking: −7.4 (2.6)[a] Bedroom formaldehyde × morning × smoking: 0.59 (0.13)[a] Bedroom formaldehyde^2 × morning × smoking: −0.007 (0.001)[a] Constant: 491.7 (8.5) [a]$p < 0.05$, [b]$0.05 < p < 0.10$ In adults, only the morning PEFR values were affected by formaldehyde concentrations. Smoking status was shown to affect the relationship between PEFR and formaldehyde exposure.
Reference: Bentayeb et al. (2015) Cross-sectional study, 2009−2011; 7 European countries. **Population:** 600 elderly residents (20 randomly selected per home) permanently living in randomly selected nursing homes (8 per city) in selected city in seven countries. Exclusion criteria stated (neurological or psychiatric disorders), 71.8% female, 62.8% ≥80 years old, 35% active smokers, 13.8% passive smoking. **Exposure:** Measurements in common room; 1-week samples; also measured particulates, NO_2, ozone, temperature, humidity and CO_2; range of 1 week averages 0.001−0.021 mg/m^3, median 0.006 mg/m^3; categorical (low and high) based on median concentration in each nursing home. **Methods:** Assessed by same team in all countries; medical visit and standardized questionnaire (European Community Respiratory Health Survey); lifetime COPD (ever told by doctor; spirometry (ATS/European Respiratory Society guidelines), percentage predicted. General estimating equations analysis, accounting for correlations within nursing homes; adjusted OR (95% CI) for risk of values <20% of distribution; stratification by presence of ventilation. **Evaluation:**[a] SB: ; IB: ; Cf: ; Oth: ; Overall Confidence: **Medium**	**Association of formaldehyde (cutpoint median in the nursing home) with pulmonary function among elderly nursing home residents** aOR[a]: FEV_1 1.12 (0.97−1.28); FVC 1.16 (1.06−1.28); FEV_1/FVC < 70% 0.46 (0.12−1.66) [a]aOR: adjusted OR Stratification by poor (n = 436) or adequate (n = 105) ventilation. FEV_1 aOR (95% CI), 2.65 (1.29, 5.45).

Study and Design	Results
Confounding by coexposures was not assessed; range of average concentrations within low and high exposure categories associated with overall effects is not known.	
Reference: Broder et al. (1988b, 1988c); Broder et al. (1988a) Cross-sectional study, February 1983−March 1984, Toronto, Canada. **Population:** 1,726 occupants from 517 households with urea formaldehyde foam insulation (UFFI) identified from registry maintained by Urea Formaldehyde Foam Insulation Information and Coordination Centre, Consumer and Corporate Affairs, Canada (50% male, mean age 40 years, 80% over 16 years, 18% current smokers). 231 referent households (n = 720) selected at random from streets adjacent to UFFI households (49% male, mean age 35 years, 20% current smokers). Interviewers and respondents were not blinded with respect to the focus of the study or the presence of UFFI insulation. **Exposure:** Formaldehyde sampling 5 hours on 2 successive days in central hallway, all bedrooms and in yard. Inside: referent 0.035 ppm, range 0.006−0.112 ppm [0.043 mg/m^3, range 0.007−0.138 mg/m^3].[b] 90% 0.061; UFFI 0.043 ppm, range 0.007−0.227 [0.053 mg/m^3, range 0.009−0.279 mg/m^3],[b] 90% 0.073 ppm. Outside: referent 0.005 ppm, UFFI 0.005 ppm. Carbon dioxide sampled in central hallway and in yard (as indication of ventilation). **Methods:** Questionnaire on symptoms and household characteristics, spirometry (minimum of three satisfactory tests, recorded largest value). Testing on ages 10 years and older. Statistical comparisons by group and within group (multiple linear regression), adjusted for date of examination, gender, age, race, height, smoking, total hours spent in house per week. **Evaluation:**[a]  For within-group analyses. Results not presented quantitatively for formaldehyde.	Formaldehyde concentration within group was not associated with pulmonary function in multiple regression models adjusting for covariates listed in column, "Study and Design," (results not presented). Between-group comparisons were not informative for formaldehyde associations because formaldehyde concentrations were comparable.
Reference: Norback et al. (1995) Cross-sectional study, Uppsala, Sweden. **Population:** 88 men and women (47 with asthma symptoms and 41 without) who agreed to participate (57%) from a group of 154 eligible randomly selected from 488 preliminary subjects from general population of Uppsala in 1990, aged 20−44 years. Mean duration in homes 6 years (range 0.5−31 years). **Exposure:** Field measurements: October 1991−April 1992. Formaldehyde (one 2-hour sample) and guanine (house dust mites) in the bedroom at pillow height. Room temperature, air humidity, VOCs, respirable dust, and CO_2 in living room and bedroom. Formaldehyde mean (range): 29 (<5−110 µg/m^3) in homes of those with nocturnal breathlessness.	FEV_1 mean percentage predicted (SD): 106% (13%). PEF mean variability (range): 5% (1−18%). FEV_1 percentage predicted and PEF variability (during the day) were not associated with log-transformed formaldehyde concentration using Kendall's rank correlation test (data not presented).

Study and Design	Results
17 (<5–60 µg/m^3) in homes without symptoms. Formaldehyde and VOCs concentrations were correlated and could not be evaluated in same regression model (no data presented). **Methods**: Structured interview, spirometry (*N* = 82), blinded to exposure. FEV_1 spirometry, percentage predicted; multiple regression model, Kendall's rank correlation test. **Evaluation:**[a] SB IB Cf Oth — Overall Confidence: **Low** Exposure: Low sensitivity, most exposed to concentration <LOQ; study population selected for high prevalence of asthma symptoms; correlated coexposure: VOCs.	

[a]Evaluation of sources of bias or study limitations (see details in Appendix A.5.1 and A.5.3).3). SB = selection bias; IB = information bias; Cf = confounding; Oth = other feature of design or analysis. Extent of column shading reflects degree of limitation. Direction of anticipated bias indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact would be likely to be away from the null (i.e., spurious or inflated effect estimate).
[b]Concentrations reported by authors as ppm or ppb converted to mg/m^3.

Children

A cross-sectional study of residential formaldehyde exposure in a large (298 children), population-based sample observed a linear relationship between increased formaldehyde exposure and decreased peak expiratory flow rate (PEFR) among children exposed to average concentrations of 0.032 mg/m^3 (26 ppb) (Krzyzanowski et al., 1990). As presented in Figure 1-6, the investigators reported a statistically significant decrease of −1.28 ± 0.46 L/minute in PEFR per ppb household mean formaldehyde. The figure shows the incremental decrement in PEFR measured at bedtime versus morning and shows differences in the morning among asthmatics and nonasthmatics. Asthmatic children (15.8% of the total) showed a steeper decline in PEFR in the morning at formaldehyde concentrations less than 0.049 mg/m^3 (40 ppb). Data analyses were based on daily measurements of PEFR in the morning and at bedtime for 12 days (first 2 days excluded) by study participants trained in the use of Mini-Wright flow meters. The analysis of multiple PEFR measurements resulted in an increased statistical power to detect an association at the lower formaldehyde levels present in the homes. The statistical model adjusted for potential confounders including asthma status, smoking status, socioeconomic status, NO_2 levels, episodes of acute respiratory illness, and the time of day.

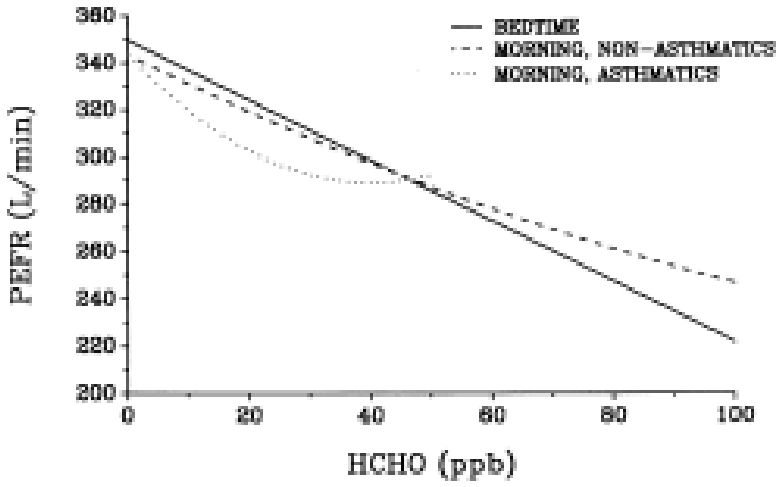


Figure 1-6. Association of PEFR measured at bedtime and in the morning with household mean formaldehyde concentration among children less than 15 years of age (Krzyzanowski et al., 1990).

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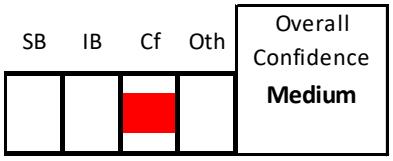
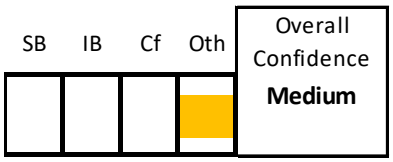
Two other studies among children evaluated exposure to formaldehyde at home (Franklin et al., 2000) and at school (Wallner et al., 2012). The range of formaldehyde concentrations was similar to those in the homes evaluated by Krzyzanowski et al. (1990). While no associations were reported for FVC or FEV_1 by either of the two studies that evaluated these measures (Wallner et al., 2012; Franklin et al., 2000), Wallner et al. (2012) also measured maximal expiratory flow at 50 or 75% of FVC (MEF_{50} and MEF_{75}) and observed an approximate 3% decrease per standard deviation increase in formaldehyde concentration measured in elementary school classrooms. Several pollutants were evaluated by this study, and a few also were associated with MEF_{75}. These pollutants, benzylbutylphthalate and polybrominated diphenylether congeners, both measured in dust, would be expected to originate from different sources than formaldehyde, and therefore, would not be expected to be highly correlated with formaldehyde in air. The exposure contrast in the homes evaluated by Franklin et al. (2000) was relatively small, limiting the ability of the study to detect an association with formaldehyde. The interquartile range was 0.011–0.035 mg/m^3, and concentrations between 0.062 and 0.107 mg/m^3, which was the range in the higher exposure group, were found only in 10 homes.

The studies of formaldehyde exposure in homes and schools are limited in their ability to detect a small reduction in pulmonary function associated with formaldehyde exposure at concentrations below 0.1 mg/m^3 (see Table 1-9). However, a methodologically robust study reported an association with reductions in peak expiratory flow rate (PEFR) in this concentration range (Krzyzanowski et al., 1990). These findings are supported by declines in MEF_{50} and MEF_{75} (but not other measures) in a second, more limited study (Wallner et al., 2012).

Table 1-9. Formaldehyde effects on pulmonary function among children in residential or school settings

Study and design	Results
Reference: Krzyzanowski et al. (1990); Quackenboss et al. (1987) Cross-sectional study, Arizona. **Population:** A stratified random sample of 202 households of municipal employees, selected based on information about potential exposure (age of housing) and potential susceptibility obtained from an initial screening questionnaire. Households with children aged 5−15 years (613 adults and 298 children) were eligible for inclusion. Mean age: <15: 9.3 years, percentage male: <15: 50.2%, percentage white: <15: 67.3%, Asthma prevalence: <15: 15.8%. **Exposure:** Sampling: two 1-week samples from each individual's kitchen, living area, and bedroom using passive sampling tubes (sensitivity 12 µg/m^3 for 1 week, 15% accuracy). Average concentration, 26 ppb [0.032 mg/m^3],[b][a] maximum 140 ppb, (0.172 mg/m^3).[b] The majority of subjects (83%) lived in homes with 2-week average concentrations below 40 ppb (0.049 mg/m^3).[b] **Methods:** Trained subjects measured peak expiratory flow rates (PEFRs) using Mini-Wright peak flow meters four times daily, in the morning, at noon, in the early evening, and before bed, for 2 weeks. The largest of three test results was recorded for each daily test period (e.g., morning, bedtime). Analysis of PEFR in relation to indoor formaldehyde concentration, random effects longitudinal model including morning and bedtime formaldehyde concentration, adjusting for asthma status, smoking status, SES, NO_2 levels, episodes of acute respiratory illness, and time of day. Analysis performed separately for ages younger and older than 15 years. **Evaluation:**[a] SB: ; IB: ; Cf: ; Oth: ; Overall Confidence: **High**	**Change in PEFR (L/min) in relation to indoor formaldehyde, random effects longitudinal model, ages ≤15 (*N* = 208; 3,021 observations)** Factor: β (SE) Formaldehyde (household mean, ppb): −1.28 (0.46)[a] Morning formaldehyde (vs. bedtime): −6.1 (3.0)[a] Bedroom formaldehyde *morning: 0.09 (0.15) Bedroom formaldehyde squared *morning: 0.0031 (0.0015)[a] Morning*asthma: 4.59 (9.60) Bedroom formaldehyde*morning* asthma: −1.45 (0.53)[a] Bedroom formaldehyde squared *morning*asthma: 0.031 (0.006)[a] Constant: 349.6 (13.2) [a]$p < 0.05$, [b]$0.05 < p < 0.10$ PEFR decreased in children as formaldehyde concentrations increased with a difference noted between the measurements taken in the morning vs. bedtime. The morning PEFR was further decreased in children with asthma.
Reference: Wallner et al. (2012) Cross-sectional study; Austria. **Population:** 433 children (aged 6−10 years) with spirometry of 596 eligible (72.7%) in two classrooms each at 9 of 19 schools that volunteered to participate in study (50% male). 53% of the children were exposed to environmental tobacco smoke at home. **Exposure:** Pollutant measurements for 252 agents: 2 samples in each classroom, 1 per season (autumn, spring). Formaldehyde: 24-hour sampling period. 34 chemicals selected for statistical analysis were those with substantial variation across schools based on an arbitrarily selected criterion (ratio of between-school variance to the pooled within-school variance >4). **Methods:** Questionnaire completed by parents, spirometry assessed at school between 8:30 am and 12:30 pm by trained technician, ATS protocol except 6-second minimum exhalation time (not feasible in children). Values expressed as percentage of reference based on age, gender, height, and weight. Regression of log-transformed values on mean concentration of chemical adjusted for education and occupation of parents, urban/rural	Percentage change in pulmonary function (95% CI) per 1 SD change in formaldehyde concentration % Change / 95% CI FVC[a]: −0.94 / −3.29, 1.35 FEV_1[a]: −2.16 / −4.80, 0.41 MEF_{75}[b]: −3.31 / −6.6, −0.08 MEF_{50}: −2.60 / −4.31, −0.91 [a]Associations with ethylbenzene, *m*-, *p*-xylene, and *o*-xylene in air, tris (1,3-dichlor-2-propyl)-phosphate in particulate matter, and benzylbutylphthalate (FEV_1 only) and polybrominated diphenylether congeners in dust were statistically significant. [b]Associations with benzylbutylphthalate and polybrominated diphenylether congeners in dust also were statistically significant.

<table>
<tr><th>Study and design</th><th>Results</th></tr>
<tr><td>residence, and # smokers at home. No adjustment of statistical significance criterion for multiple comparisons (exploratory).
Evaluation:[a]
 

No adjustment for coexposures in classroom that were also associated with pulmonary function, but correlation not anticipated.</td><td></td></tr>
<tr><td>Reference: Franklin et al. (2000)
Cross-sectional study, Australia.
Population: 224 healthy children (116 girls, 108 boys) with no current or history of upper or lower respiratory tract disease based on responses to respiratory health questionnaire and household inventory distributed through local primary schools.
Age provided by author: <50 ppb, 9.5 years (SD 1.6); ≥50 ppb, 9.2 years (SD 1.9).
Exposure: 3 to 4-day passive samples collected in the child's bedroom and the main living area of the house, average of both rooms; 214 homes.
TWA categorized into two groups: <50 ppb (0.062 mg/m^3)[b] and ≥50 ppb (10 homes).
Additional information from author:
Mean (SD): 20.1 ppb (15.6) (0.025 mg/m^3)[a]; range ND–86.6 ppb (ND–0.107 mg/m^3)[b].
Median (IQR): 15.6 ppb (0.019 mg/m^3)[a] (range 9.2–28.1) (0.011–0.035 mg/m^3).[b]
Methods: Clinical respiratory measures obtained at children's hospital. Measured spirometry (ATS guidelines), exhaled nitric oxide, and skin prick tests for seven common allergens.
Evaluation:[a]
 

Limited exposure contrast; few subjects in high exposure group.</td><td>Mean pulmonary function (SD) by exposure group[a]
<table><tr><th></th><th><50 ppb</th><th>≥50 ppb</th></tr><tr><td>FVC (L)</td><td>2.21 (0.55)</td><td>2.18 (0.46)</td></tr><tr><td>Percentage predicted</td><td>99.1 (10.2)</td><td>101.4 (7.3)</td></tr><tr><td>FEV_1</td><td>1.89 (0.46)</td><td>1.83 (0.24)</td></tr><tr><td>Percentage predicted</td><td>96.3 (11.1)</td><td>97.2 (5.4)</td></tr><tr><td>FEV/FVC (%)</td><td>89.1 (9.2)</td><td>93.1 (11.3)</td></tr></table>[a]Not reported; data provided to EPA by author; percentage predicted based on age, sex, and height.

eNO levels by exposure category
<table><tr><th>HCHO (ppb)</th><th>eNO (ppb)</th><th>Range</th></tr><tr><td>≥50</td><td>15.5</td><td>10.5–22.9</td></tr><tr><td><50</td><td>8.7[a]</td><td>7.9–9.6</td></tr></table>[a]p = 0.002, linear regression adjusted for age, atopic status.</td></tr>
</table>

[a]Evaluation of sources of bias or study limitations (see details in Appendix A.5.1 and A.5.3).3). SB = selection bias; IB = information bias; Cf = confounding; Oth = other feature of design or analysis. Extent of column shading reflects degree of limitation. Direction of anticipated bias indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact would be likely to be away from the null (i.e., spurious or inflated effect estimate).
[b]Concentrations reported by authors as ppm or ppb converted to mg/m^3.

Evidence on Mode of Action for Decrements in Pulmonary Function

Although an MOA for formaldehyde-related effects on pulmonary function remains incompletely defined, it is considered likely that these associations involve the indirect activation of sensory nerve endings in the lower respiratory tract (LRT) or increases in airway eosinophils, or both (see Figure 1-7). Moderate evidence exists for the mechanistic changes that could be directly related to decrements in pulmonary function (e.g., inflammatory changes in airway structure), and

moderate or robust evidence supports the linkages between events in this pathway. However, the initial cellular or tissue modifications that ultimately lead to these later events are not understood, and given the limitations of the available studies, it is unclear whether certain events would be triggered at low-exposure levels. It is also possible that structural and functional changes in the upper respiratory tract (URT) might contribute to decreased pulmonary function, for example, through narrowing of the upper airways or an altered release of cytokines or other soluble mediators in the URT; however, these possibilities are considered unlikely to be significant drivers of these effects (see additional discussion below). Overall, the airway inflammatory changes, which may be at least partially related to indirect activation of sensory nerve endings, is judged as likely to be an incomplete mechanism by which formaldehyde inhalation could cause decreased pulmonary function. As the mechanistic event(s) critical to understanding the observed relationship remain unknown, including how sensory nerve endings in the LRT might be stimulated without distribution of inhaled formaldehyde to the LRT, it is expected that important insights would be gained with additional study, particularly studies testing longer exposure durations. Although much of the mechanistic support is from studies in experimental animals, it is expected that related mechanisms are operant in exposed humans and could contribute to the consistent decrements in pulmonary function observed in the available epidemiology studies. Variation in sensitivity is likely to be affected by underlying respiratory health status and the exposure history of the individuals, including exposure to known allergens.

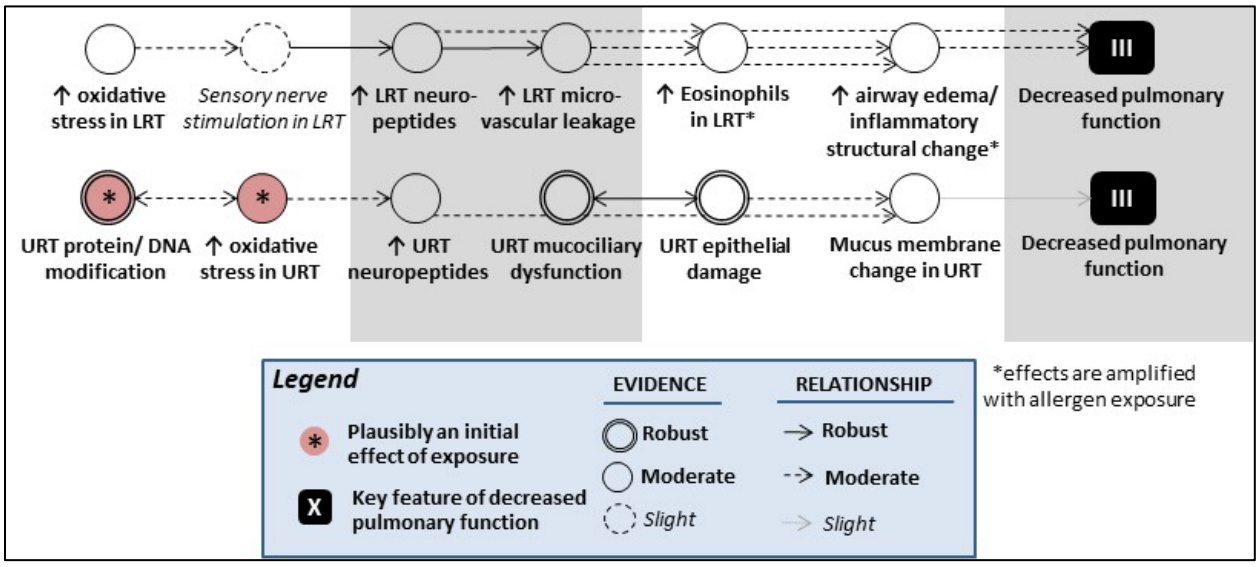


Figure 1-7. Possible mechanistic associations between formaldehyde exposure and decreased pulmonary function.

An evaluation of the formaldehyde exposure-specific mechanistic evidence informing the potential for formaldehyde exposure to cause respiratory health effects (see Table 1-10 and Appendix A.5.6) identified these sequences of mechanistic events as those most directly relevant to interpreting effects on pulmonary function. Evidence of airway inflammatory changes, including eosinophil recruitment to both

the upper and lower respiratory tract (URT and LRT; upper pathway), is considered as likely to represent an incomplete mechanism by which formaldehyde inhalation could cause decreased pulmonary function, although whether certain events occur at lower exposure levels is unclear, and other unexplored mechanistic events are expected to contribute. URT modifications, primarily structural changes (bottom pathway), may also contribute; however, this is not interpreted as likely to be a significant contributing mechanism.

The most plausible support for a mechanism(s) that explains the observed decreases in pulmonary function includes evidence of increased airway eosinophils and other immunogenic changes that could be attributed to sensory nerve activation in the LRT (presumably, the vagus nerve) of exposed rodents, although the potential involvement of LRT sensory nerve stimulation is poorly studied (i.e., slight evidence). It is expected that LRT sensory nerve activation would be reliant on a secondary response to TRP channel-activating stimuli increased in the LRT via indirect mechanisms, such as increased LRT oxidative stress or inflammatory mediators, or both, released from activated immune cells. This response is unlikely to result from direct stimulation of the nerve by inhaled formaldehyde or in response to cellular damage, as inhaled formaldehyde is unlikely to reach the LRT in appreciable amounts and overt epithelial damage in the LRT is not supported by the available evidence (see Appendix A.5.6). While it might also be explained by a central trigeminal-to-vagal neural reflex response to irritation of the URT (i.e., a "nasobronchial" reflex[8]), the existence of this reflex in humans is debated and a clear scientific consensus does not exist (Giavina-Bianchi et al., 2016; Sahin-Yilmaz and Naclerio, 2011; Togias, 2004, 1999).

Stimulation of sensory nerve endings can cause a localized release of neuropeptides. Accordingly, moderate evidence indicates that formaldehyde exposure results in increased LRT neuropeptides, including substance P, typically at formaldehyde concentrations ≥2.5 mg/m^3, with coherent moderate evidence for rapid activation of the primary receptor for substance P, the neurokinin (NK1) receptor, after acute exposure to higher formaldehyde levels. Further, the activation of the substance P pathway has been experimentally linked to formaldehyde-induced leakage of the LRT microvasculature. Airway edema and related inflammatory structural changes (i.e., in airway bronchi), which have been reported in experimental animals following short-term formaldehyde exposures ranging from >0.3 to >3 mg/m^3 and which appear to be exacerbated by prior allergen exposure, may represent consequences of increased microvascular leakage and inflammation (see below). To date, potential experimental linkages between these structural changes and sensory nerve stimulation or substance P signaling have not been studied after formaldehyde exposure. Similarly, while these changes could lead to an increased permeability to bronchoconstrictors such as histamine, and while substance P itself can increase the responsiveness of airway smooth muscle, these endpoints were generally unexamined in the available studies. Any or all of these immunogenic changes could plausibly contribute to airway

[8]Note: neural reflexes involving afferent and efferent activity of the vagus nerve (e.g., across different LRT regions), some of which may involve C fibers and TRP channels, are better established (Mazzone and Undem, 2016).

narrowing or obstruction and affect pulmonary function, although airway obstruction would generally be expected to require much higher exposure levels or effects that cumulate over an extended period of time. Importantly, however, the majority of the evidence available to inform these immunogenic changes is from studies of short-term exposure.

Substance P and NK1R signaling has been implicated in establishing the successful recruitment and adhesion of eosinophils to inflamed airways, and it can promote immune cell survival and activation through the release of cytokines and chemokines (Mashaghi et al., 2016). Moderate evidence for an association between formaldehyde exposure and increases in LRT eosinophils was identified, including amplification of the response of these cells in rodents previously exposed to allergens. Considering the evidence across the URT and LRT, a generalized increase in airway eosinophils after formaldehyde exposure is supported by robust evidence. Increased airway eosinophils have been reported following exposure of laboratory rodents for several weeks at effective concentrations above 0.5 mg/m^3, with increases generally not being observed following acute exposure. Recruitment of eosinophils to the airways might be related to the moderate evidence for LRT markers of oxidative stress, as eosinophils can release toxic mediators, including lipid-active factors and reactive oxygen species (again noting that it is considered more likely that any oxidative stress increases would result from changes in inflammatory factors and immune cells in the LRT, rather than LRT epithelial damage). However, the activation characteristics of the recruited airway eosinophils, including factors released, have not been defined, preventing a more complete understanding of whether and how these cells might decrease pulmonary function in these contexts.

As noted above, modifications to the URT respiratory epithelium could also result in changes that might indirectly affect pulmonary function. Such modifications include potential effects on immunological functions, such as an altered release of secreted factors from damaged epithelial cells, or effects on structural functions (e.g., modified clearance or barrier processes due to dysfunction of the mucociliary apparatus or cell type transitions, or narrowing of upper airways due to inflammation or proliferation). If increased URT cytokines or other soluble mediators were to reach the LRT, they could contribute to decreased pulmonary function through airway hyperreactivity or hypersensitivity to challenges such as allergen exposure (Hulsmann and Dejongste, 1996). However, it is expected that most immune factors released from URT respiratory epithelial cells are tightly controlled and locally acting, and that modest increases would be unlikely to have significant effects on the lower airways and lungs. Similarly, it is reasonable to presume that physical modifications to the URT would need to be severe to cause a noticeable change in function, which would not be expected with typical exposure scenarios. Direct, formaldehyde-specific examinations of any such associations between the robust evidence for structural URT changes and LRT effects were not identified, further limiting the interpretation of this potential association.

While evidence for some events at low formaldehyde levels (e.g., <1 mg/m^3) exists, some of the more convincing associations have only been tested at high formaldehyde concentrations. Additionally, the supporting mechanistic evidence is generally from studies of short-term (i.e., days to weeks) exposure. Therefore, the relevance and sensitivity of the proposed mechanistic pathways to chronic, low-level exposure scenarios is uncertain. It is also presumed that several important mechanistic events are currently unidentified. In particular, the initial effects of formaldehyde exposure that lead to the LRT changes remain undefined, although speculative, untested scenarios explaining the associations can be hypothesized based on the data available. Similarly, no explanation exists for the observed exaggerated effects on some mechanistic events following prior allergen exposure. Overall, however, although a definitive MOA has not been fully identified, several contributing mechanistic events interpreted with moderate or robust evidence appear to impact pulmonary function and, taken together, these data provide support for the biological plausibility of formaldehyde exposure-induced decreases in pulmonary function (See Table 1-10).

Table 1-10. Mechanistic evidence most informative to the occurrence of decreased pulmonary function after formaldehyde inhalation

Endpoint		Endpoint-specific findings and confidence	Summary of evidence	Conclusion
Modifications in the nose and upper airways				
Modification of biological macro-molecules (see Appendix A.2 and A.4 on ADME and Genotoxicity for additional detail)	*High or Medium*	*Human*: No direct evidence [note: binding of formaldehyde to albumin and other soluble proteins in human mucus has been demonstrated in vitro; e.g., (Bogdanffy et al., 1987)]; hemoglobin adducts are observable after months-to-years exposure at ~0.2 mg/m^3 (Bono et al., 2012).	Consistent with its known chemistry, formaldehyde can modify cellular macromolecules, including DNA, and interact with soluble factors such as albumin and glutathione, after exposure to low levels (e.g., <0.5 mg/m^3) across a wide range of exposure durations.	Robust
		Animal: Multiple animal studies testing various exposure durations demonstrate that inhaled formaldehyde can bind and modify biological macromolecules, which is consistent with the known biological reactivity of formaldehyde; evidence includes increased DNA-protein crosslinks (DPXs), hydroxymethyl (hm) DNA adducts, and reactions with glutathione [e.g., increased DPXs are observed at ≥0.37 mg/m^3 (Casanova et al., 1989)]; and hmDNA adducts and protein adducts are observed at ≥0.86 mg/m^3 (Edrissi et al., 2013b; Lu et al., 2011; Lu et al., 2010a).		
	Low	N/A: Sufficient information for 'robust' from *high or medium* confidence studies.		
Impaired mucociliary function (see Appendix A.5.6 for additional detail and discussion)	*High or Medium*	*Human*: Decreased mucus flow at ≥0.3 mg/m^3 after acute exposure and pathological changes in mucociliary clearance in workers at mean exposed levels of 0.25–0.26 mg/m^3 after chronic exposure (Holmström and Wilhelmsson, 1988; Andersen and Molhave, 1983).	Decreased mucus flow and ciliary beat, and impaired clearance, in humans and rats at ≥0.25 and ≥2.5 mg/m^3, respectively (observed across exposure durations), eventually leading to cilia loss.	Robust
		Animal: Mucociliary function was generally unaffected at <0.57 mg/m^3 after short-term exposure, with minor changes noted at the next exposure level, around 2.5 mg/m^3; robust changes were observed at the next highest concentrations		

Endpoint	Endpoint-specific findings and confidence		Summary of evidence	Conclusion
		tested, ≥7.27 mg/m^3 after acute or short-term exposure; there was a general lack of recovery with longer exposure duration (e.g., (Monticello et al., 1989; Morgan et al., 1986a; Morgan et al., 1986c); see Appendix A.5.6).		
	Low	*Human*: Increases in ciliary activity at 1.23 mg/m^3 in dissociated human nasal epithelial cells (Wang et al., 2014), with decreased ciliary beating frequency in human epithelial cells at ≥3.46 mg/m^3 (Wang et al., 2014; Schafer et al., 1999): in vitro, acute exposure.	Suggestive of decreased ciliary beat and ciliastasis at ≥5 mg/m^3 in humans and animals with acute exposure, and ciliary damage at ≥0.5 mg/m^3 with short-term exposure; usually preceded by initial effects including slight increases in activity.	
		Animal: Ciliastasis and mucostasis after acute exposure in vitro (Morgan et al., 1984): frog palates at ≥5.36 mg/m^3 (with early activity increases, even at 1.69 mg/m^3); structural cilia changes were also observed (Monteiro-Riviere and Popp, 1986): short-term exposure at ≥0.5 mg/m^3; and (Abreu et al., 2016): acute exposure at 0.25, but not 1.2–3.7 mg/m^3.		
Structural change in URT mucus membrane or nasal obstruction	*High or*	*Human*: Membrane hypertrophy, atrophy, rhinitis (Lyapina et al., 2004): chronic (yrs) exposure at 0.87 mg/m^3.	Mucus membrane damage and swelling in humans at 0.87 mg/m^3 with chronic exposure	Moderate (particularly in persons with nasal damage)
		Animal: None		
	Low	*Human*: Data suggest increased mucosal swelling, nasal obstruction or rhinitis in workers by (Holmström and Wilhelmsson, 1988): chronic exposure at 0.26 mg/m^3, and (Norback et al., 2000): short-term exposure at ≤0.016 mg/m^3, which did not increase in severity with longer exposure; increased mucosal swelling was also noted in symptomatic nasal distress patients, but not healthy controls (Falk et al., 1994): acute (2-hr) exposure at ≥0.073 mg/m^3.	Observations at ≤0.26 mg/m^3 in humans or at >3.5 mg/m^3 in rats support data from the chronic duration study and suggest increased acute vulnerability of people with a prior nasal condition.	
		Animal: Rhinitis and necrosis in rats after acute or short-term exposure, generally at ≥3.5 mg/m^3 (see Appendix A.5.5).		
URT epithelial damage or dysfunction (see Section 1.2.4 for additional detail)	*High or Medium*	*Human*: Indirect data indicating epithelial damage, including loss of ciliated cells, in occupational studies at 0.1 to >2 mg/m^3 (Ballarin et al., 1992; Holmstrom et al., 1989c; Edling et al., 1988; Holmström and Wilhelmsson, 1988; Edling et al., 1987a), with some equivocal findings (Boysen et al., 1990); however, these histopathological symptom scores included hyperplasia and metaplasia, which complicate interpretation.	Duration-dependent epithelial damage, typically at ≥2.5 mg/m^3 in subchronic or chronic rat studies, and with supportive indirect findings from human studies at 0.1–0.2 mg/m^3, generally correlates with inhibited mucociliary activity.	Robust
		Animal: Increased epithelial damage and related nasal lesions [e.g., (Andersen et al., 2010)]: duration dependent, typically ≥2.46 mg/m^3 in subchronic and chronic studies, with general correlation with inhibited mucociliary activity; goblet cell loss noted in monkeys (Monticello et al., 1989): short-term (1 wk) exposure at 7.38 mg/m^3;		

Endpoint	Endpoint-specific findings and confidence		Summary of evidence	Conclusion
		indirect evidence mRNA or miRNA changes associated with apoptosis (Rager et al., 2014; Rager et al., 2013): short-term (2-d in macques or 28-d in rats) exposure at ≥2.46 mg/m^3.		
	Low	*Human*: None *Animal*: Goblet cell damage and decreased junctional proteins between epithelial cells in rats (Arican et al., 2009): subchronic (12-wk) exposure at 18.5 mg/m^3; mRNA changes in DNA repair in rats (Andersen et al., 2010): short-term (1-wk) exposure, but not longer (4- to 13-wk) durations at ≥12.3 mg/m^3; rhinitis and necrosis in rats after acute or short-term (1- to 3-d) exposure at ≥3.94 or 4.43 mg/m^3.	Studies suggest that nasal epithelial damage is increased, even in short-term studies, at ≥2.5 mg/m^3.	
↑ **URT oxidative stress**	*See Section 1.2.1, Evidence on mode of action…,* for a description of the direct and indirect evidence of elevated reactive oxygen species (ROS), possibly at very low concentrations (e.g., at >0.066 mg/m^3) with prolonged exposure.			Moderate

Endpoint		Endpoint-specific findings and confidence	Summary of evidence	Conclusion
↑ **Neuro-peptide release**	*High or Medium*	*Human*: None *Animal*: Increased substance P **in plasma** in mice (Fujimaki et al., 2004b): subchronic exposure at 2.46 mg/m^3; microvascular leakage in rats (Ito et al., 1996): acute exposure to 18.45 mg/m^3; this was inhibited by NK1 receptor antagonists (note: substance P binds NK1R).	Indirect evidence after subchronic exposure in a mouse study at 2.46 mg/m^3; Indirect evidence for acute activation of the receptor for substance P in rats at >18 mg/m^3.	Moderate (for ↑ neuro-peptides) Moderate (for NK1R stimulation) (note: relevant to both URT and LRT)
	Low	*Human*: Substance P in nasal lavage (**in URT**) is increased in human volunteers with ocular exposure (He et al., 2005): 4-d (5-min/d) exposure at 3 mg/m^3, not 1 mg/m^3. *Animal*: **In URT** models, formaldehyde stimulates release of calcitonin gene-related protein (CGRP) in in vitro models relevant to inhalation exposure of the URT (Kunkler et al., 2011); experiments using the related chemical, acrolein, suggest this is TRPA1-mediated (Kunkler et al., 2011). **In LRT** models, inhibition of substance P receptor (NK1R) inhibited formaldehyde-induced currents in isolated rat trachea (Luo et al., 2013); increased substance P and CGRP in mouse BAL, both amplified with ovalbumin (OVA) sensitization, and both involved TRP activation (Wu et al., 2013): short-term exposure at 3 mg/m^3.	Data suggest formaldehyde activates TRP channels on sensory neurons, leading to release of CGRP and substance P, with acute or short-term exposure at >1 mg/m^3. An inhibitor study in isolated rat LRT tissue provides evidence of NK1R involvement, although the relevant inhalation exposure levels are unknown.	
Nasal cellular inflammatory response	*High or Medium*	*Human*: None *Animal*: Increased inflammatory response, mostly neutrophils but also mention of lymphocytes and other inflammatory cells (e.g., assumed monocytes, basophils and eosinophils) (Monticello et al., 1989): short-term (1- or 6-wk) exposure at 7.38 mg/m^3; "inflammatory cell" infiltration (Andersen et al., 2008): acute or short-term (1-d to 3-wk) exposure at 7.38 mg/m^3; miRNA changes associated with inflammation in rats and nonhuman primates (Rager et al., 2014; Rager et al., 2013): short-term (1- or 4- wk, with some miRNA changes reversible with 1-week recovery) exposure at 2.46 mg/m^3; in rats, 35 formaldehyde-responsive transcripts in the nose known to be related to immune cells indirectly indicated increases in granulocytes (i.e., eosinophil and neutrophil markers) and lymphocyte changes (Andersen et al., 2010): short-term (1-wk, but not ≥4-wk) exposure at ≥12.3 mg/m^3.	Cellular infiltration observed by histology, primarily neutrophils, but indirectly supporting other immune cell infiltration, in short-term animal studies at 7.38 mg/m^3. Indirect evidence of increases in granulocytes (and possibly lymphocytes) at 2.46 mg/m^3 with short-term exposure.	Moderate (↑ granulo-cytes: neutrophils and eosinophils) (Note: data on lympho-cytes were indeterm-inate)
	Low	*Human*: N/C in nasal lavage cell counts, but increased total protein (Priha et al., 2004): occupationally exposed (8-hr shift) 0.19 mg/m^3; allergy-independent increased eosinophils, permeability (albumin index) and total protein in lavage (Pazdrak et al., 1993): acute (2-hr) exposure at 0.5 mg/m^3; increased eosinophils, leukocytes, and permeability (albumin index) in lavage (Krakowiak et al., 1998): acute (2-hr) exposure at 0.5 mg/m^3 (reversible); indirect evidence of eosinophil infiltration (increased	Suggestive of cellular inflammation, particularly eosinophils, at 0.5 mg/m^3 and indirect markers of eosinophil recruitment at lower levels in humans, following *acute* exposure; neutrophil inflammation observed at ≥6 mg/m^3 in	

Endpoint		Endpoint-specific findings and confidence	Summary of evidence	Conclusion
		markers: lysozyme and eosinophil cationic protein), but not neutrophils, at very low levels (Norback et al., 2000): <0.02 mg/m^3 for unknown duration (likely ≥months) in schools. *Animal*: Neutrophil inflammation (Monteiro-Riviere and Popp, 1986): short-term exposure at ≥6 mg/m^3.	rats with *short-term* exposure.	
Modifications in the lower airways				
↑ Lower respiratory tract (LRT) microvascular leakage	*High or Medium*	*Human*: None *Animal*: Increased in rats (Ito et al., 1996): acute exposure at ≥6.15 mg/m^3; note: inhibited at 18.45 mg/m^3 by NK1 receptor antagonist (note: substance P binds NK1R), but not histamine or bradykinin antagonists.	Demonstrated increased leakage from acute exposure ≥6.15 mg/m^3 in 1 study, which appears to be mediated by substance P.	Moderate (only examined in acute studies)
	Low	*Human*: None *Animal*: Transiently increased in rats (Kimura et al., 2010): acute exposure at ≥1.23 mg/m^3 (duration-independent); note: leakage blocked by inhibiting mast cells, but not blocking cyclooxygenases; indirect mechanistic data following injection of formalin into the trachea, causing leakage that appeared to be dependent on substance P release after stimulation of C-fiber afferents (Lundberg and Saria, 1983).	One study suggests acute exposure as low as 1.23 mg/m^3 induces microvascular leakage, although continued exposure appeared (at least in the near-term) to result in less leakage.	
↑ Airway edema or other inflammatory structural changes	*High or Medium*	*Human*: None *Animal*: Increased edema in lung bronchi, but not alveoli, without signs of inflammation in lower airways in guinea pigs (Riedel et al., 1996): 5 d at 0.31 mg/m^3, not at 0.16 mg/m^3.	Bronchial edema in one short-term study at 0.31 mg/m^3.	Moderate (may require high exposure levels or allergen sensitization to elicit pronounced changes)
	Low	*Human*: None *Animal*: Airway structural changes consistent with inflammation (e.g., wall thickening; cell infiltration) in mice (Jung et al., 2007), some evidence for which was slight (Wu et al., 2013; Liu et al., 2011a), and in mice and rats sensitized with OVA (Wu et al., 2013; Liu et al., 2011a; Qiao et al., 2009), but not in nonsensitized rats (Qiao et al., 2009): all 2- to 3-wk exposure at ≥3 mg/m^3 [Note: most studied bronchial airways].	Airway structural changes with allergen sensitization in two species (and, to a lesser extent, without sensitization) with short-term exposure at ≥3 mg/m^3.	
LRT sensory nerve activation	*High or*	*Human*: None *Animal*: None	No evidence to evaluate	Slight (levels required for potential activation are unknown; may involve TRPA1 binding)
	Low	*Human*: None *Animal*: With acute exposure, dose-dependent increase in nerve currents and Cl^- release in intact rat trachea (Luo et al., 2013), with supporting evidence of substance P and NK receptor involvement. Indirectly, increased substance P and CGRP were observed in mouse lung tissue, both were amplified with OVA, and both were dependent on TRP activation (Wu et al., 2013): short-term exposure at 3 mg/m^3. Note: the potential involvement of	A single acute rat study and indirect evidence from potentially related exposures suggest that lower airway sensory nerve afferents may be activated, but the inhaled formaldehyde levels required for such potential activation have not been	

Endpoint	Endpoint-specific findings and confidence	Summary of evidence	Conclusion
	tracheobronchial reflexes, as is shown with direct LRT stimulation by irritants including cigarette smoke constituents and capsaicin (e.g., (Widdicombe, 1998)), may provide indirect support.	experimentally demonstrated.	

Endpoint		Endpoint-specific findings and confidence	Summary of evidence	Conclusion
↑ **LRT oxidative stress**	*High or Medium*	*Human*: Increased exhaled nitric oxide, a noninvasive marker of lower airway inflammation and oxidative stress, in healthy or asthmatic children (Flamant-Hulin et al., 2010; Franklin et al., 2000): unknown duration (likely months to years: classrooms or homes) at 0.04–0.06 mg/m^3, but not in elderly nursing home patients at lower levels (Bentayeb et al., 2015) for unknown duration (likely months to years) at 0.005–0.01 mg/m^3.	Increased biomarkers (indirect evidence) of oxidative stress in children at ≥0.04 mg/m^3, but not in elderly individuals at ≤0.01 mg/m^3 with prolonged (months–years) exposure, with indirect support from a subchronic rat study at >6 mg/m^3.	Moderate (observed in children at low levels: ~0.04 mg/m^3)
		Animal: Increased iron and zinc, indirect markers of potential oxidative stress, in lungs of male rats: 13 weeks at ≥6.15 mg/m^3 (Ozen et al., 2003).		
	Low	*Human*: None	Multiple studies in two species suggest elevated oxidative stress at ≥1 mg/m^3 with short-term exposure.	
		Animal: **In mice**: NO and NOS activity increased with 3 d exposure at 3 mg/m^3 (Yan et al., 2005), GSH levels decreased with 3-wk exposure at ≥0.5 mg/m^3 (Ye et al., 2013b), and increased ROS or lipid peroxidation markers were observed with 3-wk exposure at ≥1 mg/m^3 (Ye et al., 2013b) or 2-wk exposure at ≥6.15 mg/m^3 (Jung et al., 2007), but decreased with acute exposure in one study (Matsuoka et al., 2010): 24-h exposure at 0.12 mg/m^3. **In rats**: short-term studies at ≥12.3 mg/m^3 demonstrated increased total oxidant levels and decreased total antioxidant level (Aydin et al., 2014), increased lipid peroxidation markers and protein oxidation markers (Sul et al., 2007), and decreased gamma-glutamyl transpeptidase (indirect evidence) (Dinsdale et al., 1993).		
↑ **LRT eosinophils**[b] (see **Appendix A.5.6** for discussion of LRT evidence on other cell types and soluble factors)	*High or*	*Human*: None	Increased after subchronic exposure to 2.5 mg/m^3 in mice coexposed to antigen.	Moderate (with short-term exposure at ≥0.5 mg/m^3; note: moderate evidence for increases in total BAL cells or total white blood cells, under similar conditions; see Appendix A.5.6)
		Animal: ↑ in rats at 2.5 mg/m^3 with coexposure to the antigen, ovalbumin (OVA) (Fujimaki et al., 2004b).		
	Low	*Human*: Two studies did not observe increases following acute exposure at 0.1 mg/m^3 ((Casset et al., 2007); note: trend toward ↑) and 0.5 mg/m^3 (Ezratty et al., 2007) with allergen coexposure (i.e., dust mite antigen; pollen).	Evidence of increases with short-term exposure (in general, at ≥0.5 mg/m^3) in both rats and mice; the data suggest that changes may not occur after acute exposure.	
		Animal: ↑ in four short-term studies of mice in the absence of antigen [12.3 mg/m^3; (Jung et al., 2007)], with antigen (>~12.3 mg/m^3 with house dust mite antigen; (Sadakane et al., 2002)[a]), or both with and without antigen (at 0.5–3 mg/m^3 ± OVA (Liu et al., 2011a), and at 3 mg/m^3 ± OVA (Wu et al., 2013)); ↑ in one short-term rat study at 0.5–3.1 mg/m^3 with OVA antigen (Qiao et al., 2009) One acute rat study did not observe effects at 6.2 mg/m^3 without antigen (Kimura et al., 2010).		

[a]Reported as 0.5% formaldehyde solution; concentration assumed to be >12.3 mg/m^3 (Sadakane et al., 2002).
[b]There was also slight evidence for increases in eosinophil attractant and adhesion factors (see Appendix A.5.6).

Integrated Summary of Evidence for Pulmonary Function

Duration of exposure appears to play an important role in epidemiological associations for pulmonary function. Declines in pulmonary function measures have not been observed by controlled human exposure studies of short-term formaldehyde exposure among healthy volunteers, although one research group reported that longer exercise periods (15 minutes) resulted in small changes. Controlled studies of pulmonary function responses to formaldehyde inhalation among volunteers with asthma also did not observe changes in this potentially sensitive group (see Section 1.2.3, Table 1-19). One exception was a heightened response to a dust mite challenge in the formaldehyde inhalation arm compared to the clean air exposure in one study that used nose clips, although a different study did not observe an increased response in a study with a similar design but using a pollen challenge and no nose clip. Studies of change across the work shift or during pathology labs reported mixed results, which are difficult to interpret because most studies did not evaluate changes in an appropriate referent group.

Associations with long-term formaldehyde exposure were observed more consistently; measures of FEV_1, FVC, FEV_1/FVC, and expiratory flow rates were generally lower in highly exposed occupational groups compared to their nonexposed or lesser-exposed comparison groups. While the direction of the associations was generally consistent, some effect estimates were imprecise. The differences may be a result of individual variability, lower sensitivity in some studies to detect small mean differences or changes, or random variation. Another source of variation may be incomplete control for confounders (e.g., smoking, dust, other pollutant exposure), although some studies did adjust for these factors and still observed an independent association with formaldehyde, and associations were found among groups with different exposure settings.

Smoking, health status, and lifestage may increase sensitivity to inhaled formaldehyde. The limited number of population-based studies evaluating lower exposure levels indicates that while, in general, no associations were observed among adults, declines were reported for smokers and the elderly living in nursing homes. The study with the strongest design and methods found an association with declines in PEFR among adult smokers and increasing average formaldehyde concentration between 0.049 and 0.172 mg/m^3 (Krzyzanowski et al., 1990). In this large, population-based sample, the investigators also observed a linear relationship between increased formaldehyde exposure and decreased peak expiratory flow rate (PEFR) among children exposed to average concentrations of 0.032 mg/m^3 (26 ppb), and a stronger response was observed among children with asthma. This finding is supported by declines in some of the pulmonary function measures in a more limited study in schools (Wallner et al., 2012).

While there were very few studies in humans that inform potential biological mechanisms (i.e., several studies indirectly support inflammatory changes in the LRT), experimental evidence

primarily from animal studies provides robust or moderate evidence of mechanistic changes that can be plausibly associated with effects on pulmonary function, including increases in airway eosinophils and other inflammatory airway changes that appear to be at least partially dependent on indirect activation of sensory nerve endings in the LRT. Taken together, the data provide what is likely to be an incomplete mechanism explaining how formaldehyde exposure might result in decreased pulmonary function. Uncertainties remain regarding the initial cellular or tissue modifications that ultimately lead to the observed mechanistic changes in the lower airways, and it is unclear whether certain events would be triggered with chronic, low-level exposure.

Overall, based on *moderate* human evidence from observational epidemiology studies, with corresponding *slight* evidence for an effect in animals based on mechanistic studies supporting biological plausibility, the **evidence indicates** that long-term inhalation of formaldehyde likely causes decreased pulmonary function in humans given the appropriate exposure circumstances. The primary support for this conclusion includes a study of children and adults in a residential setting (mean, 0.03 mg/m^3, maximum 0.17 mg/m^3) and several studies of workers with long-term exposure to >0.2 mg/m^3 (see Table 1-11). The **evidence** is **inadequate** to interpret whether acute or intermediate-term (hour to weeks) formaldehyde exposure might cause this effect (see Table 1-11).

Table 1-11. Evidence integration summary for effects on pulmonary function

Evidence	Evidence judgment	Hazard determination
Long-term Exposure (years)		
Human	*Moderate for Long-Term Exposure (years)*, based on: *Human health effect studies:* • 1 *high* and two *medium* confidence studies in residential and school populations indicating that susceptible individuals may experience reduced pulmonary function at lower average concentrations (<0.05 mg/m^3). • Numerous *high* and *medium* confidence studies showing a pattern of reduced mean pulmonary function in formaldehyde-exposed occupational groups across a variety of exposure settings and countries. However, some inconsistencies were noted for specific measures; possible explanations may be random variation and low study sensitivity. • Concentration-related associations from four *high* and *medium* confidence adjusted analyses indicate an independent association for formaldehyde exposure suggesting confounding is not an alternative explanation. • Longitudinal declines were reported for one occupational population and a panel study of medical students, but null or equivocal associations were identified from other studies, all with possible differential loss to follow-up and low sensitivity. *Biological Plausibility:* Some indirectly supportive mechanistic information from well-conducted human studies exists related to increased lower airway oxidative stress following exposures likely to span months to years.	The **evidence indicates** that long-term inhalation of formaldehyde likely causes decreased pulmonary function in humans given appropriate exposure circumstances[a] Primarily based on a study of children and adults in a residential setting (mean, 0.03 mg/m^3, maximum 0.17mg/m^3) and several studies of workers with long-term exposure to >0.2 mg/m^3 *Potential Susceptibilities:* Variation in sensitivity is anticipated to depend on age and respiratory health, with the potential for children to be more sensitive.
Animal	*Slight*, based on:	

	Biological Plausibility: Robust and moderate evidence for several mechanistic events, primarily from experimental animal studies, provides support for inflammatory changes in the lower airways, including eosinophil increases, which appear to be at least partially dependent on indirect stimulation of sensory nerve endings. While evidence exists for some changes in the range of 0.3−0.5 mg/m^3 with exposure for several weeks, some potential associations in the identified, incomplete MOA pathway have only been tested at higher (i.e., >1 mg/m^3) levels and with shorter-term exposures. *Animal health effect studies*: Not formally evaluated.	
Other inferences	*Relevance to humans:* The observed mechanistic changes are expected to occur in humans, given similarities across species in the systems that appear to be involved, and some support is based on studies in both humans and animals (e.g., lower airway oxidative stress). *MOA*: Not established, but likely to involve airway eosinophil increases and stimulation of airway sensory nerve endings.	
Acute or Intermediate-Term Exposure (hours to weeks)		
Humans	*Indeterminate for Acute or Intermediate-Term Exposure (hours to weeks),* based on: *Human health effect studies*: Small reductions in two controlled human exposure studies of healthy volunteers (1 lab) with longer exercise periods (15 min), but no associations with other exposure protocols (including those with ≤10 min exercise periods) in studies involving healthy subjects or asthmatics (see discussion above and Section 1.2.3 for pulmonary function results in asthmatics); inconsistent results among studies of medical school dissection labs and cross-shift measurements in occupational studies. *Biological Plausibility:* Increases in lower airway eosinophils were not observed in the few *low* confidence acute studies in humans available.	The **evidence** is **inadequate** to draw judgments regarding acute or intermediate-term exposure (hours to weeks)
Animals	*Indeterminate*, based on: *Biological Plausibility:* Although some mechanistic changes relevant to pulmonary function, including most of the immunogenic effects, were altered after short-term exposure in animals, given the dependence of some of the key mechanistic events (e.g., URT damage or dysfunction; LRT oxidataive stress) on exposure duration, it remains unclear whether the potential mechanistic pathways would be relevant to interpreting acute or short-term exposure scenarios. *Animal health effect studies*: Not formally evaluated.	

[a]The "appropriate exposure circumstances" are more fully evaluated and defined through dose-response analysis in Section 2

1.2.3. Immune-mediated Conditions, Focusing on Allergies and Asthma

This section examines the evidence pertaining to the effect of formaldehyde exposure on immune-mediated responses, primarily in the respiratory system, focusing on allergy-related conditions (e.g., rhinitis, rhinoconjunctivitis) and asthma; sensitization related to dermal exposure is not a focus of this review. Experimental animal studies were ultimately concluded to be unsuitable models (i.e., *indeterminate*) for evaluating allergy-related conditions and asthma as apical outcomes (see discussion in *Immune-mediated Conditions, Focusing on Allergies and Asthma, in Animal Studies*). Additionally, a few studies that indirectly suggested that respiratory immune

function (i.e., the ability to respond to infection) could be affected by formaldehyde exposure are introduced. However, in the context of the health effects data available, it was determined that these particular findings were better suited to discuss within the wider context of potential mechanistic changes that might explain respiratory health hazards (see Appendix A.5.6 and discussion below in *Evidence on MOA for Immune-mediated Conditions*), rather than as an independent health hazard to be evaluated. The mechanistic studies considered most relevant to these health outcomes provided biological support for the immune-mediated conditions observed in humans, although complete and definitive MOAs could not be established and several changes thought to be important to the development or progression of asthma, in particular, were not identified. The few available studies on developmental immunotoxicity in animals (hypersensitivity studies) were *indeterminate* in regard to the information necessary to draw conclusions.

The general population studies in children and adults provided evidence of an association between formaldehyde exposure and prevalence of rhinitis or rhinoconjunctivitis, with a relative risk of approximately 1.2 for formaldehyde exposures of around 0.04–0.06 mg/m^3. Although the effect size was small, these are relatively common conditions and could result in a large impact in the population. A stronger association (two-fold risk) was seen in the only study of eczema. Eczema, while not indicative of an allergic respiratory response, is often associated with other allergic disorders, including those affecting the respiratory system [e.g., allergic rhinitis; (Weidinger and Novak, 2016a, b), and it appears that some inhaled allergens may have the potential to exacerbate this condition (Mendell et al., 2011; Morren et al., 1994). The available general population studies also provided evidence of an association between formaldehyde exposure and the prevalence of current asthma, as determined by symptoms or medication use in the past 12 months in studies with some participants exposed above 0.05 mg/m^3, but associations were not seen in settings with an exposure range less than 0.05 mg/m^3. The two studies examining asthma control or severity among children with asthma suggest associations may be seen at lower exposures (e.g., 0.04 mg/m^3) in this potentially susceptible population. Relatively strong associations were seen in studies examining prevalence of current asthma in relation to formaldehyde exposure in occupational settings (exposures above 0.10 mg/m^3). The mechanistic evidence indicates that formaldehyde exposure can induce bronchoconstriction and lead to the development of hyperresponsive airways,[9] particularly with allergen sensitization. These heightened responses may be due to a combination of potentially progressive changes, including neurogenic increases in tachykinins and eosinophil recruitment and activation in the lung. The mechanistic studies also provided consistent evidence that formaldehyde may stimulate a number

[9]Hyperresponsive airways (or hyperresponsiveness) represents a mechanistic event (supported by *robust* evidence) and a potential key feature of respiratory health hazards that is defined to encompass any of a range of relevant airway features, including hyperreactivity (exaggerated response) and hypersensitivity (lower dose to elicit response). See Appendix A.5.

of immunological and neurological processes related to asthmatic responses; however, a molecular understanding of how formaldehyde exposure favors asthmatic T-helper 2 (T_H2) responses has not been experimentally established.

Overall, based primarily on a *moderate* level of human evidence supporting an association from the available epidemiological studies, with corresponding *slight* evidence for an effect in animals based on mechanistic studies in animals supporting biological plausibility, the **evidence indicates** that inhalation of formaldehyde likely causes an increased risk of prevalent allergic conditions and prevalent asthma symptoms, as well as decreased control of asthma symptoms, given the appropriate exposure circumstances. The primary basis for this conclusion involves studies of occupational settings (>0.1 mg/m^3) and population studies where formaldehyde concentrations measured in schools and homes averaged between 0.03 and <0.1 mg/m^3.

Literature Search Strategy

The primary databases used for the literature search were PubMed, Web of Science, and Toxline, with the last update of the search completed in September 2016 (see Appendix A.5.4 and A.5.6), and a systematic evidence map updating the literature through 2021 (see Appendix F). The focus of this review was on studies with a direct measure of formaldehyde exposure in relation to measures of allergic conditions or asthma, reflecting the question of whether formaldehyde exposure influences the sensitization response to respiratory allergens. This included the identification of studies of specific health outcomes and particular exposure scenarios in studies of exposed humans (Appendix A.5.4), studies of hypersensitivity in animals (Appendix A.5.4 and A.5.6), and relevant mechanistic data identified and evaluated as part of the overarching review of mechanistic data relevant to potential respiratory health effects (Appendix A.5.6). For the human health effect studies, several exposure settings and scenarios were included that encompassed different exposure durations and time windows. These included controlled human exposure studies among asthmatics, residential and school settings, as well as occupational studies. Controlled human exposure studies of pulmonary function change among asthmatic volunteers, including two studies that assessed whether formaldehyde exposure changed the response to an allergen challenge, are summarized in this section, but their results are most informative to the pulmonary function outcome and are included in the integration of evidence in that section (see Section 1.2.2). Specific types of outcome measures within the category of allergic conditions include questionnaire-based ascertainment of history of rhinitis, rhinoconjunctivitis, hay fever, pet allergy, eczema, or dermatitis; physician documentation of a specific diagnosis (e.g., atopic dermatitis); and allergic sensitization based on skin prick tests. Allergic conditions were grouped by site (nose and eyes, skin). Eczema is not a contact allergy but can be triggered by reactions to respiratory and other types of allergens (as well as by other factors). Food allergies were not included in the literature search. Measures of asthma include questionnaire-based ascertainment of prevalence of current asthma (e.g., within past 12 months), incidence of asthma, and measures of asthma control (based on symptom frequency and medication use in the past 2–4 weeks).

While not a particular focus of this review, the search also encompassed several studies of lower respiratory infection. Given the frequency and general transiency of upper respiratory infections such as the common cold in human populations (which may complicate epidemiological evaluations), as well as their generally benign nature, this endpoint is not discussed in detail in this section, although they were identified and evaluated in the wider context of potential mechanisms for respiratory health hazards (see Appendix A.5.6).

One potential mechanism for inducing hypersensitivity is the potential to elicit a formaldehyde-specific antibody response, specifically IgE. The presence of formaldehyde-specific IgE in workers occupationally exposed to formaldehyde was described in case reports (Vandenplas et al., 2004; Kim et al., 2001), but larger studies in exposed populations or in asthma patients indicate this is a relatively uncommon occurrence, seen in no or only a few individuals (Hisamitsu et al., 2011; Doi et al., 2003; Krakowiak et al., 1998; Wantke et al., 1996b; Grammer et al., 1990; Thrasher et al., 1990). Formaldehyde-specific IgE was not included as an outcome for analysis in this section. However, a broader consideration of antibody responses following formaldehyde exposure is considered in the mechanistic evaluation of potential respiratory effects (see Appendix A.5.6).

The bibliographic databases, search terms, and specific strategies used to search them are provided in Appendix A.5.4 and A.5.6, as are the specific PECO criteria. Literature flow diagrams summarize the results of the sorting process using these criteria and indicate the number of studies that were selected for consideration in the assessment through 2016 (see Appendix F for the identification of newer studies through 2021). The relevant human health effect studies (i.e., meeting the requirements outlined above), studies of hypersensitivity in animals, and mechanistic data informative to immune-related conditions and asthma were evaluated to ascertain the level of confidence in the study results for hazard identification (see Appendix A.5.4 and A.5.6).

Methodological issues considered in evaluation of studies

The evaluation criteria were developed after discussions with two groups of clinical and epidemiology experts in allergy[10] and asthma[11] regarding sensitivity, specificity, and interpretation of various types of outcome measures used in the identified observational epidemiological studies. These discussions were conducted without regard to the magnitude or direction of results

[10]Dr. Hasan Arshad, University of Southampton, Southhampton, U.K.; Dr. Peter Gergen, National Institute of Allergy and Infectious Diseases, Bethesda, Maryland; Dr. Elizabeth Matsui, Johns Hopkins University, Baltimore, Maryland; Dr. Dan Norbäck, Uppsala University, Uppsala, Sweden; Dr. Matthew Perzanowski, Columbia University, New York, New York.

[11]Asthma: Dr. Lara Akinbami, Centers for Disease Control and Prevention, Atlanta, Georgia; Dr. Peter Gergen, National Institute of Allergy and Infectious Diseases, Bethesda, Maryland; Dr. Christine Joseph, University of Michigan, Ann Arbor, Michigan; Dr. Felicia Rabito, Tulane University, New Orleans, Louisiana; Dr. Carl-Gustaf Bornehag, Karlstad University, Karlstad, Sweden.

pertaining to formaldehyde or other exposures. Three studies were reclassified from asthma to lower respiratory symptoms in infants and toddlers; see discussion in Appendix A.5.4.

EPA also evaluated the exposure measurement protocol used in the epidemiological studies, considering the length of the exposure period, consideration of temperature, relative humidity, and LOD and percentage <LOD, and the distribution of exposure encompassed within the study population. As is discussed in Appendix A.5.1, longer sampling periods (e.g., 1- to 2-week duration) were preferable, as they were considered to be reflective of usual average exposure levels experienced by occupants.

Five studies involved occupational exposures (Neghab et al., 2011; Herbert and Rietschel, 2004; Fransman et al., 2003; Herbert et al., 1994; Malaka and Kodama, 1990). These studies represent the highest exposure scenarios, from >0.1 to >0.5 mg/m^3. The remaining were general population studies of adults and children, with exposure measured in homes or schools or with a personal monitor. In the general population settings, most exposures were <0.050 mg/m^3, with relatively few results for exposures from >0.05 to approximately 0.1 mg/m^3. EPA used 0.05 mg/m^3 as a cutpoint to examine results in lower exposure groups compared to higher general population exposures.

The study evaluation conclusions are indicated with the summaries of study results. Within each subsection of a table (e.g., sections of studies of children or studies of adults), studies are further grouped by confidence level (i.e., *high*, *medium*, and *low* categories). Results from *low* confidence studies are shaded in gray. The corresponding synthesis of evidence focuses on the *medium* and *high* confidence studies, taking into account differences in populations (i.e., children, adults) and exposure levels.

One study was difficult to classify (Smedje and Norback, 2001). This is the only study that examined incidence of allergies or asthma; the prospective design is a considerable strength of the study. However, the exposure assessment (conducted in classrooms in the baseline year and in Year 3 of the 4-year follow-up) was limited by a high prevalence of values below the detection limit: (54% of 1993 samples and 24% of 1997 samples were below 0.005 mg/m^3; geometric mean 0.004 and mean 0.008 mg/m^3). The analysis was conducted using formaldehyde as a continuous variable, without discussing the influence of the values below the detection limit. Thus, EPA classified this as a *low* confidence study because of uncertainties regarding the analysis. However, given that this was the only study that evaluated incidence of allergies or asthma using prospective study design, this section also considers the potential impact of this study (Smedje and Norback, 2001) on overall conclusions if it had been characterized as a *medium* confidence study.

In this section, where feasible (based on similar type of measures, referent groups, and analysis), EPA conducted a meta-analysis to calculate a summary effect estimate for related results. These analyses used random effects models with a restricted maximum likelihood estimator, weighing the studies based on variance.

Immune-mediated Conditions, Focusing on Allergies and Asthma, in Human Studies

In the following sections, the evidence regarding allergic conditions (symptoms, skin prick tests) from general population studies is discussed by age category (i.e., children, adults). For asthma, general population studies of asthma incidence and prevalence and degree of control among children and adults are discussed by exposure setting (general population, occupational). In addition, responses among asthmatics to acute exposure are described (controlled human exposure studies), followed by other respiratory conditions in infants and toddlers, and a discussion of factors that may increase susceptibility. The studies are summarized in tables for these outcomes (see Tables 1-12 through 1-21) that are ordered by age group, confidence in study results, and publication year. The three tables of asthma prevalence (see Tables 1-15 through 1-17) group studies of populations with exposure to relatively low levels or relatively high levels of formaldehyde in residential or school settings and occupational groups exposed to higher levels.

Allergic conditions

The *high* and *medium* confidence general population studies provided evidence that formaldehyde exposure is associated with an increased prevalence of rhinitis or rhinoconjunctivitis (see Figure 1-8A, Table 1-12). These studies were conducted in school children in France (Annesi-Maesano et al., 2012), Romania (Neamtiu et al., 2019), and Korea (Yon et al., 2019), and in adults in France (Billionnet et al., 2011) and Japan (Matsunaga et al., 2008). The exposure range was similar in these studies and estimated RRs were comparable for rhinitis endoints ranging from 1.14 to 1.21 for comparisons of the higher exposed to the referent groups. One study of school children in Malaysia measured very low formaldehyde concentrations in classrooms (mean 4.2 ug/m^3, max 18.0 ug/m^3), and did not observe an association with rhinitis prevalence (Norbäck et al., 2017). The classification of rhinoconjunctivitis by Annesi-Maesano et al. (2012) was the most sensitive and specific of the measures, and the narrower confidence intervals in this study reflected the larger sample size. No other pollutants (e.g., NO_X, $PM_{2.5}$, acetaldehyde, acrolein, ETS) analyzed by this study were associated with rhinoconjunctivitis. For eczema, only one study was available, with a two-fold risk seen at exposures of approximately 0.06 mg/m^3 (Matsunaga et al., 2008). Neamtiu et al. (2019) studied "allergy-like symptoms" in school children occurring in the past week using a translated ISAAC questionnaire. The definition for allergy-like symptoms included a combination of symptoms involving the eyes, rhinitis symptoms, and skin conditions. Students exposed to formaldehyde concentrations in classrooms >0.035 mg/m^3 (median 0.045 mg/m^3) had a 3-fold odds of experiencing allergy-like symptoms within the past week compared to students exposed to <0.035 mg/m^3 (OR 3.23, 95% CI 1.31, 8.00). Two studies examined more than two exposure groups (Annesi-Maesano et al., 2012; Matsunaga et al., 2008) and observed the highest relative risk in the highest exposure group compared to the referent group, with weaker or no associations seen in the lower exposure categories (see Figure 1-8B). Further, an analysis by categories of rhinitis severity in children observed a statistically significant increasing trend in risk (Yon et al., 2019). The

inclusion of the study by Smedje and Norback (2001) as a *medium* confidence study did not change the interpretation of the evidence.

A relative risk of 1.4 for formaldehyde exposures above approximately 0.035 mg/m^3 and atopy based on skin prick tests was also seen in a study in children (Garrett et al., 1999), but not in the study by Palczynski et al. (1999) (see Table 1-13). Both of these were classified as *medium* confidence with respect to the results in children. The exposure range examined in Garrett et al. (1999) is wider than that in Palczynski et al. (1999), and the exposure measurement protocol (four 1-day samples in different seasons) was an additional strength of the study by Garrett et al. (1999). This study also reported associations between formaldehyde exposure and both wheal size and the number of positive tests (from a mean of approximately 1.5 in the lowest to 4.0 in the highest category of exposure). A limitation of the skin prick test studies was the uncertainty regarding the congruence between the exposure measure and the exposure during the relevant time window with respect to development of sensitization. In particular, all of the residences in the study by Palczynski et al. (1999) had been built 10 years prior to enrollment in the study, and sensitization may have occurred years before the exposure assessment, possibly when exposure levels were higher. A similar concern was raised for Garrett et al. (1999), as the authors did not report the age of the housing stock for participants and 74% of the children had lived in their homes at least 5 years.

Results from the two occupational studies were mixed (see Table 1-14). Both are considered *low* confidence based primarily on limitations of the outcome ascertainment used in these studies.

Because of the limitations noted above with respect to interpretation of skin prick tests, EPA has higher confidence in the studies of allergy-related conditions. Consistent results were observed across this set of studies in children and adults comprising diverse populations. The pattern of exposure-response seen in the studies with sufficient sample size and range of exposure to examine these patterns suggests that formaldehyde exposure at levels seen in the general population studies can enhance the immune hypersensitivity response to allergens. The studies of allergy-related conditions are summarized in Figure 1-8.

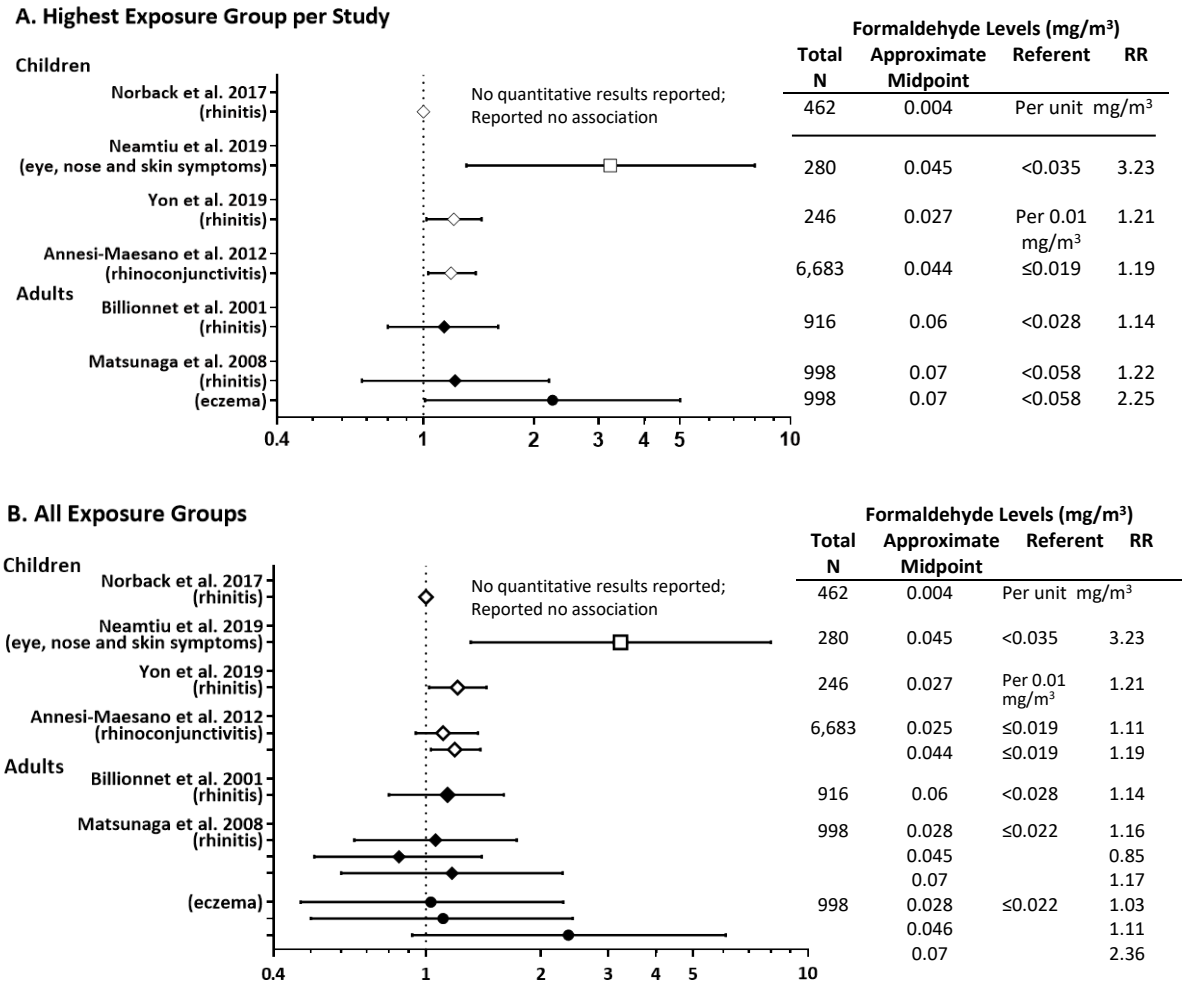
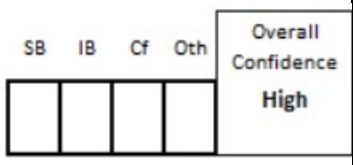
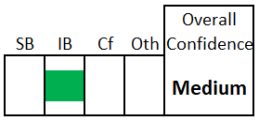
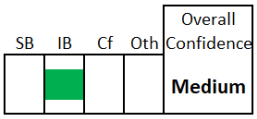


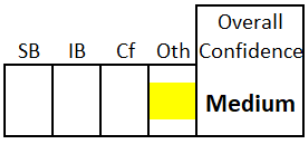
Figure 1-8. Relative risk estimates for prevalence of allergy-related conditions in children and adults in relation to formaldehyde in residential and school settings.

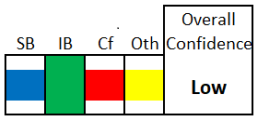
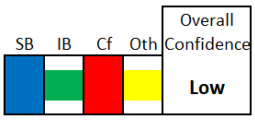
Results are depicted for rhinitis (diamond), eczema (circle) and symptom combinations (square). Study details are described in Table 1-12. *High* and *medium* confidence studies are included in figure. Open symbols are for studies in children; closed symbols are for studies in adults. Panel A depicts the results from the highest exposure group in each study; Panel B depicts the results from all exposure groups in each study.

Table 1-12. History of allergy-related conditions in relation to formaldehyde exposure, by age group

Study and design[a]	Results	
	Nasal and ocular	Dermatologic
Children		
Annesi-Maesano et al. (2012) (France) Prevalence survey, *n* = 6,683, ages 9–10 years, participation rate 69%. Sampling from 108 schools, all classes of specified grade level per school. **Exposure:** 5-day samples in classrooms. Median (75th percentile) 0.027 (0.034) mg/m^3 *(estimated from Figure 1 in paper).* **Outcome:** Parent report, sneezing and runny nose, with itchy eyes, without a cold, in past 12 months. **Evaluation[a]:** 	**Rhinoconjunctivitis** prevalence 11.8%, OR (95% CI) (adjusted) ≤0.0191 mg/m^3 1.0 (referent) >0.0191–0.0284 1.11 (0.94, 1.37) >0.0284–~0.055 1.19 (1.03, 1.39) *(Confidence intervals estimated from Figure 3 in paper)* Adjusted for age, gender, passive smoking, maternal and paternal history of asthma and allergic diseases.	Not examined
Yon et al. (2019) (Seongnam City, Korea) Prevalence study, n = 427 school children recruited from 22 randomly selected classrooms at 11 elementary schools; 68.9% participation rate, ages 10–14 years. Exposure: Formaldehyde sampling in each classroom using monitors with pumps during the 1st and 2nd half of the school year. Mean 0.027 ± 0.077 mg/m^3; as high as 0.06 mg/m^3 in some classrooms. Duration and sampling methods were not described. Outcome: rhinitis definition: presence of characteristic symptoms and /or signs during the previous 12 months using ISAAC questionnaire, Self report. Rhinitis severity: low, medium, high.	**Rhinitis prevalence**: 57.6%, n = 246 OR (95% CI) per 1 µg/m^3 1.019 (1.002, 1.037) adjusted for age, sex, environmental tobacco smoke exposure, and physician-diagnosed allergic rhinitis in parents. **Rhinitis severity** Control 181 Reference Mild 44 1.019 (0.991, 1.048) Moderate/ Severe 202 1.025 (1.007, 1.044) p_{trend} = 0.014	

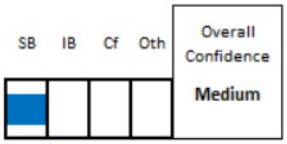
Study and design[a]	Results	
	Nasal and ocular	Dermatologic
Evaluation:  Letter to the editor providing minimal details on formaldehyde distribution and demographic characteristics.		
Neamtiu et al. (2019) (Romania) Prevalence survey; n = 139 males and 141 females, 89.7% participation rate. Sampling from five primary schools in one county, 3 classrooms per school. **Exposure:** 5-day samples in each classroom. Median (75th percentile) 0.035 (0.045) mg/m^3, maximum = 0.066 mg/m^3. **Outcome:** Allergy-like symptoms in the past week based on ISAAC questionnaire, as skin conditions (e.g., rash, itch, eczema), eye disorders (e.g., red, dry, swollen, itching, or burning eyes, or sensation of "sand in the eyes," and rhinitis symptoms (e.g., itching nose, sneezes, and/or stuffy or blocked nose. **Evaluation[a]**  Selection of schools was part of a larger European framework. Appropriate methods for exposure assessment and outcome ascertainment instruments appear to have been used. Outcome definition for allergy-like symptoms using ISAAC questionnaire included combined symptoms of rhinitis (nose), eye and skin conditions.	**Allergy-like symptoms (eyes, nose and skin)** OR (95% CI), above compared to below median (0.035 mg/m^3): 3.23 (1.31, 8.00). Logistic regression model adjusted for age, gender, NO_2, CO, CO_2, temperature, relative humidity, ventilation rate, and tobacco smoke exposure for the past week.	
Norbäck et al. (2017) (Malaysia) Prevalence survey, n = 462 randomly selected children	**Rhinitis,** weekly symptoms during previous 3 months. Prevalence 18.8%.	

Study and design[a]	Results	
	Nasal and ocular	**Dermatologic**
recruited from 8 randomly selected schools (15 students in each of 4 randomly selected classes per school). 96% participation rate. Mean age 14 years (range 14–16 years), 48% male. **Exposure:** Formaldehyde sampled continuously over 7 days in each classroom using diffusion samplers. Samplers placed 2 meters above floor, methods described. Mean concentrations formaldehyde indoor 4.2 µg/m^3, max 18.0 ug/m^3, 100% samples above the detection limit. Outside 5.5 ug/m^3, max 6.0 µg/m^3, 100% samples above the detection limit. **Outcome:** Rhinitis defined by two questions combined regarding nasal catarrh or nasal congestion in standardized questionnaire. Cases defined by reporting symptoms weekly over a 3-month period. **Evaluation[a]:**  Quantitative results were not reported. Very low indoor formaldehyde concentrations.	No association with formaldehyde in initial model; quantitative results were not reported. Initial stepwise multiple logistic regression model including indoor exposures (CO_2, NO_2, formaldehyde and VOC), personal factors (sex, race, current smoking, atopy, parental asthma/allergy) and home environment factors (ETS, dampness/mold, recent indoor painting).	
Isa et al. (2020) (Malaysia) Prevalence survey; n = 182 males and 288 females, participation not reported. 8 randomly selected schools (4 urban, 4 suburban), randomly selected students from 4 classes (Form two, aged 14 years) during August-November 2018 & February 2019. **Exposure:** One-hour samples in four classes during class session. Median (IQR) Urban: 13.2 (9.3) µg/m^3, Suburban: 3.1 (5.2) µg/m^3 (reported as mg/m^3 but likely µg/m^3). **Outcome:** Allergy information and symptoms within defined period	**Rhinitis** in last 12 months 55.5% OR (95% CI) per 10 units formaldehyde (reported as mg/m^3 but likely µg/m^3). 3.32 (1.69, 6.51) Adjusted for atopy, sex, doctor's diagnosed asthma, parental asthma/ allergy and urban/suburban location. Association observed for NO_2 OR (95% CI) per µg/m^3 2.07 (1.10, 3.89)	**Skin allergy** in last 12 months 14.5% OR (95% CI) per 10 units formaldehyde (reported as mg/m^3 but likely µg/m^3). 2.41 (0.96, 6.07) Adjusted for atopy, sex, doctor's diagnosed asthma, parental asthma/ allergy and urban/suburban location. Association observed for NO_2 OR (95% CI) per µg/m^3 3.68 (1.07, 12.69)

Study and design[a]	Results	
	Nasal and ocular	Dermatologic
using ECRHS and ISAAC questionnaires. Allergic symptoms in last 12 months: rhinitis, skin allergy. **Evaluation:**  Uncertainty in exposure concentrations and distribution given short sampling duration, very low concentrations in half the schools with unclear proportion of samples less than the LOD, and analysis using concentration as a continuous variable. Participation details not reported. Unknown impact of potential confounding by NO_2 on formaldehyde associations.		
Huang et al. (2017) (Shanghai, China) Case-control study, n = 409 children, aged 5–10 years, who were participants in a previous cross-sectional study (2011–2012) selected from 88 kindergartens located in 6 Shanghai districts. Eligible children lived in homes not renovated in prior two years and agreed to home inspection during March 2013-December 2014. **Exposure**: Formaldehyde sampling in child's bedroom, 24 hours, in breathing zone (detection range: 0.012-0.08 mg/m^3). Average concentration (µg/m^3), 24-hr 21.5 ± 13; 6-hr 22.2 ± 17.9. Range 6.0–60.0 µg/m^3, 2 homes above. **Outcome**: History of airway diseases using translated ISAAC questionnaire; Current rhinitis: In the past 12 months, has your child had a problem with sneezing, or a runny, or a blocked nose when he/she did not have a cold or the flu? **Evaluation[a]**:  	**Current rhinitis** 41.4% OR (95% CI) per IQR (15.2 µg/m^3) 0.72 (0.47, 1.10). Logistic regression adjusted for age, sex, family history of atopy, family annual income, household (ETS), early and current household dampness-related exposures, early antibiotics exposure, early home decoration, and the inspection season.	

Study and design[a]	Results	
	Nasal and ocular	Dermatologic
Concern for selection bias (eligibility based on home renovation and asthma status), difference in ventilation methods by case status suggests uncontrolled confounding, low formaldehyde concentrations		
Hsu et al. (2012) (Taiwan) Case-control study, *n* = 48 allergic rhinitis cases, 36 eczema cases 42 controls, recruited through kindergartens and day care centers, ages 3–9 years at enrollment. Participation rate (clinic exam and home measures) approximately 5% of potential cases and controls (but differential at various steps). **Exposure:** 2-hour household sample (probably bedroom; converted from ppb) Median (25th, 75th percentile): Controls 0.017 (0.005, 0.030) mg/m^3 **Outcome:** Initial screening through parent report of history (ages 2–6) with confirmation (1–3 years later) by clinical examination. **Evaluation[a]:**  Low and differential (at various steps) participation rate. Short exposure sampling period and no information on protocol. Limited analysis. Uncertainty regarding distribution (percentage <LOD).	**Allergic rhinitis** Formaldehyde concentrations lower in cases than in controls: (*n*) Median (25th, 75th percentile) mg/m^3 Controls (42) 0.017 (0.005, 0.030) Allergic rhinitis (48) 0.005 (0.005, 0.020) (*p* = 0.02) Mann-Whitney nonparametric test	**Eczema** Formaldehyde concentrations lower in cases than in controls: (*n*) Median (25th, 75th percentile) mg/m^3 Controls (42) 0.017 (0.005, 0.030) Eczema (36) 0.006 (0.005, 0.018) (*p* = 0.07) Mann-Whitney nonparametric test
Choi et al. (2009) (Korea) Case-control study, *n* = 50 atopic dermatitis cases, 28 controls, recruited through university outpatient clinic; recruitment procedures not described. Mean age (SD) 15.4 years (3.4) and 16.2 years (4.1) in atopic dermatitis cases and controls, respectively. Housing age and type: cases 58% <3 years old and 72% apartments; controls 29% <3 years old and 50% apartments.	Not examined	**Formaldehyde levels (mg/m^3):** Cases: Geometric mean 0.100; 75th percentile 0.220 Controls: Geometric mean 0.043; 75th percentile 0.115 *p* < 0.01

Study and design[a]	Results	
	Nasal and ocular	Dermatologic
Location: 44 and 21% near road for cases and controls, respectively. **Exposure:** Household sample (sampling period not reported, but closed windows and use of duplicates). Geometric mean, 25th, and 75th percentiles in controls: 0.043 (0.024, 0.115) mg/m^3. **Outcome:** Atopic dermatitis based on medical history, skin prick test and IgE (criteria not provided). **Evaluation[a]:**  Selection and recruitment process not reported; sampling period not reported and specific criteria for case definition not reported; potential confounders not addressed (age and type of housing and location differed between cases and controls, as measure of socioeconomic status). Limited analysis.		
Smedje and Norback (2001) (Sweden) Prospective (incidence) study, children, 1,258 without asthma at baseline, 88 incident cases of pollen allergy and 50 incident cases of pet allergy in 4-year follow-up; 78% participation in follow-up, mean age 10.3 years at baseline. School-based sample; 1st, 4th, and 7th grades. **Exposure:** Two 4-hour samples in 2−5 classrooms per school; measured in 1993 (*n* = 98) and 1995 (*n* = 101). mean 0.008 mg/m^3, geometric mean 0.004 mg/m^3 (min, max) (<0.005, 0.072) mg/m^3, 54% of 1993 samples and 24% of 1995 samples below detection limit (0.005 mg/m^3); median among those above detection limit = 0.010 mg/m^3. Individual student values based on average of 1993 and 1995 classrooms (<0.005 to 0.042 mg/m^3).	**Allergies** (incidence) RR (95% CI) per 0.010 mg/m^3, Pollen allergy: 1.3 (0.95, 1.7) Pet allergy: 1.1 (0.7, 1.7) Adjusted for sex, age, history of atopy, smoking.	Not examined

Study and design[a]	Results	
	Nasal and ocular	Dermatologic
Outcome: Parent report, hay fever/pollen allergy or pet dander allergy. **Evaluation[a]:**  Exposure measures in only 2 of the 4 years; uncertainty about distribution; relatively high percentage <LOD. Confounding by other exposures not fully addressed but pattern of results differed among the exposures examined. **Alternative Evaluation**: Medium (based on strengths of prospective study of incidence). **Related References:** Smedje et al. (1997).		
Adults		
Billionnet et al. (2011) (France) Prevalence survey, *n* = 916 adults from 490 dwellings (drawn from nationally representative sample; 13.6% participation rate), median age 44 (15–89); 48% men. **Exposure:** 1-week sample in bedroom Median, 75th percentile (minimum, maximum) 0.0194, 0.028 (0.013, 0.0863) mg/m^3. **Outcome:** Self-report, wheezing, running or blocked nose without cold or respiratory infection, in past 12 months. **Evaluation[a]:**  Low participation rate but potential for differential participation (by formaldehyde exposure and disease status) unlikely.	**Rhinitis** prevalence 38.3% OR (95% CI), above vs. below 75th percentile: 0.028 to 0.0863 vs. <0.028 mg/m^3 1.14 (0.8, 1.6) Adjusted for age, gender, smoking, education, relative humidity, time of survey, pets, mold, outdoor pollution measures.	Not examined
Matsunaga et al. (2008) (Osaka, Japan) Prevalence survey. Adults, *n* = 998 women, median 17th week of	**Allergic rhinitis** (14.0% prevalence) mg/m^3 | *n* | OR | (95% CI) <0.022 | 298 | 1.0 | (referent) 0.022– | 299 | 1.06 | (0.65, 1.73)	**Atopic eczema** (5.7% prevalence) mg/m^3 | *n* | OR | (95% CI) <0.022 | 298 | 1.0 | (referent) 0.022–0.033 | 299 | 1.03 | (0.47, 2.29)

Study and design[a]	Results	
	Nasal and ocular	**Dermatologic**
pregnancy, median age ~30. Recruited through obstetric clinics and public health nurses. **Exposure:** 24-hour personal sample (converted from ppb). Median 0.030, maximum 0.161 mg/m^3. Cutpoints based on 30th, 60th, and 90th percentiles (<0.022, 0.022–0.033, 0.034–0.57, and ≥0.058 mg/m3). **Outcome:** Self-report, treatment for allergic rhinitis or atopic eczema in past 12 months. **Evaluation[a]:**  Low participation rate but potential for differential participation (by formaldehyde exposure and disease status) unlikely. Lack of data pertaining to sensitivity and specificity of the ascertainment method for these conditions.	0.033 0.034–0.057 301 0.85 (0.51, 1.40) 0.058–0.131 100 1.17 (0.60, 2.28) (trend *p*-value) (0.91) 0.058–0.161 vs. <0.058 1.22 (0.68, 2.20) Adjusted for age, gestation, parity, family history (of asthma, atopic eczema, allergic rhinitis), smoking status, current passive smoking at home and work, mold in kitchen, indoor domestic pets, dust mite antigen level, family income, education, and season. (Midpoint of highest quartile estimated as 0.0.07 mg/m^3 based on personal communication (Matsunaga, 2012))	0.034–0.057 301 1.11 (0.50, 2.42) 0.058–0.131 100 2.36 (0.92, 6.09) (trend *p*-value) (0.08) 0.058–0.161 vs. <0.058 2.25 (1.01, 5.01) per 12.3 mg/m^3 1.16 (0.99, 1.35) Adjusted for same factors as allergic rhinitis analysis. Additional analyses examined effect modification by family history of asthma, atopic eczema, or allergic rhinitis, see Figure 1-11 in this report. (Midpoint of highest quartile estimated as 0.0.07 mg/m^3 based on personal communication (Matsunaga, 2012)).

[a]Evaluation of sources of bias or study limitations (see details in Appendices A.5.1 and A.5.4). SB = selection bias; IB = information bias; Cf = confounding; Oth = other feature of design or analysis. Extent of column shading reflects degree of limitation. Direction of anticipated bias indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact would be likely to be away from the null (i.e., spurious or inflated effect estimate).

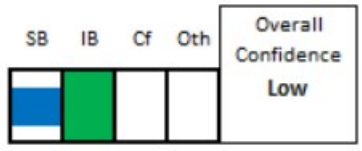
Table 1-13. Skin prick tests in relation to formaldehyde exposure, by age group

Study and design	Results
Children	
Garrett et al. (1999) (Australia) Prevalence survey, *n* = 148 (53 asthma cases, 95 controls; combined for this analysis; some cases and controls from same household; three excluded for total *n* = 145), ages 7–14 (mean 10.2) years. **Exposure:** 4-day (one per season) measures in home (bedroom, living room, kitchens, outdoors). 74% of the children had lived in the house for at least 5 years; 34% for entire life. Median (maximum) 0.0158 (0.139) mg/m^3. **Outcome:** Atopy based on skin prick tests to 12 allergens (cat, dog, grass mix #7, Bermuda grass, house dust, two dust mite, five fungi).	**Atopy** prevalence: 88/145 = 0.61 Exposure (mg/m^3) *N* Proportion with atopy <0.020 30 0.33 0.020–0.050 75 0.64 0.050–0.139 40 0.75 (trend *p*-value) (<0.001) per 0.020 mg/m^3 increase OR 1.42 (0.99, 2.04) Odds ratio, adjusted for parental asthma history, sex; other factors examined (passive smoke, pets, indoor NO_2, fungal spores, house dust mite allergens). (Similar trend seen based on bedroom measure: prevalence 0.50, 0.59, 0.74, trend *p* = 0.06.) Exposure (mg/m^3) *N* Number of allergens[a] Wheal size[a]

Study and design	Results
Evaluation[a]:  Uncertainty about effect of recruitment process and about time window of exposure measurement with respect to skin prick test results.	<0.020 30 1.3 0.5 0.020–0.050 75 3.4 1.0 0.050–0.139 40 3.9 1.3 (trend *p*-value) (0.004) (0.002) [a]Estimated from Figure 1 (Garrett et al., 1999)
Children and adults (stratified)	
Palczynski et al. (1999) (Poland) Prevalence survey, *n* = 278 adults ages 16–65 years; *n* = 186 children ages 5–16 years from 120 households with children (random selection from 10-year-old apartment houses). Participation rate not reported. **Exposure:** 24-hour household sample (area not specified) Mean (±SD) (minimum, maximum) 0.026 (±0.011) (0.002, 0.067) mg/m^3; 2% >0.050. **Outcome:** Allergy based on skin prick tests (SPT) to five allergens (dust, dust mites, feathers, grasses) **Evaluation[a]** **Children:**  **Adults:**  Uncertainty about time window of exposure measurement for skin prick test results (greater uncertainty in adults than in children). Not informative above 0.050 mg/m^3 because of sample size (≤5).	Positive Skin Prick Test (%) (*n*) / IgE (>100 kU/L) (%) Children <0.025 mg/m^3 (101) 34.7 37.6 0.025–0.050 (82) 28.0 32.9 0.051–0.067 (4) 25.0 25.0 Adults <0.025 mg/m^3 (142) 29.6 26.1 0.025–0.050 (131) 28.2 25.6 0.051–0.067 (5) 60.3 40.0 Additional analyses demonstrated effect modification by environmental tobacco smoke, see Table 1-21 in this report.

Abbreviations: SB = selection bias; IB = information bias; Cf = confounding; Oth = other feature of design or analysis.
[a]Evaluation of sources of bias or study limitations (see details in Appendix 3.5.3.2 and Table C.5.3.2-2). Extent of column shading reflects degree of limitation. Direction of anticipated bias indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact would be likely to be away from the null (i.e., spurious or inflated effect estimate).

Table 1-14. Allergy symptoms or skin prick tests in relation to formaldehyde exposure in workers

Study and design	Results
Allergy symptoms	
Fransman et al. (2003) (New Zealand) Prevalence survey. Plywood mill workers, *n* = 112. Participation rate 66%. Mean age 34.5 years, 71% men, mean duration 4.7 years. **Exposure:** Personal samples (15-minute samples) in jobs held by 49 workers: (*n*), geometric mean (±geometric standard deviation) (mg/m^3). all (22) 0.080 (3.0) dryers (14) 0.070 (3.2) (one outlier) pressing (5) 0.160 (2.7) other areas 0.030–0.040 mg/m^3 (at or near detection limit) Total inhalable dust (full-shift personal samples): geometric mean 0.7 mg/m^3. **Outcome:** Self-report, allergy symptoms based on sensitivity to house dust, food, animals or grasses/plants. **Evaluation[a]:**  Uncertain impact of outcome classification (includes food allergies). Selection out of the exposed work force of "affecteds" possible in this type of prevalence study. "Low" exposure group exposed to levels of formaldehyde up to 0.080 mg/m^3. Either limitation would result in reduced (attenuated) effect estimate.	**Allergy symptoms** prevalence Low (<0.080 mg/m^3, *n* = 38) 31.6% High (>0.080 mg/m^3; *n* = 11) 45.5% OR (95% CI) (>0.080 vs. <0080 mg/m^3): 2.4 (0.5, 11.8) Adjusted for age, sex, ethnicity, smoking. Internal comparison by exposure category limited to the 49 workers with same job titles as those with the 22 air sample measurements. Dust not related to high formaldehyde exposure. Not clear if these specific symptoms were or were not related to other exposures (e.g., endotoxin).
Skin prick tests	
Herbert et al. (1994) (Canada) Prevalence survey. Oriented strand board manufacturing (*n* = 99). Comparison group (*n* = 165) oil field workers, not exposed to gas or vapors. Participation rate 98% in workers, 82% in comparison group. Mean age ~35 years in both groups. **Exposure:** 21 hours continuous area sampling, 2 consecutive days Saw line, debarking: 0.090–0.160 mg/m^3 Postheat, press conveyor, packaging, storage: 0.200–0.290 mg/m^3 Preheat conveyor: 0. 330 mg/m^3 Total dust: mean 0.27 mg/m^3, median aerodynamic equivalent diameter = 2.5 µm. **Outcome:** Atopy based on SPT to six allergens (wheat, rye, *Alternaria*, cat, house dust, birch; four of these are common allergens in this area). **Evaluation[a]:**  Uncertainty about time window of exposure measurement with respect to skin prick test results; some uncertainty about referent group.	**Atopy** prevalence not reported OR (95% CI) 0.75 (0.40, 1.35) Dust exposure considered low; not included in analysis.

[a]Evaluation of sources of bias or study limitations (see details in Appendix A.5.1 and A.5.4). SB = selection bias; IB = information bias; Cf = confounding; Oth = other feature of design or analysis. Extent of column shading reflects degree of limitation. Direction of anticipated bias indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact would be likely to be away from the null (i.e., spurious or inflated effect estimate).

Asthma

Asthma affects approximately 5–10% of the U.S. population, and results in a significant individual and societal burden in terms of morbidity, health care costs, and indirect costs [e.g., due to absences from work (Shenolikar et al., 2011; Bahadori et al., 2009)]. The potential for formaldehyde to induce or exacerbate asthma symptoms has been described in occupational settings in reports spanning several decades (see for example, Nordman et al., 1985; Popa et al., 1969). Characterization of this risk on a population level requires more extensive evaluation. Epidemiological studies have investigated potential associations between formaldehyde and asthma in children and adults using formaldehyde measurements conducted in occupational, residential, and school-based settings. The outcomes studied include the incidence of asthma (i.e., the number of people newly diagnosed with asthma in a period of time), prevalence of current asthma (typically ascertained through a set of questions pertaining to symptoms or medication use over a period of time, e.g., past 12 months), and asthma control (typically ascertained through a larger set of symptoms, medication, and medical care use over a shorter period of time, e.g., 2–4 weeks). Asthma control pertains to the extent to which symptoms can be reduced or eliminated with medication. The prevalence of current asthma includes newly diagnosed patients, as well as previously diagnosed patients who are experiencing the expression (and thus the costs and burden) of this condition. EPA considered "ever had asthma" to be of limited use in this review, as the formaldehyde measures available do not reflect cumulative exposures that could be related to cumulative risk, and thus EPA did not include results using the definition, "ever had asthma." However, there were a small number of studies where asthma was not defined clearly but study details appeared to indicate that the definition was not "ever had asthma"; these were included but the limitation was noted. Altered lung function in people with asthma, examined in acute controlled exposure studies, is also discussed in this section, although these acute, high exposure scenarios are of less direct relevance to the question of risks of chronic exposures.

Asthma prevalence and incidence studies

The collection of studies evaluated associations between formaldehyde exposure and prevalence of current asthma, as determined by symptoms or medication use in the past 12 months. The six *medium* or *high* confidence studies in homes or schools with relatively low exposures (<0.05 mg/m^3, most from approximately 0.02 to 0.04 mg/m^3) reported relative risks around 1.0 (see Table 1-15, Figure 1-9A). This set of studies included a variety of designs and populations; the school-based studies are large (from 1,014 to 6,683 total participants). The case definition of wheezing during the past year used by Venn et al. (2003) is interpreted to be relevant to a definition of current asthma as used in this assessment since 88% of the cases also reported using a reliever inhaler in the past year. The results of Smedje and Norback (2001) are consistent with these studies, and so the inclusion of this as a *medium* confidence study would not change the interpretation of the evidence. A study that assessed a definition of "asthma-like" symptoms among

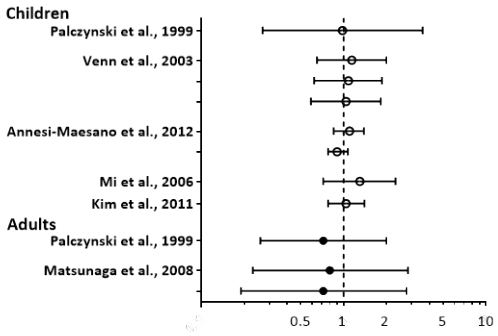
school children indicates that asthma symptoms, a less specific outcome compared to "current asthma" may occur at lower formaldehyde concentrations (Neamtiu et al., 2019). This study in Romania observed an OR of 2.7 (95% CI: 1.04, 6.97) with the prevalence of asthma-like symptoms in the past week comparing children exposed to formaldehyde concentrations above and below the median (0.035 mg/m^3, maximum 0.066 mg/m^3).

Six *medium* confidence general population studies in children or adults where a proportion of the study sample had exposures of 0.05–0.1 mg/m^3 were available (see Table 1-16; Figure 1-9B). Two of these included both children and adults (Zhai et al., 2013; Krzyzanowski et al., 1990), and each provides evidence of a greater susceptibility in children. Both studies compared effects in groups exposed to levels approximately 0.08 mg/m^3 or above to lower exposed groups; a limitation of the Krzyzanowski et al. (1990) analysis is the relatively small number in the highest exposure group (n = 21). The sRR in children for these two studies was 4.5 (95% CI: 0.76, 27). One other study of children (mean age 10 years) was a hospital-based case-control study that diagnosed prevalent asthma using the ISAAC questionnaire over 3 or more months, and an FEV_1 increase of 15% in response to β-agonist inhalation (Liu et al., 2018). The authors reported an association with formaldehyde levels based on a regression analysis using quartiles of formaldehyde concentration (OR = 2.736, 95% CI: 1.098, 5.516). Exposure levels in the highest quartile ranged from 0.05 to 0.14 mg/m^3. Of note, a Canadian intervention study of impacts on symptom exacerbation among asthmatic children from increasing ventilation rates in homes reported that a 50% reduction in formaldehyde concentrations in the bedroom was associated with a 14 to 20% decrease in the annual change in some symptoms or medical care in the intervention group (Lajoie et al., 2014). Geometric mean concentrations of 0.037 mg/m^3 were measured in the intervention group at baseline. However, other coexposures were reduced by the intervention resulting in uncertainty in the independent effect of formaldehyde, although the reductions were to a lessor extent and separate effects of the other factors were not analyzed. Two other *medium* confidence studies with exposures above 0.05 mg/m^3 were conducted only in adults (Billionnet et al., 2011; Matsunaga et al., 2008). Billionnet et al. (2011) compared the asthma outcome for subjects exposed to exposures greater than the 75th percentile of 0.028 mg/m^3 to those exposed to less than the 75th percentile. While most of the study population was exposed to lower concentrations, a portion were exposed to concentrations as high as 0.09 mg/m^3, which likely influenced the observed RR of 1.4. EPA has lower confidence in the results of Matsunaga et al. (2008) because of the lower sensitivity and specificity of the asthma ascertainment. The pattern of results in this exposure range of 0.05–0.1 mg/m^3 was indicative of an elevated risk, as none of the point estimates were below 1.0; however, the confidence intervals around each of the estimates indicated some variability in the data (see Figure 1-9).

Epidemiological studies in occupational settings examining the incidence of asthma in a cohort of individuals after they initially enter a workplace have not been conducted. The available studies generally did not attempt to examine the timing of symptoms in relation to when the

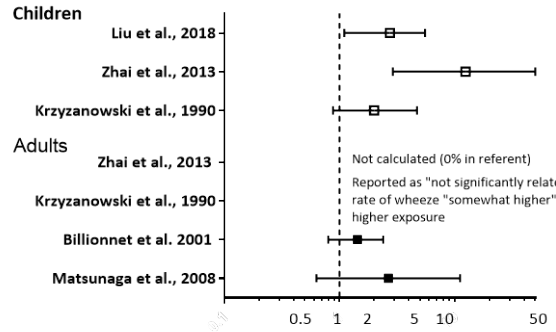
subjects are present in the workplace (i.e., over the course of a workday or comparison between workdays and weekend days) and so would not have the level of detail that would be included in a clinical workup of occupational asthma; rather, these studies can be thought of as studies of the prevalence of current asthma among workers exposed to formaldehyde. The occupational exposure literature included three *medium* confidence studies of plywood and other layered wood manufacturing workers in Canada (Herbert et al., 1994), New Zealand (Fransman et al., 2003), and Indonesia (Malaka and Kodama, 1990); each of these studies included between 93 and 112 exposed workers (see Table 1-17). Exposure levels varied by work area, but generally ranged from 0.10 to >0.50 mg/m^3. A greater than three-fold increased risk of asthma was seen in each of these studies; the sRR for these three studies was 3.79 (95% CI 1.98, 7.28). One of the wood worker studies addressed potential confounding by dust exposure by the inclusion of this variable in the analysis (Malaka and Kodama, 1990), and another study specifically noted that the measured dust levels were not related to high formaldehyde exposure and that the asthma symptoms were not strongly related to other exposures including endotoxin measures (Fransman et al., 2003). The results from these studies may represent underestimates of risk; two factors contribute to this concern. All of the studies were prevalence surveys of workers who have remained in a workplace for some time (e.g., 2 or more years), which could be biased by the loss of affected individuals from the workforce (e.g., because of the "healthy worker effect" inherent in this type of study design). In addition, in two of the studies, the comparison group included workers who may have also been exposed to formaldehyde or other respiratory irritants (Fransman et al., 2003; Herbert et al., 1994). Inclusion of this type of exposure in the comparison group reduces the possibility that the observed associations were influenced by differential reporting of asthma among the exposed but raises the possibility that the relative risk estimated against this comparison group underestimates the risk that would be represented by a comparison with a population that does not have these other exposures. Another limitation to note is that the sensitivity and specificity of the symptom-based questionnaire measures may be lower in occupational settings than in general population studies; EPA did not find validation data specific to these types of wood manufacturing settings. However, given the strength of the relative risks, the consistency of the associations seen in the three different workplaces and populations, and the likelihood that the observed associations were underestimates of the true associations, these studies collectively support a strong association between formaldehyde concentrations above approximately 0.100 mg/m^3 in occupational settings and increased prevalence of current asthma (see Figure 1-9).

A. General Population, Low Exposures (< 0.050 mg/m^3)



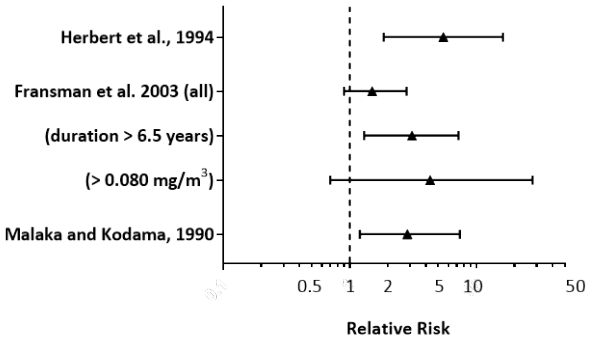
Total N	Formaldehyde Levels (mg/m³) Approximate Midpoint	Referent	RR
187	0.037	<0.025	0.98
190	0.019	<0.016	1.14
	0.027		1.08
	0.041		1.04
6,683	0.025	≤0.019	1.10
	0.044		0.90
1,414	0.010	per 0.010 mg/m^3	1.30
1,028	0.030	per 0.010 mg/m^3	1.04
278	0.037	<0.025	0.72
998	0.028	≤0.022	0.80
	0.046		0.72

B. General Population, High Exposures (> 0.050 mg/m^3)



Total N	Formaldehyde Levels (mg/m³) Approximate Midpoint	Referent	RR
360	0.05	per quartile	2.74
82	0.115	<0.08	12
298	0.09	<0.049	2
186	0.115	<0.08	
613	0.09	<0.049	
916	0.046	<0.028	1.43
998	0.07	<0.058	2.65

C. Occupational Settings (> 0.01 mg/m^3)

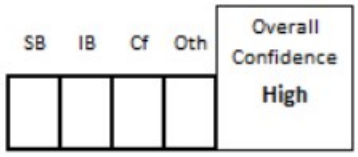


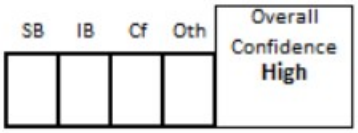
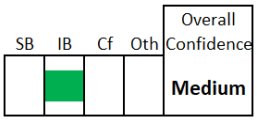
Total N	Formaldehyde Levels (mg/m³) Approximate Midpoint	Referent	RR
99	0.20	<0.08	12
112	0.08	<0.049	1.5
	0.08	<0.08	3.1
	0.16	<0.049	4.3
93	0.12	<0.058	2.65

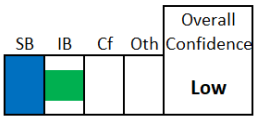
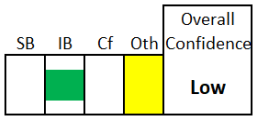
Figure 1-9. Relative risk estimates for prevalence of asthma in children and adults in relation to formaldehyde by exposure level in general population and occupational studies.

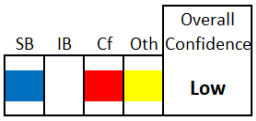
Study details are described in Tables 1-15 (Panel A), 1-16 (Panel B), and 1-17 (Panel C). High and medium confidence studies included in figures. Lajoie et al. (2014) was not included in the figure because the study assessed percent change in current asthma symptoms over 12 months, not relative effect. Levels for most of the participants in the study groups in Panel A, low exposure, were < 0.05 mg/m^3. The exposure value for Liu et al. (2018) is the 75% percentile concentration, which resulted in classifying the study as high exposure. Exposure levels in Billionnet et al. (2011) ranged to a maximum of 0.09 mg/m^3, which resulted in classifying the study as high exposure. Effect estimates are RR or OR.

Table 1-15. Prevalence of asthma in children or adults in relation to residential or school formaldehyde exposure in studies with relatively low exposures (≤0.05 mg/m^3)

Study and design[a]	Results
Studies in children and adults (stratified)	
Palczynski et al. (1999) (Poland) Prevalence survey; *n* = 278, ages 16–65 years and *n* = 187, ages 5–15 years from 120 households with children (random selection, 10-year old apartments). Participation rate not reported. **Exposure:** 24-hour household sample (area not specified). Mean (±SD) (minimum, maximum) 0.026 (±0.011) (0.002, 0.067) mg/m^3 2% >0.050 mg/m^3 **Outcome:** Bronchial asthma diagnosed using American Thoracic Society criteria. **Evaluation[a]:**  Uncertainty regarding asthma definition. Not informative above 0.050 mg/m^3 because of sample size (*n* = 4).	**Children results:** Asthma prevalence 4.8% Exposure category (*n*) prevalence All children <0.025 mg/m (101) 5.0% 0.025–0.050 (82) 4.9% 0.0501–0.067 (4) 0.0% **Adult results**: Asthma prevalence: 5.8% Exposure category (*n*) prevalence All adults <0.025 mg/m^3 (142) 6.3% 0.025–0.050 (131) 4.6% 0.0501–0.067 (5) 20.0%
Studies in children	
Annesi-Maesano et al. (2012) (France) Prevalence survey; *n* = 6,683, ages 9–10 years, participation rate 69%. Sampling from 108 schools, all classes of specified grade level per school. **Exposure:** 5-day samples in classrooms. Median (75th percentile) 0.027 (0.034) mg/m^3 (estimated from Figure 1 in paper). **Outcome:** Asthma based on International Study of Asthma and Allergies in Childhood questionnaire. **Evaluation[a]:**  	Prevalence 6.9%, OR (95% CI) ≤0.0191 mg/m^3 1.0 (referent) >0.0191–0.0284 1.10 (0.85, 1.39) >0.0284–~0.055 0.90 (0.78, 1.07) (Confidence intervals estimated from Figure 4 in paper.) Adjusted for age, gender, passive smoking, and paternal or maternal history of asthma or allergic disease. Additional analyses examined effect modification by atopy status, see Figure 1-11 in this report.
Kim et al. (2011) (Korea)	Prevalence of asthma: 6.9% OR (95% CI), per 0.010 mg/m^3: Asthma, current 1.04 (0.78, 1.40).

Study and design[a]	Results
Prevalence survey; *n* = 1,028, mean age 10 years, participation rate 96%. Sampling from 12 schools, 2–3 classes per school. **Exposure:** 7-day samples in classrooms (*n* = 34) and one outdoor area per school (*n* = 12) (all samples collected in same season). Mean (±SD), (minimum, maximum) Indoor 0.028 (±0.0083) 0.016, 0.047 mg/m^3. **Outcome:** Asthma based on current use of asthma medication or asthma attack in past 12 months. **Evaluation[a]:** 	Adjusted for age, sex, self-reported pet or pollen allergy, environmental tobacco smoke at home, other home environment (indoor dampness, remodeling, changing floor, age of home).
Neamtiu et al. (2019) (Romania) Prevalence survey; n = 139 males and 141 females, 89.7% participation rate Sampling from five primary schools in one county, 3 classrooms per school. **Exposure:** 5-day samples in each classroom. Median (75th percentile) 0.035 (0.045) mg/m^3, maximum = 0.066 mg/m^3. **Outcome:** Asthma-like symptoms based on International Study of Asthma and Allergies in Childhood questionnaire, asthma-like symptoms defined as difficult breathing, dry cough and wheezing in the past week (any symptom). **Evaluation[a]**  **Medium** Appropriate methods for exposure assessment and outcome ascertainment instruments appear to have been used although outcome definition (asthma-like symptoms) is not specific for current asthma.	**Asthma-like symptoms** OR (95% CI), above compared to below median (0.035 mg/m^3): 2.7 (1.04, 6.97) Logistic regression model adjusted for age, gender, NO_2, CO, CO_2, temperature, relative humidity, ventilation rate, and tobacco smoke exposure for the past week.
Mi et al. (2006) (Shanghai, China) Prevalence survey; *n* = 1,414, ages 12–17 (mean 13) years, percentage with environmental tobacco smoke not reported, participation rate 99%. Sampling from 10 schools, 3 7th-grade classes per school. **Exposure:** 4-hour samples in 30 classrooms. Mean (±SD), (minimum, maximum) 0.009 (±0.0089) (0.003, 0.020) mg/m^3. No information on LOD or percentage <LOD. Weak correlation (Spearman r ranged from−0.15 to 0.08) with other exposures (NO_2 and ozone, indoor and outdoor measurements). Moderate correlation (Spearman r ~0.40) with room temperature and relative humidity. **Outcome:** Current asthma (medication use or asthma attack in past 12 months), symptoms in past 12 months (wheeze or whistling in the chest, daytime breathlessness attack at rest or after exercise, nighttime breathlessness attack). **Evaluation[a]:**  Uncertainty about exposure distribution and analysis (e.g., percentage <LOD and treatment in analysis as continuous variable).	Prevalence of: Asthma, current 3.1% Wheeze, whistling 3.1% Daytime attack 23.0% Nighttime attack 2.6% OR (95% CI), per 0.010 mg/m^3: Asthma, current 1.30 (0.72, 2.32) Symptoms in past 12 months Wheeze, whistling 1.01 (0.56, 1.81) Daytime attack 1.09 (0.86, 1.38) Nighttime attack 1.26 (0.63, 2.53) Adjusted for age, gender, smoking, observed water leakage and indoor molds.
Venn et al. (2003) (United Kingdom)	(*n* cases), OR (95% CI):

Study and design[a]	Results
Nested case-control; *n* = 190 persistent wheeze cases, 214 controls, ages 9–11 years. Participation rate 79% among cases, 59% among controls. **Exposure:** 3-day samples in bedroom; median ~0.022 mg/m^3; median in top quartile 0.041 mg/m^3. **Outcome:** Parent report, wheeze in past year (reported for both of two periods, 1995–1996 and 1998), validated by medical records for 115 cases and 164 controls. **Evaluation[a]:**  Uncertainty about time window of exposure measure.	<0.016 mg/m^3 (49) 1.0 (referent) 0.020–0.022 (46) 1.14 (0.65, 2.00) 0.022–0.032 (51) 1.08 (0.62, 1.86) 0.032–0.123 (44) 1.04 (0.59, 1.82) (trend *p* = 0.93) Adjusted for age, sex, socioeconomic status. Similar results in group with validation of case status from prescription asthma medication records. (Median in top quartile provided in email from Dr. Venn, March 29, 2012.)
Branco et al. (2020) (Portugal) Prevalence survey: School children, n=648 preschoolers (3-5 years) and n=882 primary school children (6-10 years) randomly recruited from urban and rural nursery (n=17) and primary schools (n=8), participation rate 39%. **Exposure**: Daily exposure based on time-averaged air concentration and reported time in specific school locations. Continuous monitoring in each room (24 h to 9 days). Mean formaldehyde concentration (SD) 35.3 (43.1) µg/m^3; Table in article also stated that these values were the median (IQR). **Outcome**: Asthma diagnosis by study physicians based on either reported symptoms using ISAAC questionnaire or a report of ever having 1 or more symtoms plus spirometry before and after bronchodilator (ERS/ATS and Global Initiative for Asthma guidelines). Evaluation[a]:  Concern regarding potential for selection bias (low participation and missing values) and decreased specificity of asthma diagnosis by including very young children (<5 years), 42% of sample.	OR (95% CI) per IQR increase in exposure 0.66 (0.37, 1.21). OR (95% CI) above compared to below the median 1.19 (0.60, 2.39). Logistic regression models adjusted for site (urban, rural), study phase, sex, age group, BMI and parental history of asthma. Also controlled for surrogates of home indoor exposure including mother's education, living with smoker. Other covariates for contact with farm animals during 1st year of life, pets at home in previous year &/or 1st year of life.
Yon et al. (2019) (Seongnam City, Korea) Prevalence study, n = 427 school children recruited from 22 randomly selected classrooms at 11 elementary schools; 68.9% participation rate, ages 10–14 years. **Exposure**: Formaldehyde sampling in each classroom using monitors with pumps during the 1st and 2nd half of the school year. Mean 0.027 ± 0.077 mg/m^3; as high as 0.06 mg/m^3 in some classrooms. Duration and sampling methods were not described. **Outcome**: current asthma definition: presence of characteristic symptoms and /or signs during the previous 12 months using ISAAC questionnaire, Self report. Evaluation:  Few children with asthma contributed to analyses Letter to the editor providing minimal details on formaldehyde distribution and demographic characteristics	Current asthma prevalence n = 10 OR (95% CI) per 1 µg/m^3 1.023 (0.96, 1.089) adjusted age, sex, environmental tobacco smoke exposure, keeping a pet at home, and physician-diagnosed asthma and allergic dermatitis in parents.

Study and design[a]	Results
Madureira et al. (2016) (Porto, Portugal) Children, case-control, October 2012–April 2013, random recruitment of 38 residences among asthmatic children and 30 residences among nonasthmatic children previously identified in a cross-sectional study (Madureira et al., 2015). n=1099 children (aged 8–10 years, 69% of recruited). Excluded respondents with a recent renovation or who had moved since responding. **Exposure:** Continuous passive sampling in bedroom over 7 days. Formaldehyde concentrations all above the detection limit. **Outcome:** For asthma cases, parents responded yes to both of 2 questions in ISAAC questionnaire: 1) Has your child ever had asthma diagnosed by a doctor? and 2) In the past 12 months, has your child had wheezing or whistling in the chest? Parents of controls responded no to both questions. **Evaluation:**  Small sample size, potential for selection bias, no adjustment for confounding and some differences noted between cases and controls.	Formaldehyde concentration in bedroom, mg/m^3 Cases: N = 38; Mean (SD) 0.015 (0.010); Median (SD) 0.011; IQR 0.007-0.018; Min-max 0.004-0.051 Controls: N = 30; Mean (SD) 0.017 (0.095); Median (SD) 0.015; IQR 0.009-0.022; Min-max 0.005-0.043 *p* value = 0.199
Hsu et al. (2012) (Taiwan) Case-control study; *n* = 9 cases, 42 controls, recruited through kindergartens and day care centers, ages 3–9 years at enrollment. Participation rate (clinic exam and home measures) approximately 5% of potential cases and controls). **Exposure:** 2-hour household sample (probably bedroom; converted from ppb) Median (25th, 75th percentile): Controls 0.017 (0.005, 0.030) mg/m^3. **Outcome:** Initial screening through parent report of history (ages 2–6 years) with confirmation by clinical examination. **Evaluation[a]:**  Low and differential (at various steps) participation rate. Short exposure sampling period and no information on protocol. Limited analysis. Uncertainty regarding distribution (percentage <LOD). In addition, small sample size (*n* = 9) for asthma.	Formaldehyde concentrations lower in cases than in controls: (*n*) Median (25th, 75th percentile) mg/m^3 Controls (42) 0.017 (0.005, 0.030) Asthma cases (9) 0.005 (0.004, 0.012) (*p* = 0.03) Nonparametric (Mann-Whitney) comparison of formaldehyde by group.
Hwang et al. (2011) (Korea) Case-control study drawn from 1,005 elementary students (one school, all grades; 84% participation rate). 33 cases (out of 129) and 40 controls (out of unspecified number) agreed to participate in environmental measurement study. Controls selected from respondents with no asthma symptoms or diagnosis, age- and sex-matched to cases. **Exposure:** 3-day household sample (2 rooms) and personal sample Geometric mean (±geometric SD) mg/m^3 in controls: 0.036 (±0.002) household; 0.029 (±0.002) personal **Outcome**: Parent report of asthma based on ISAAC questionnaire. **Evaluation[a]:**	Formaldehyde level, geometric mean (SD) mg/m^3, by group: Cases: Household sample 0.031 (0.002); Personal sample 0.027 (0.002) Controls: Household sample 0.036 (0.002); Personal sample 0.029 (0.002) OR (95% CI), per unit increase in formaldehyde: 1.0 (1.0, 1.1) Comparison of distributions of exposure (*t*-tests); logistic regression adjusted for gender, age, income, education level of parents, passive smoking.

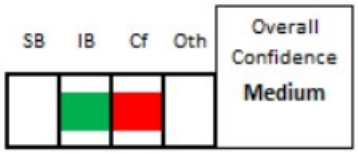
Study and design[a]	Results
 Asthma definition includes current asthma and ever asthma. Uncertainty regarding selection processes (high prevalence of family history of asthma in cases [86%] and controls [96%]); uncertainty about analysis and distribution.	
Hulin et al. (2010) (France) Case-control; (*n* = 32 urban cases, 31 urban controls; *n* = 24 rural cases, 24 rural controls), mean age 12.5 years. Drawn from previous school-based surveys. Participation rates 22 and 13% in urban cases and controls, 52 and 75% in rural cases and controls, respectively. **Exposure:** 7-day sample in living room; median (minimum, maximum) Total (*n* = 112) 0.019 (0.004, 0.075) mg/m^3 Urban, winter (*n* = 36) 0.020 (0.007, 0.075) mg/m^3 Urban, summer (*n* = 27) 0.021 (0.004, 0.060) mg/m^3 Rural, summer (*n* = 49) 0.016 (0.005, 0.063) mg/m^3 **Outcome:** Parent report of child's history of asthma, use of asthma medications, or wheezing in past 12 months. **Evaluation[a]:**  Small sample size and uncertain interpretation of the stratified analyses (and unspecified *n* in analysis of current asthma).	OR (95% CI) for above vs. below median) Total sample: 1.7 (0.7, 4.4) urban OR = 0.24 (0.04, 1.5) rural OR = 9.0 (1.0, 98) (interaction $p \leq 0.05$) (Confidence intervals estimated from figure in the paper.) Adjusted for age, sex, family history of allergy, passive smoke exposure during childhood, and allergic rhinitis. Levels of other pollutants that are risk factors for asthma were higher in urban areas.
Smedje and Norback (2001) (Sweden). Prospective (incidence) study. 1,258 without asthma at baseline, 56 incident cases of asthma in 4-year follow-up (incidence rate 1.1% per year); 78% participation in follow-up, mean age 10.3 years at baseline. School-based sample; 1st, 4th, and 7th grades. **Exposure:** Two 4-hour samples in 2−5 classrooms per school; measured in 1993 (*n* = 98) and 1995 (*n* = 101). Mean 0.008 mg/m^3, geometric mean 0.004 mg/m^3, (min, max) (<0.005, 0.072) mg/m^3, 54% of 1993 samples and 24% of 1997 samples below detection limit (0.005 mg/m^3); median among those above detection limit = 0.010 mg/m^3. Individual student values based on average of 1993 and 1997 classrooms (<0.005 to 0.042 mg/m^3).[c] **Outcome:** Parent report of physician diagnosis of asthma and six lower respiratory symptom questions; previous validation study (73% sensitivity, 99% specificity). **Analysis:** Odds ratio, adjusted for sex, age, history of atopy, smoking. **Evaluation[a]:**  Exposure measures in only 2 of the 4 years; uncertainty about distribution; relatively high percentage <LOD. Confounding by other exposures not fully addressed but pattern of results differed among the exposures examined.	OR (95% CI) per 0.010 mg/m^3: total sample: 1.2 (0.8, 1.7) with history of atopy: 0.6 (0.3, 1.3) no history of atopy: 1.7 (1.1, 2.6) (Atopy defined at baseline based on positive response to questions on childhood eczema, allergy to pollen, or allergy to pet dander.) Additional analyses examined effect modification by atopy status, see Figure 1-11 in this report.

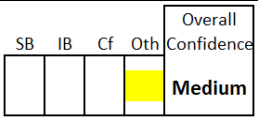
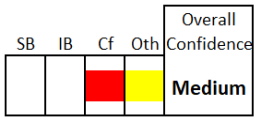
Study and design[a]	Results
Alternative Evaluation: Medium (based on strengths of prospective study of incidence). **Related References:** Smedje et al. (1997).	
Studies in adults	
Norback et al. (1995) (Sweden) Nested case-control within random population sample; *n* = 47 cases, *n* = 41 controls, ages 20–44 (mean 32) years. Participation rate 64 and 57%, respectively, among selected cases and controls. **Exposure:** 2-hour sample measured in bedroom. Mean (Min, Max) 0.029 (<0.005, 0.110) mg/m^3. Strongly correlated with total volatile organic compounds (correlation coefficient not shown). Mean duration in home = 6 years (minimum 0.5, maximum 31). **Outcome:** Cases defined by positive response to: asthma attack in past 2 months, nocturnal breathlessness in past 12 months, or current use of asthma medication. Controls responded "no" to all three questions. **Analysis:** Odds ratio, adjusted for age, sex, current smoking, wall-to-wall carpets, and house dust mites. **Evaluation[a]:**  Uncertainty about exposure (most values <LOQ). Similar results for volatile organic compounds, and not possible to distinguish effects of formaldehyde and these other compounds; could result in inflated effect estimate.	Mean (minimum, maximum) formaldehyde levels for nocturnal breathlessness: With symptom 0.029 (<0.005, 0.110) mg/m^3 Controls 0.017 (<0.005, 0.060) mg/m^3 (p < 0.01) OR 12.5 (2.0, 77.9) per 10-fold increase in formaldehyde (log-transformed), similar results for volatile organic compounds.

[a]Evaluation of sources of bias or study limitations (see Appendix A.5.1 and A.5.4SB = selection bias; IB = information bias; Cf = confounding; Oth = other feature of design or analysis. Extent of column shading reflects degree of limitation. The direction of anticipated bias is indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact is likely to be away from the null (i.e., spurious or inflated effect estimate).

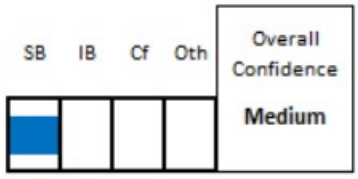
Table 1-16. Prevalence of asthma in children or adults in relation to residential formaldehyde exposure in studies with relatively high exposures (>0.05 mg/m^3)

Study and design[a]	Results
Studies of children and adults (stratified)	
Zhai et al. (2013) (China) Household survey with random selection of participants within household; 186 homes 186 adults, 82 children. **Exposure:** Samples in three rooms per house (bedroom, living room, kitchen); sampling time not specified. 64% of the 186 houses, and 24% of the 82 houses with children were >0.08 mg/m^3 ("polluted"). **Outcome:** Ferris (1978) questionnaire **Evaluation[a]:**	Prevalence by exposure category Children *n* (%) <0.08 mg/m^3 62 3.22 0.08–0.15 mg/m^3 20 40.0 RR 12.4 (2.9, 53.7) [calculated by EPA] Adults <0.08 mg/m^3 66 0.0 0.08–0.15 mg/m^3 120 1.6 RR not calculated

Study and design[a]	Results
 Uncertainty regarding exposure measurement period and validation of case ascertainment in this population. Although potential confounders were not considered in asthma-only analysis, given the magnitude of the results, the formaldehyde association is unlikely to be explained only by confounders. For adults, small number of positive responses.	
Krzyzanowski et al. (1990) (United States, Arizona) Prevalence survey. Adults (*n* = 613 ages >15 years, mean 37) and children (*n* = 298 ages 5–15 years, mean 9.3) from 202 households (stratified sample from municipal employees). Participation rate not reported. 67% white. **Exposure:** Two 1-week samples (opposite seasons) in kitchen, living area, and bedroom (converted from ppb) Household: mean 0.032 mg/m^3 <0.049 mg/m^3 83.7% 0.049–0.074 10.0% 0.074–0.172 6.3% Only a few values above 0.111 mg/m^3 **Outcome:** Ferris (1978) questionnaire (physician diagnosed). **Evaluation[a]:** **Children and Adults**  For children, relatively small *n* in higher exposure categories; for adults, incomplete reporting **Related references:** Quackenboss et al. (1989a); Quackenboss et al. (1989b).	**Children:** Prevalence asthma, current (physician diagnosed) 15.8% (*n*), asthma prevalence by exposure category, <0.049 mg/m^3 (248) 11.7% 0.049–0.074 (24) 4.2% 0.074–0.172 (21) 23.8% (trend $p < 0.03$) Log-linear models, stratified by environmental tobacco smoke, adjusted for socioeconomic status, ethnicity. Highest vs. lowest group: RR (95% CI) 2.0 (0.88, 4.8) (EPA calculation, unadjusted) Additional analyses demonstrated effect modification by environmental tobacco smoke, see Table 1-21 in this report. **Adults:** Prevalence of asthma 12.9% wheeze without a cold 21.5% shortness of breath with wheezing 14.0% Reported as "not significantly related" but rate of wheeze was "somewhat higher" with higher exposure.
Studies of children	
Liu et al. (2018) (China) Hospital based case-control study. *n* = 180 cases, 180 controls, mean age 10 years, sex and age comparable. Participation rate not reported. **Exposure:** Two-month samples in living room and bedroom. NO_2 and PM also measured. Household: median (range), 75th pct Cases 0.0384 (0.012–0.142), 0.057 mg/m^3 Control 0.0251 (0.012–0.094), 0.046 mg/m^3 **Outcome:** Asthma diagnosis via ISAAC questionnaire (2 or more incidents of cough, wheezing, and dyspnea for 3 or more consecutive days). Plus FEV_1 increased by >15% after β-agonist inhalation and persistent asthma was stable for 3 or more months prior to study. **Evaluation[a]:**	**Current asthma** OR (95% CI), formaldehyde by quartile 2.736 (1.098, 5.516) Regression models adjusted for history of allergy, breastfeeding, ETS and $PM_{2.5}$ Association of lower magnitude (OR = 2.029) also was reported for $PM_{2.5}$ Note: the units for the odds ratio were not provided, but authors stated that quartiles of concentration were included in the model.

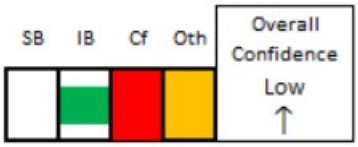
Study and design[a]	Results
 While reporting details were brief, citations were given and appropriate methods for exposure and outcome ascertainment appear to have been used and the sampling period for formaldehyde was adequate. Coexposures to PM and NO_2 were simultaneously controlled. Lack of clarity for exposure units in regression results.	
Lajoie et al. (2014) (Quebec, Canada) Intervention study October 2008–June 2011, n = 43 intervention group, n = 40 control group; Asthmatic children with exacerbation requiring medical care in the past year referred by physicians at tertiary care center, 3–12 years old, (n=83, 71.5% of those meeting inclusion criteria) in homes with low ventilation rates (<0.30 ACH). Randomly assigned to intervention to increase ventilation rates by 0.15 ACH. **Exposure:** Passive air sampling for formaldehyde in bedroom, 6–8 days, during winter and summer seasons; intervention group pre- and post-intervention, Fall/winter measurements: Pre- geometric mean 0.037 (0.032–0.043) mg/m^3; 30.1% homes ≥ 0.050 mg/m^3; post- geometric mean 0.024 (0.021–0.028) mg/m^3; 0% homes ≥ 0.050 mg/m^3; Control group, Pre- geometric mean 0.037 (0.031–0.043) mg/m^3; 25.5% homes ≥ 0.050 mg/m^3; post- geometric 0.035 (0.030–0.041) mg/m^3; 22.9% homes ≥ 0.050 mg/m^3; **Outcome:** Symptom prevalence or medical care over last 12 months, ISAAC questionnaire administered to parents; **Evaluation:**  Small sample size Other coexposures that have been associated in literature with asthma symptoms also declined in intervention group (toluene, ethylbenzene, styrene, limonene, alpha-pinene, airborne mold spores), although formaldehyde reduction was greatest.	**Current asthma** Change from year 1 to year 2 in prevalence of asthma symptoms and medical care in the past year associated with a 50% reduction in formaldehyde concentration. Analyses in intervention group, n = 43: **Outcome** **% Change (95% CI)** **p value** **≥ 1 episode** Wheezing -14.8 (-28.6, -0.9) 0.037 Night cough -20.4 (-35.7, -5.0) 0.010 ≥ 1 emergency Room visit -16.0 (-30.5, -1.5) 0.031 Analyses used mixed linear models with repeated measures. adjusted for age and eczema. Other outcomes analyzed with no statistically significant decrease were disturbed sleep, severe wheezing, ≥ 4 episodes wheezing, effort wheezing, rhinitis, ≥ 1 hospitalization
Tavernier et al. (2006) (United Kingdom) Case-control study. *n* = 105 cases, 95 controls (from two primary care practices, age- and sex-matched), ages 4–16 years, lower socioeconomic status. Participation rate 50%. **Exposure:** 5-day sample in living room and bedroom. **Outcome:** Asthma based on validated screening questionnaire (84% positive predictive value; but included questions on respiratory infection). **Analysis:** Odds ratio, conditional logistic regression, adjusted for measured exposures (e.g., endotoxin, Der p 1, particulate matter) and other risk factors. **Evaluation[a]:**  Uncertainty regarding selection process and loss of almost half of the cases. Outcome classification includes questions that are not specific to asthma.	OR (95% CI), by exposure tertile (exposure levels not reported; median in Gee et al. (2005) reported as 0.037 and 0.049 mg/m^3 in living room and bedroom, respectively) Living room Bedroom Lowest 1.0 (referent) 1.0 (referent) Middle 0.82 (0.33, 2.05) 1.26 (0.47, 3.40) Highest 1.22 (0.49, 3.07) 0.99 (0.39, 2.52)

Study and design[a]	Results
Uncertainty as to exposure range, particularly upper tertile (no response from email to corresponding author). **Related Reference:** Gee et al. (2005)	
Garrett et al. (1999) (Australia) Case-control study. 53 cases (physician diagnosis), 88 controls (no asthma diagnosis) from 80 households (some cases and controls from same household), ages 7–14 (mean 10.2) years. **Exposure:** 4-day (1 per season) measures in home (bedroom, living room, kitchen), and outdoors. Median (maximum) Indoor 0.0158 (0.139) mg/m^3 **Outcome:** Parent report, doctor-diagnosed asthma, and respiratory symptom questionnaire. **Evaluation[a]:**  Uncertainty about asthma definition (current asthma or ever asthma?). Uncertainty about effect of recruitment process and ability to fully address household correlation of cases and controls; could result in attenuated effect estimate. Incomplete reporting of results (adjusted results reported as "not statistically significant").	Incomplete reporting of results (*n*), proportion with asthma (overall proportion 53/148 = 0.36): <0.020 mg/m^3 (31) 0.16 0.020–0.050 (76) 0.39 0.050–0.139 (41) 0.44 (trend = 0.02) Adjusted for parental asthma history, sex. **Adjusted results reported as "not statistically significant" (numeric results not reported).**

<table>
<tr><th>Study and design[a]</th><th>Results</th></tr>
<tr><td colspan="2">Studies of adults</td></tr>
<tr><td>Billionnet et al. (2011) (France)
Prevalence survey, n = 905 adults from 490 dwellings (drawn from nationally representative sample; 13.6% participation rate), median age 44 (15−89) years; 48% men.
Exposure: One-week sample in bedroom
Median, 75th percentile (minimum, maximum) 0.0194, 0.028 (0.0013, 0.0863) mg/m^3
Outcome: Asthma based on self-report, asthma attack, woken by shortness of breath, or using asthma medication in past 12 months
Evaluation[a]:
 

Low participation rate but potential for differential participation (by formaldehyde exposure and disease status) unlikely.</td><td>Prevalence of asthma: 8.6%
OR (95% CI), adjusted for multiple risk factors, above vs. below 75th percentile (0.028−0.0863 vs. <0.028 mg/m^3):
1.43 (0.8, 2.4)
(Confidence intervals estimated from graph)
Adjusted for age, gender, smoking status, relative humidity, mold, pets, outdoor sources of pollution within 500-meter radius, highest education level in household, time of data collection.</td></tr>
<tr><td>Matsunaga et al. (2008) (Japan)
Prevalence survey. Adults, n = 998 women, mean 17th week of pregnancy, median age ~30 years. Recruited through obstetric clinics and public health nurses. Osaka prefecture, Japan. Participation rate 17% of pregnant women in the area.
Exposure: 24-hour personal sample (converted from ppb)
Median 0.030, maximum 0.161 mg/m^3
Cutpoints based on 30th, 60th, and 90th percentiles (<0.022, 0.022−0.033, 0.034−0.57, and ≥0.058 mg/m^3)
Outcome: Self-report, treatment for asthma in past 12 months
Evaluation[a]:
 

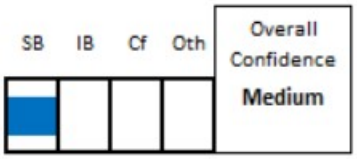
Low participation rate but potential for differential participation (by formaldehyde exposure and disease status) unlikely. Potential low sensitivity of outcome measure; uncertainty regarding specificity but COPD unlikely to be common in this population.</td><td>Asthma (2.1% prevalence)
<table><tr><th>mg/m^3</th><th>n</th><th>OR</th><th>(95% CI)</th></tr><tr><td><0.022</td><td>298</td><td>1.0</td><td>(referent)</td></tr><tr><td>0.022−0.033</td><td>299</td><td>0.80</td><td>(0.23, 2.84)</td></tr><tr><td>0.034−0.057</td><td>301</td><td>0.72</td><td>(0.19, 2.77)</td></tr><tr><td>0.058−0.161</td><td>100</td><td>2.15</td><td>(0.41, 11.3)</td></tr><tr><td colspan="2">(trend p-value)</td><td></td><td>(0.47)</td></tr><tr><td colspan="2">0.058 to 0.161 vs. <0.058</td><td>2.65</td><td>(0.63, 11.1)</td></tr></table>
Adjusted for age, gestation, parity, family history (asthma, atopic eczema, allergic rhinitis), smoking, passive smoking, mold in kitchen, indoor domestic pets, dust mite antigen level, family income, education, season of data collection.
(Midpoint of highest quartile estimated as 0.07 mg/m^3 based on personal communication (Matsunaga, 2012)</td></tr>
<tr><td colspan="2">Studies of children and adults (combined analysis)</td></tr>
<tr><td>Yeatts et al. (2012) (United Arab Emirates)
Prevalence survey; n = 1,590 (1,007 ages 19−50 years, 583 ages 6−18 years from 628 nationally representative sample of household (75% household participation).
Outcome: Asthma, wheeze symptoms based on several standardized questionnaires.
Analysis: Odds ratio, adjusted for sex, urban/rural area, age group, household tobacco smoke; children and adults combined in analysis.
Exposure: 7-day sample (living room)
71% <limit of quantification (0.0074 mg/m^3); 95th percentile 0.059 mg/m^3; 99th percentile 0.114 mg/m^3 (converted from ppm)
Correlation with sulfur dioxide relatively high (r = 0.63); also higher in homes using incense >1 per week</td><td><table><tr><th></th><th>Prevalence (%)</th><th>OR (95% CI)</th></tr><tr><td>Wheezing in past 12 months</td><td>9.2</td><td>0.64 (0.71, 2.42)</td></tr><tr><td>Wheezing in past 4 weeks</td><td>6.1</td><td>3.5 (0.81, 14.9)</td></tr><tr><td>Difficulty breathing or chest tightness in past 12 months</td><td>12.0</td><td>1.43 (0.83, 2.46)</td></tr><tr><td>Difficulty breathing or chest tightness</td><td>7.0</td><td>6.5 (1.9, 22.3)</td></tr></table></td></tr>
</table>

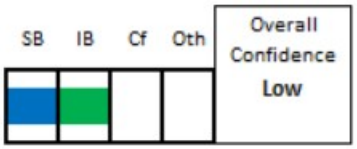
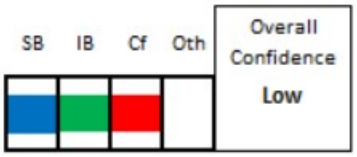
Study and design[a]	Results
Evaluation[a]:  Difficult to disentangle possible effects of sulfur dioxide from those of formaldehyde (similar effect sizes; moderate–strong correlation; could result in inflated effect estimate. Does not separate analysis of children and adults; only 29% above LOD—analyzed as above vs. below LOD	once or more times a month Similar results seen with sulfur dioxide.
Choi et al. (2009) (Korea) Case-control study. *n* = 36 allergic asthma cases, 28 controls, recruited through university outpatient clinic; recruitment procedures not described. Mean age cases 15.4 years (SD = 3.4; controls 16.2 years (SD = 4.1). Housing age and type: cases 58% <3 years old and 72% apartments; controls 29% <3 years old and 50% apartments. Location: 44 and 21% near road for cases and controls, respectively. **Exposure:** Household sample (sampling period and area not reported, but closed windows and use of duplicates). Geometric mean, 25th, and 75th percentiles in controls: 0.043 (0.024, 0.115) mg/m^3 **Outcome:** "Allergic asthma" based on medical history, skin prick test, and IgE (criteria not provided). **Evaluation[a]:**  Selection and recruitment process not reported; sampling period not reported and specific criteria for case definition not reported; potential confounders (age and type of housing and location differed between cases and controls, as measure of socioeconomic status) not addressed. Limited analysis.	Formaldehyde levels (mg/m^3): Geometric mean: Cases 0.054; Controls 0.043 75th percentile: Cases 0.108; Controls 0.115 *p*-value not reported (>0.05)

[a]Evaluation of sources of bias or study limitations (see details in Appendix A.5.1 and A.5.4). SB = selection bias; IB = information bias; Cf = confounding; Oth = other feature of design or analysis. Extent of column shading reflects degree of limitation. Direction of anticipated bias indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact would be likely to be away from the null (i.e., spurious or inflated effect estimate).

Table 1-17. Prevalence of asthma in relation to occupational formaldehyde exposure

Study and design[a]	Results
Fransman et al. (2003) (New Zealand) Prevalence survey. Plywood mill workers, *n* = 112. Participation rate 66%. Mean age 34.5 years, 71% men, mean duration 4.7 years. Internal comparison by exposure level and external comparison group (*n* = 415) from general population (random sample) surveys in the study area. **Exposure:** Personal samples (15-minute samples) in jobs held by 49 workers: (*n*), geometric mean (±geometric standard deviation) (mg/m^3)	Prevalence of asthma in exposed workers, external comparison group 20.5%, 12.5% (*n*) OR (95% CI): All workers (112) 1.5 (0.9, 2.8) By duration: <2 years (34) 0.5 (0.2, 1.7) 2–6.5 years (39) 1.0 (0.3, 2.7) >6.5 years (39) 3.1 (1.3, 7.2)

Study and design[a]	Results
all (22) 0.080 (3.0) dryers (14) 0.070 (3.2) (one outlier) pressing (5) 0.160 (2.7) other areas 0.030–0.040 mg/m^3 (at or near detection limit) Total inhalable dust (full-shift personal samples): geometric mean 0.7 mg/m^3. Dust levels highest among composers; formaldehyde levels in this group were <detection limit (0.030 mg/m^3) **Outcome:** Current use of asthma medications or history in past 12 months of an asthma attack or being woken by shortness of breath **Evaluation[a]:**  Selection out of the exposed work force of "affecteds" possible in this type of prevalence study. "Low" exposure group exposed to levels of formaldehyde up to 0.080 mg/m^3. Either limitation would result in reduced (attenuated) effect estimate.	By category: Low (<0.080 mg/m^3) (38) 1.0 (referent) High (>0.080 mg/m^3) (11) 4.3 (0.7, 27.7) Weaker association with terpenes (OR 2.0 for high vs. low exposure); no association with other exposures (e.g., dust, endotoxin) examined in this study. Adjusted for age, sex, ethnicity, smoking. Internal comparison by exposure category based on job title (limited to workers with same job titles as those with the 22 air sample measurements).
Herbert et al. (1994) (Canada) Prevalence survey. Oriented strand board manufacturing (n = 99). Comparison group (n = 165) oil field workers, not exposed to gas or vapors. Participation rate 98% in workers, 82% in comparison group. Mean age ~35 years. **Exposure:** 21 hours continuous area sampling, two consecutive days Saw line, debarking: 0.090–0.160 mg/m^3 Postheat, press conveyor, packaging, storage 0.200–0.290 mg/m^3 Preheat conveyor 0. 330 mg/m^3 Total dust: mean 0.27 mg/m^3, median aerodynamic equivalent diameter = 2.5 µm **Outcome:** International Union Against Tuberculosis and Lung Disease (1986) questionnaire (symptoms past 12 months). **Evaluation[a]:**  Selection out of the exposed work force of "affecteds" possible in this type of prevalence study, and some uncertainty about referent group.	Prevalence in exposed workers, comparison group Asthma 13.3%, 3.0% Wheeze attacks 25.3%, 9.7% Woken by shortness of breath 8.1%, 1.2% OR (95% CI) Asthma 5.48 (1.85, 16.2) Wheeze attacks 3.34 (1.66, 6.73) Woken by shortness of breath 6.78 (1.40, 32.7) Adjusted for age, smoking. Dust exposure considered low, not included in analysis.
Malaka and Kodama (1990) (Indonesia) Prevalence survey. Plywood workers, n = 93 exposed (93% participation rate), 93 unexposed from same plant, matched by age, ethnicity, smoking history (all men). Mean age ~27 years, mean duration 6 years. **Exposure:** Personal and area samples (duration not reported) Mean by area (converted from ppm) Exposed—Plywood: 0.78 mg/m^3; Particle board: 2.9; Block board: 0.62 mg/m^3 Other ("unexposed"): ≤0.086 mg/m^3 **Outcome:** Ferris (1978) questionnaire. Asthma based on "ever had attack of wheezing that made you feel short of breath?" or ever diagnosed with asthma and experienced currently; occupational asthma not defined. **Evaluation[a]:**	Prevalence in exposed workers, comparison group Occupational asthma 14%, 8% Asthma 30%, 8% OR (95% CI): Occupational asthma 2.84 (not reported) (p = 0.02) Asthma 6.31 (not reported) (p < 0.01) Adjusted for age, smoking, dust

Study and design[a]	Results
 Selection out of the exposed work force of "affecteds" possible in this type of prevalence study. "Unexposed" exposure group exposed to levels of formaldehyde up to 0.086 mg/m^3. Either limitation would result in reduced (attenuated) effect estimate, "occupational asthma" not defined, and lack of clarity in asthma definition pertaining to current prevalence.	
Neghab et al. (2011) (Iran) Prevalence survey, melamine-formaldehyde resin plant, *n* = 70 exposed, 24 unexposed (office workers from same plant, no present or past exposure to formaldehyde or other respiratory irritant chemicals; all men). Similar demographics, smoking history. Participation rate 100%. Duration ≥2 years. **Exposure:** Area samples (40 minutes) in seven workshops and one area sample in office area (converted from ppm) Exposed (mean ±SD) 0.96 (±0.49) mg/m^3; unexposed nondetectable **Outcome:** Ferris (1978) questionnaire, wheezing symptoms (period not specified). **Evaluation[a]:**  Potential low specificity and low sensitivity of outcome measure; modified outcome definition	Prevalence in exposed workers, comparison group: Wheezing symptoms 48.6%, 8.3%; OR (95% CI not reported) OR 10.4 (p = 0.001)
Holness and Nethercott (1989) (Canada) Prevalence survey, funeral home workers, *n* = 84 exposed (funeral directors and apprentices); 38 unexposed (from community service organization and students). Participation rate 87% of invited funeral home workers. Average exposure (embalming) duration 10 years. **Exposure:** 2 area samples during embalming, 30 to 180 minutes. Range in exposed 0.10–1.0 mg/m^3, referent mean 0.025 mg/m^3 **Outcome:** Ferris (1978) questionnaire: wheeze (no details of questions). **Evaluation[a]:**  Uncertainty regarding asthma definition. Selection out of the exposed work force of "affecteds" possible in this type of prevalence study; would result in reduced (attenuated) effect estimate. No consideration of potential confounding.	Prevalence in exposed workers, comparison group: Wheeze 19%, 11% p = 0.32

[a]Evaluation of sources of bias or study limitations (see Appendix A.5.1 and A.5.4). SB = selection bias; IB = information bias; Cf = confounding; Oth = other feature of design or analysis. Extent of column shading reflects degree of limitation. Direction of anticipated bias indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact would be likely to be away from the null (i.e., spurious or inflated effect estimate).

Asthma control studies

The previous discussion focused on the association between formaldehyde and prevalence of current asthma (i.e., symptoms or use of medications in the past 12 months). A different question concerns the association between formaldehyde and asthma control among people with asthma. This population could represent a group with greater susceptibility or vulnerability than the general population. EPA identified two studies that examined symptom frequency and medication use in the past 4 weeks (see Table 1-18). In the United Kingdom, Venn et al. (2003) examined symptoms recorded in daily diaries over the course of 1 month in relation to formaldehyde levels measured in the child's home (3-day samples from bedrooms). No association was seen with the prevalence of wheezing during the past year in the case-control analysis (as discussed in the previous section), but among the 193 cases, a two- to three-fold increased risk of frequent symptoms (defined as symptoms recorded on ≥10 consecutive days) was seen in the highest quartile of exposure (>0.032 mg/m^3) compared with <0.016 mg/m^3, with some evidence of an increased risk at even lower exposures (see Figure 1-10; *p*-value for trend = 0.05). For nighttime symptoms, which may be most relevant with respect to measurements taken in the bedroom, the relative risk estimate was 3.33 (95% CI 1.23, 9.02; *p*-value for trend = 0.02). The case definition of wheezing during the past year is interpreted as relevant to the definition of current asthma as used in this assessment, since 88% of the cases also reported using a reliever inhaler in the past year. These results were not impacted by inclusion of measures of room dampness in the models and were stronger when limited to patients with atopy (based on positive skin prick test results). In a smaller study of 37 low-income children in Boston, Dannemiller et al. (2013) observed higher formaldehyde levels in homes of children with poor asthma control compared to those with better asthma control (geometric mean 0.066 and 0.042 mg/m^3, $p = 0.078$; see Table 1-18).

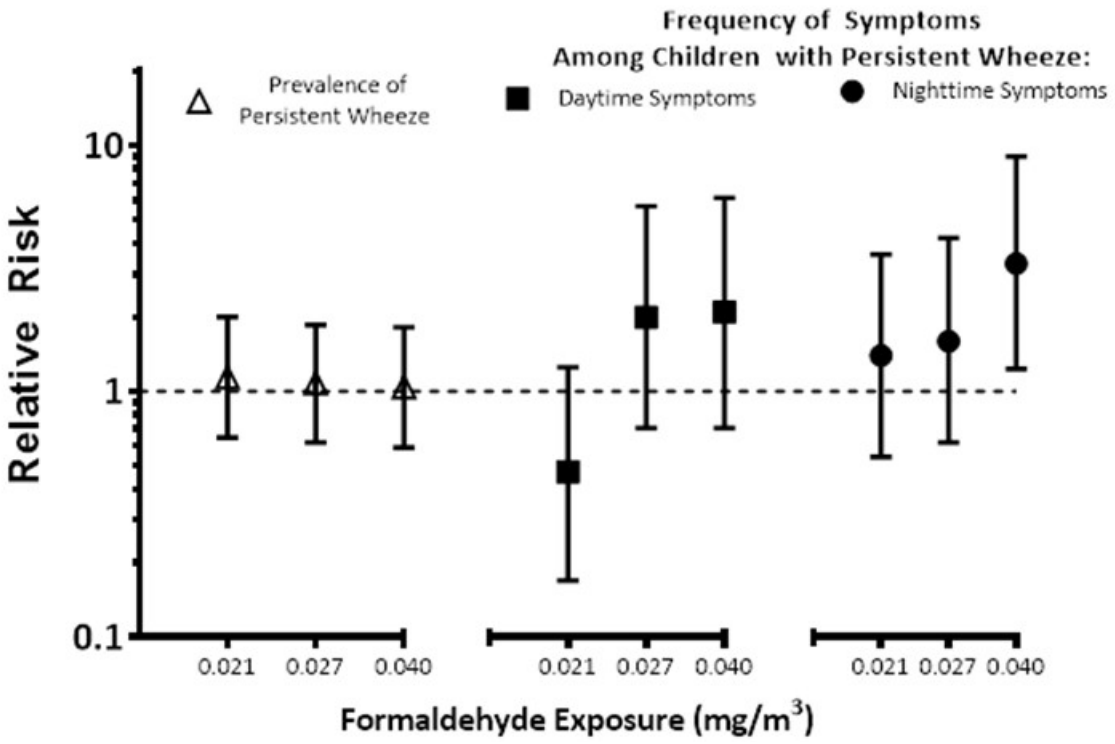
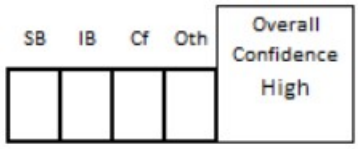


Figure 1-10. Relative risk of persistent wheeze and of increased frequency of symptoms among children with wheeze in relation to residential formaldehyde exposure.

Effect modification by disease status: comparison of formaldehyde associations with prevalence of current asthma (persistent wheeze) and with increased frequency of symptoms only among cases. Data from Venn et al. (2003); study details in Table 1-18.

Table 1-18. Exacerbation of asthma symptoms in relation to residential formaldehyde exposure

Study and design[a]	Results
Venn et al. (2003) (United Kingdom) Symptom control among persistent wheeze cases (symptoms during past year) (*n* = 193), ages 9–11 years. Participation rate 79%. **Exposure:** 3-day samples in bedroom during home visit. Median ~0.022 mg/m^3 Median in top quartile 0.039 mg/m^3 (Maximum and median in top quartile provided in email from Dr. Venn to Glinda Cooper, March 29, 2012.) **Outcome:** 1-month daily diaries recording symptoms: daytime and nighttime wheezing, chest tightness, breathlessness, and cough, each measured on 0-to-5 scale. "Frequent" symptoms defined as recorded on ≥10 days.	(*n* cases, percentage with frequent symptoms), OR (95% CI), adjusted for age, sex, socioeconomic status (Carstairs deprivation index): Frequent nighttime symptoms <0.016 mg/m^3 (39, 41%) 1.0 (referent) 0.020–0.022 (35, 49%) 1.40 (0.54, 3.62) 0.022–0.032 (36, 53%) 1.61 (0.62, 4.19) 0.032–0.083 (33, 67%) 3.33 (1.23, 9.01) (trend *p* = 0.02) OR per quartile increase: full sample 1.45 (1.06, 1.98) limited to atopic cases 2.06 (1.37, 3.09) Frequent daytime symptoms <0.016 mg/m^3 (37, 62%) 1.0 (referent) 0.020–0.022 (34, 47%) 0.47 (0.17, 1.25) 0.022–0.032 (37, 73%) 2.00 (0.71, 5.65) 0.032–0.083 (32, 73%) 2.08 (0.71, 6.11)

<table>
<tr><th>Study and design[a]</th><th>Results</th></tr>
<tr><td>Analysis: Odds ratio, adjusted for age, sex, and Carstairs deprivation index
Evaluation:
 
</td><td>(trend p = 0.05)
OR per quartile increase:
full sample 1.40 (1.00, 1.94)
limited to atopic cases 1.68 (1.10, 2.57)
Additional adjustment for dampness or other exposures including visible mold, total VOCs, or NO_2, did not affect formaldehyde results.
Similar results in group with validation of case status from prescription asthma medication records.
(Median in top quartile provided in email from Dr. Venn, March 29, 2012.)</td></tr>
<tr><td>Dannemiller et al. (2013) (United States)
Symptom control among 37 asthma cases, mean age 10.5 years. Participation rate 79% (37 out of 47)
Exposure: 30-minute pumped sample in kitchen (converted from ppb)
Median 0.044 mg/m^3
Range 0.006–0.162 mg/m^3
31% >0.060 mg/m^3
Outcome: Five-question survey about symptom control in past 4 weeks at same time as environmental sampling.
Analysis: Examined season, temperature, and relative humidity
Evaluation[a]:
 

Recruitment is not from a well-defined population. Limited exposure measurement period (but quality control details provided).
Related reference: Sandel et al. (2014)</td><td>Asthma Control Question
Geometric mean formaldehyde (mg/m^3)
<table><tr><th>Frequency during past 4 weeks…</th><th>N (%) with most severe rating</th><th>Most severe group</th><th>All other groups</th><th>p-value</th></tr><tr><td>Asthma interfered with activities</td><td>5 (14%)</td><td>0.070</td><td>0.042</td><td>0.066</td></tr><tr><td>Shortness of breath</td><td>3 (8%)</td><td>0.079</td><td>0.043</td><td>0.086</td></tr><tr><td>Nighttime symptoms</td><td>4 (11%)</td><td>0.065</td><td>0.043</td><td>0.184</td></tr><tr><td>Used rescue inhaler or nebulizer medication</td><td>4 (11%)</td><td>0.055</td><td>0.044</td><td>0.409</td></tr><tr><td>Asthma control rating</td><td>3 (8%)</td><td>0.074</td><td>0.043</td><td>0.128</td></tr><tr><td>Score <12 (very poor control)</td><td>6 (16%)</td><td>0.066</td><td>0.042</td><td>0.078</td></tr></table>Similar results adjusted for season.</td></tr>
</table>

[a]Evaluation of sources of bias or study limitations (see details in Appendix A.5.1 and A.5.4). SB = selection bias; IB = information bias; Cf = confounding; Oth = other feature of design or analysis. Extent of column shading reflects degree of limitation. Direction of anticipated bias indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact would be likely to be away from the null (i.e., spurious or inflated effect estimate).

Acute exposure—controlled chamber studies—people with asthma

Most of the acute formaldehyde exposure studies among adults with asthma provide little or no evidence of an immediate effect on pulmonary function in response to formaldehyde inhalation (see Table 1-19); however, no controlled exposure studies have been conducted in children with asthma. The exposure duration in these studies ranges from 10 minutes to 3 hours, and so does not represent a chronic exposure scenario. The studies are fairly small (ranging from 7 to 19 participants) and use various measures of pulmonary function (e.g., FEV_1, FVC) and airway reactivity. Only two of these studies included an assessment of the response to an allergen challenge: dust mite in Casset et al. (2006) and grass pollen in Ezratty et al. (2007). One of these

studies demonstrated a reduction in the average dose of mite allergen required for a 20% decrease in FEV_1 from baseline (PD_{20} FEV_1) after a 30-minute exposure via mouth breathing only to 92.2 µg/m³ of formaldehyde compared to ambient air controls (32 µg/m³ formaldehyde) [54.7 ng versus 73.2 ng, respectively; (Casset et al., 2006)]. Formaldehyde exposure also increased the late-phase response, expressed as the maximum fall in FEV_1 from baseline observed during the 6-hour follow-up, by 15% in FEV_1 in the exposed individuals compared to an 11% reduction among controls. However, these effects were not observed in the study by Ezratty et al. (2007). One difference in these studies is that the Casset et al. (2006) protocol used a nose clip, thus resulting in inhalation solely by mouth. In addition, for all of these studies, the severity of asthma among the volunteers in these experiments is not known; thus, the results may not be generalizable to all people with asthma.

Table 1-19. Controlled acute exposure chamber studies of pulmonary function with formaldehyde exposure among people with asthma

Study and design	Exposure measures	Results	
		Pulmonary function	Bronchial challenge—airway reactivity
Studies with allergen challenge			
Ezratty et al. (2007) *n* = 12, ages 18–44, nonsmoking, positive history of pollen allergy. **Design:** Random assignment to order of exposure (2 weeks apart); double blinded. Testing pre- and every hour up to 8 hours postexposure. Grass pollen (5 allergens) challenge (protocol described). **Evaluation:** *High* confidence Randomized, double blinded, detailed data presentation	60 minutes, 0 and 0.500 mg/m³	No difference in FVC or FEV_1 before or immediately after (data not shown)	Early phase response—PD_{15} FEV_1 grass allergen: compared with placebo, higher in five and unchanged in seven after exposure Median (range) index of reactivity: Placebo 0.25 (0.10–2.0) Exposed 0.80 (0.15–2.0) (p = 0.06) Late-phase response (8 hours postexposure and allergen challenge) PD_{15} FEV_1 Placebo 0.17 (0.03–4.0) Exposed 0.23 (0.01–3.6) (p = 0.42)

Study and design	Exposure measures	Results: Pulmonary function	Results: Bronchial challenge—airway reactivity
Casset et al. (2006) *n* = 19, ages 19–35 years, nonsmoking, positive IgE to dust mites. **Design:** Random assignment to order of exposure (3 weeks apart); double blinded. Mean formaldehyde exposure at home 0.037 ± 0.004 mg/m^3 (24-hour sample). Testing pre- and every hour up to 6 hours postexposure. House dust mite challenge (Der p 1 11.08 µg/mL, 11.12 µm) (protocol described). **Evaluation:** *High* confidence Randomized, double blinded, detailed data presentation; applies to mouth breathing.	30 minutes, 0.032 (background) and 0.092 mg/m^3 Nose clip (breathing by mouth)	No difference in at-pretreatment or early-posttreatment assessment; Late-phase response— Mean ± SE reduction FEV_1: Placebo 11 ± 1.6 Exposed 15 ± 1.6 (p = 0.046)	Early phase response—PD_{20} FEV_1 Der p1 Mean ± SE; median (ng): Placebo 73.2 ± 17.3; 39.7 Exposed 54.7 ± 12.6; 28.1 (p = 0.05)
Studies without allergen challenge			
Harving et al. (1990) *n* = 15, ages 15–36, nonsmoking. **Design:** Random assignment to exposure order (one per week); double blinded. Testing pre- and near end of exposure period. **Evaluation:** *High* confidence Randomized, double blinded, detailed analysis. Related Reference: Harving et al. (1986)	90 minutes, filtered air (8), 0.120 and 0.850 mg/m^3	No difference in: FEV_1 R_{aw} SG_{aw} 0.008 mg/m^3 100.9 2.21 10.67 0.12 mg/m^3 99.4 2.23 10.63 0.85 mg/m^3 105.0 2.29 11.17	No difference in challenge test: PC_{20} PEF 0.008 mg/m^3 0.29 0.12 mg/m^3 0.36 0.85 mg/m^3 0.26
Green et al. (1987) *n* = 16, ages 19–35 years, nonsmoking. **Design:** Two 15-minute exercise segments in 60-minute exposure period. Random assignment to order of exposure; single blinded. Testing pre- and during exposure period, ~15 minute intervals. **Evaluation:** *Medium* confidence Randomized, single blinded	60 minute, clean air and 3,000 ppb [0, 3.69 mg/m^3]	No difference in FVC, FEV_1, SG_{aw}, or other lung function measures At 55 minutes FVC FEV_1 SG_{aw} Control 4.62 3.54 0.114 3 ppm 4.56 3.46 0.111	No difference in challenge test: PD_{35} SG_{aw} Control 3.69 3 ppm 3.86
Sauder et al. (1987) *n* = 9, ages 29–40, nonsmoking. **Design:** Clean air followed by formaldehyde (1 week apart); blinding of participant not specified. Testing during and at end of exposure. **Evaluation:** *Low* confidence Not randomized, blinding not specified	3 hours, clean air and 3,000 ppb [0, 3.69 mg/m^3]	No difference in FVC, FEV_1, SG_{aw}, or other lung function measures. At 180 minutes FVC FEV_1 SG_{aw} Control 4.11 3.02 0.101 3 ppm 4.16 3.07 0.106	No difference in challenge test: PD_{35} SGaw Control 0.93 3 ppm 0.96

Study and design	Exposure measures	Results	
		Pulmonary function	Bronchial challenge—airway reactivity
Witek et al. (1987); Witek et al. (1986)[b] *n* = 15, ages 18–35 years, nonsmoking **Design:** Two protocols (at rest and during exercise). Random assignment to order of exposure; double blinded. Testing during and at 10 and 30 minutes postexposure; PEFR assessed from 1 to 24 hours postexposure. **Evaluation:** *High* confidence Randomized, double blinded; nonparametric analysis could be preferred but individual data provided	40 minutes, 0 and 2,000 ppb [0, 2.46 mg/m^3]	Few difference in FVC, FEV_1, R_{aw}, or other lung function measures At 30 min postexposure, resting protocol FVC: Control 0.82; 2 ppm −2.78 FEV_1: Control −0.31; 2 ppm 0.60 R_{aw}: Control −6.64; 2 ppm −3.05 Similar patterns in exercise protocol. No decline in PEFR over 24 hours in either group.	PD_{20} FEV_1 mean ± SD; median Pre-exposure: 24.0 ± 15.7; 27.4 Postexposure: 13.6 ± 20.5; 3.1 (*p* = 0.12)
Krakowiak et al. (1998) *n* = 10, ages 23–52 years, some smokers, with occupational formaldehyde exposure **Design:** Single blinded. Testing 2 hours pre- and up to 24 hours after exposure. **Evaluation:** *Low* confidence Not randomized, single blinding, SE or SD not reported	2 hours, 0.500 mg/m^3	No difference in FEV_1 or PEF (mean values shown on graph; no indication of variability in measures)	No difference in challenge test (PD_{20} FEV_1) (mean values shown on graph; no indication of variability in measures)
Sheppard et al. (1984) *n* = 7, ages 18–37, nonsmoking **Design:** Two protocols (at rest and during exercise). ≥1 day apart; blinding of participant not specified. Testing before and 2 minutes after exposure. **Evaluation:** *Low* confidence Not randomized, blinding not specified	10 minutes, 0, 1,000, and 3,000 ppb [0, 1.23, 3.69 mg/m^3] formalin	No difference between pre- and post SG_{aw}[c] in either protocol: Resting: Control −1.0; 1 ppm 0.2; 3 ppm NC Exercise: Control 1.8; 1 ppm 2.2; 3 ppm 2.9 NC= not conducted	Not assessed

Abbreviations: Double blinded = investigator and participants unaware of which exposure; single blinded = participants were unaware of exposure. Late phase: between 4 and 6 hours after end of house dust mite bronchial challenge. PD_x = dose required to induce an x% reduction in the specified pulmonary function measure (i.e., PD_{15} FEV_1 = dose required to induce a 15% reduction in FEV_1); R_{aw} = airway resistance; SG_{aw} = specific airway conductance (corrected for lung volume); PEFR = peak expiratory flow rate.

[b]Witek et al. (1987) includes the same subjects as the Witek et al. (1986) paper, but with additional results presented in 1987.

[c]Postminus preexposure SG_{aw} (liters × cm H_2O/liter); negative value indicates lower SG_{aw} postexposure.

Other respiratory conditions in infants and toddlers

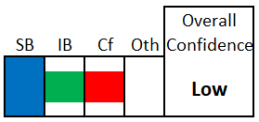
Five studies examined other respiratory conditions in infants and toddlers (see Table 1-20). Three of these were considered *medium* confidence studies and are discussed below. Roda et al. (2011) was a follow-up of 2,940 infants in a birth cohort, with questionnaires regarding respiratory symptoms including lower respiratory infections and wheeze, completed by parents at 1, 3, 6, 9 and

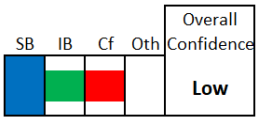
12 months. Formaldehyde exposure was modeled based on housing characteristic data and the mean of four 1-week samples taken in homes at 1, 6, 9, and 12 months in a randomly selected subset of 196 homes. The sensitivity and specificity of the modeling was estimated as 72.4 and 73.6% respectively for categorization based on the median and 57.4 and 82.1% for categorization based on tertiles. EPA noted in its evaluation, however, that the modeling was not tested on a separate sample, and thus these model characteristic estimates may be high. Rumchev et al. (2002) is a study of emergency room visits for what was characterized as asthma (based on discharge diagnosis); information on the recruitment and selection process was not presented. The relatively young age of the children (mean 24 months, range 6 to 36 months) does not reflect the phenotypic expression of asthma, and thus this study likely represents various respiratory tract infections and wheezing episodes. Two 8-hour measures, in different seasons, of formaldehyde were taken in case and control homes; the length of time between the hospital visit and the study was not specified. Both of these studies reported associations between the examined outcome and residential formaldehyde levels, with effects seen above 0.020 mg/m^3 in Roda et al. (2011) and above 0.060 mg/m^3 (possibly above 0.050 mg/m^3) in Rumchev et al. (2002). Although the conditions included in these studies do not fit within the usual classification of asthma, these respiratory conditions may have implications for subsequent disease risk, and in the case of Rumchev et al. (2002) (emergency room visits), also reflects an outcome with accompanying health care costs. The association of formaldehyde exposure with symptoms consistent with increased lower respiratory infections also may be indicative of immune suppression in the children, although this was not directly tested in the available studies, and mechanistic findings that may support these observations were similarly indirect and inconclusive (see *Evidence on Mode-of-Action* Section below). Although the congruence between the outcomes examined within these two studies is not clear, the results of these studies indicate that the relationship between indoor formaldehyde exposure and respiratory conditions in infants and toddlers is an area requiring additional research.

Table 1-20. Respiratory conditions in infants and young children in relation to residential formaldehyde exposure

Study and design[a]	Results
Roda et al. (2011) (France) Birth cohort, infants (singleton, >2,500 g) followed through age 1 year; *n* = 2,940 with 12-month questionnaire and formaldehyde measures (70% of 4,177 initial enrollees; 76% of those completing at least one questionnaire). **Exposure:** Questionnaire on home characteristics at baseline and updated at 3, 6, 9 and 12 months. *N* = 196 randomly selected for predictive modeling analysis; 4 1-week measures at 1, 6, 9 and 12 months.	OR (95% CI) Lower respiratory tract infection (Prevalence through age 1 year 45.8%) Per interquartile range increase: 1.32 (1.11, 1.55) Above vs. below median (0.02 mg/m^3): 1.20 (1.03, 1.41) Top tertile vs. lowest tertile: 1.31 (1.10, 1.57) Lower respiratory tract infection with wheeze (Prevalence through age 1 year 22.3%) Per interquartile range increase: 1.41 (1.14, 1.74)

Study and design[a]	Results
Predictive model used to assign subjects to categorical levels. LOD 0.008 mg/m^3. Median 0.020 mg/m^3; IQR 0.014, 0.027 mg/m^3. Exposure prediction model for high vs. low (based on median): Sensitivity 72.4%; Specificity 73.6% Exposure prediction model by tertile: Sensitivity 57.4%; Specificity 82.1%. **Outcome:** Parent questionnaire at 1, 3, 6, 9, and 12 months used to define lower respiratory infections with and without wheeze **Evaluation[a]:**  Did not test predictive model on separate sample (may overestimate sensitivity and specificity)	Above vs. below median (0.02 mg/m^3) 1.31 (1.07, 1.59) Top tertile vs. lowest tertile: 1.43 (1.14, 1.79) Adjusted for sex, prenatal and postnatal environmental tobacco smoke exposure, breastfeeding history, number of older siblings, day care attendance, furry pets in the home, humidity, parental history of asthma, and socioeconomic status.
Rumchev et al. (2002) (Australia) Case-control, *n* = 88 cases, *n* = 104 controls (health department); ages 6 months to 3 years (mean 25 months for cases, 20 months for controls). Participation rates not reported. **Exposure:** Two 8-hour measures (winter, summer) in home (living room, bedroom) mean (max) (mg/m^3) living room: 0.028 (0.244); bedroom: 0.030 (0.189) **Outcome:** Emergency room discharge diagnosis of asthma **Evaluation[a]:**  Recruitment process not described; uncertainty as to what is included within this case definition and length of time between emergency room visit and subsequent exposure measure. **Related References:** Rumchev et al. (2004)	OR (95% CI) by exposure category[b]: 0.010–0.029 mg/m^3 0.95 (0.8, 1.1) 0.030–0.049 0.95 (0.8, 1.2) 0.050–0.059 1.2 (0.9, 1.6) ≥0.060 1.39 (1.1, 1.7) Per 0.010 mg/m^3: 1.003 (1.002, 1.004) *(OR and 95% CI for all categories except ≥0.060 mg/m^3 estimated from figure in the paper; numbers in each exposure were not reported)* Adjusted for age, sex, allergic sensitization to common allergens, family history of asthma, relative humidity, indoor temperature, socioeconomic status, pets, air conditioning, gas appliances, smoking inside, house dust mite levels
Li et al. (2019) (Hong Kong) Birth cohort (2013-2014), Infants aged <4 months (≥2.5 kg, gestation ≥36 weeks) followed to 18 months; *n* = 963 (67% of recruited) with outcome and exposure data.	**New onset wheeze** Prevalence 12.5% at mean age of 13.4 months. HR (95% CI) per 10 µg/m^3 1.002 (1.001,1.003)

Study and design[a]	Results
Exposure: Air sampling (NO_2, formaldehyde), 72 hour samples at 6 months of age (concentrations not reported), ISAAC questionnaire included questions on environmental conditions in residence. **Outcome:** Parent questionnaire (ISAAC) prior to 4 months, weekly respiratory health diary and monthly telephone survey to 18 months. New onset wheeze (time to event) measured from 6 to 18 months of age. **Evaluation:**  Concern for selection bias. Participation rate was very low (29% of eligible agreed) and of those selected there was notable data loss, data was complete for 67%. No comparisons of participants and nonparticipants and no descriptive statistics provided for study sample. No control for smoking or ETS.	Cox proportional hazard models adjusted for NO_2 ($\mu g/m^3$), sex, neo-natal respiratory illness, sibling, keeping pets, cooking fuel, and family history of non-asthma allergy or asthma.

Study and design[a]	Results
Yu et al. (2017) (Hong Kong) Birth cohort (2009-2011), Infants aged <4 months, followed to 18 months; *n* = 535 (76.2% of recruited) with outcome and exposure data. **Exposure:** Air sampling at 6 months of age in bedroom (NO_2, formaldehyde), sampling period not reported, ISAAC questionnaire included questions on environmental conditions in residence. Mean (SD) concentrations NO_2 42.4 (30.97) µg/m^3; formaldehyde 51.09 (74.94) µg/m^3; **Outcome:** Parent questionnaire (ISAAC) prior to 4 months, weekly respiratory health diary and monthly telephone survey to 18 months. New onset wheeze (time to event) measured from 6 to 18 months of age. **Evaluation:**  No details provided for exposure measurements. Concern for selection bias. Participation rate was very low (29% of eligible agreed) and of those selected there was notable data loss, data was complete for 76%. No comparisons of participants and nonparticipants. No control for ETS	**New onset wheeze** Prevalence 11% at mean age of 11.4 months. HR (95% CI) per 10 µg/m^3 1.004 (1.001,1.007) Cox proportional hazard models adjusted for NO_2 (µg/m^3), sex, neo-natal respiratory illness, sibling, keeping pets, cooking fuel, living area (ft^2) and family history of non-asthma allergy or asthma.
Raaschou-Nielsen et al. (2010) (Denmark) Birth cohort, *n* = 343, infants of mothers with asthma (83% of 411 enrollees, 90% of 378 who participated through 18 months). **Exposure:** 10-week samples in bedrooms, 1 to 3 sampling periods (at 6, 12, and 18 months of age). Analysis of variance: 31% between and 69% within person. mean 0.020 mg/m^3 median 0.018 mg/m^3 95th percentile 0.037 mg/m^3 **Outcome:** Daily symptom diaries kept from birth to 18 months (reviewed at clinic visit every 6 months), recording of wheezing symptoms affecting activity or sleep.[b] **Evaluation[a]:** 	(*n*), OR (95% CI) by exposure quintiles. Outcome = any symptom day: <0.012 mg/m^3 (67) 1.0 (referent) 0.012–0.016 (69) 1.11 (0.47, 2.63) 0.016–0.020 (68) 1.21 (0.51. 2.92) 0.020–0.026 (71) 1.40 (0.57, 3.47) >0.026 (68) 0.67 (0.29, 1.54) (trend *p* = 0.49) Adjusted for sex, area of residence, education of mother and log-transformed baseline lung function

Study and design[a]	Results
Analysis does not take into account important features of the data (e.g., temporal variations in symptoms and in formaldehyde); could have masked an association.	

[a]Evaluation of sources of bias or study limitations (see Appendix A.5.1 and A.5.4). SB = selection bias; IB = information bias; Cf = confounding; Oth = other feature of design or analysis. Extent of column shading reflects degree of limitation. Direction of anticipated bias indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact would be likely to be away from the null (i.e., spurious or inflated effect estimate).

Susceptibility: modifying factors affecting prevalence of asthma or allergic sensitization

Asthma and atopic sensitization are hypothesized to be affected by a combination of genetic and environmental factors. Several sensitization and asthma studies included analyses pertaining to effect modification by factors that may help elucidate pathogenesis and susceptibility, such as atopy (see Figure 1-11). In the study of adult women by Matsunaga et al. (2008), the association between use of medication for atopic eczema and formaldehyde exposure was stronger among women with no family history of allergy (OR 2.96, 95% CI 0.87, 10.12) than among women with a family history of allergy (OR 1.63, 95% CI 0.58, 4.57) at exposures of 0.058 to 0.161 mg/m^3 compared with <0.058 mg/m^3. The pattern across exposure levels also revealed an increase in risk of atopic eczema at lower exposures in the negative family history group (OR 1.37, 1.88, and 4.21) compared with the positive family history group (OR 0.80, 0.92, and 1.45) (see Figure 1-11A). In the study of asthma incidence in relation to formaldehyde measures in school by Smedje and Norback (2001), the association between formaldehyde and asthma in the full sample was relatively weak (OR 1.2, 95% CI 0.8, 1.7), but there was some divergence in estimated effects in analyses stratified by history of atopy: OR 1.7 (95% CI 1.1, 2.6) among children without a positive history, and OR 0.6 (95% CI 0.3, 1.3) among children with a positive history (see Figure 1-11B). The pattern is difficult to interpret in the study by Annesi-Maesano et al. (2012) (see Figure 1-11C), as an indication of effect modification at lower exposures was not seen at higher exposures. Note that the direction of effect modification seen in Matsunaga et al. (2008) and in Smedje and Norback (2001) differ from that described in the preceding section (i.e., the stronger association between formaldehyde and asthma control among children with atopy compared to nonatopics in Venn et al. (2003). Examination of the presence of interactions and the factors contributing to them requires large studies designed to test specific hypotheses defined a priori; thus, additional research is needed to address the question of potential effect modification of atopic eczema or asthma symptom prevalence by atopy status.

Tobacco smoke represents an environmental factor that may increase the incidence of hypersensitivity responses in formaldehyde-exposed individuals. Two studies included IgE or asthma analyses stratified by environmental tobacco smoke exposure among children and adults (nonsmokers) (Palczynski et al., 1999; Krzyzanowski et al., 1990). There was some evidence of

effect modification by environmental tobacco smoke (i.e., stronger associations, or associations seen at lower formaldehyde exposures, seen with this coexposure). In the Palczynski et al. (1999) study, there was no association between formaldehyde and either IgE levels or asthma prevalence in the full sample of children or of adults. Analyses stratified by the presence of environmental tobacco smoke exposure in the home, however, indicated associations between formaldehyde (at levels of 0.025–0.050 mg/m^3) and (1) elevated IgE in children (but not adults), and (2) asthma in adults (but not in children). In the study by Krzyzanowski et al. (1990), an association between formaldehyde and asthma was seen in children exposed to environmental tobacco smoke, but evidence of this type of effect modification was not seen in adults (see Table 1-21). Additional studies are needed to establish if this interaction is seen only in children, only in adults, in adults and children, or in neither group.

One other source of effect modification was examined in the study by Hulin et al. (2010), a case-control study conducted in an urban and a rural area in France, with 32 and 24 cases, respectively, in each area. The formaldehyde levels were similar in the two areas, but a strong effect modification by area was seen, with an elevated risk seen in the rural area (OR 9.0) and a decreased risk seen in the urban area (OR 0.24). Both estimates have wide confidence intervals. These findings could be due to chance or could reflect interactions with other exposures or other differences between the areas. The uncertainty in interpreting these stratified results contributed to the *low* confidence rating for this study. Additional studies examining modifying factors would be informative.

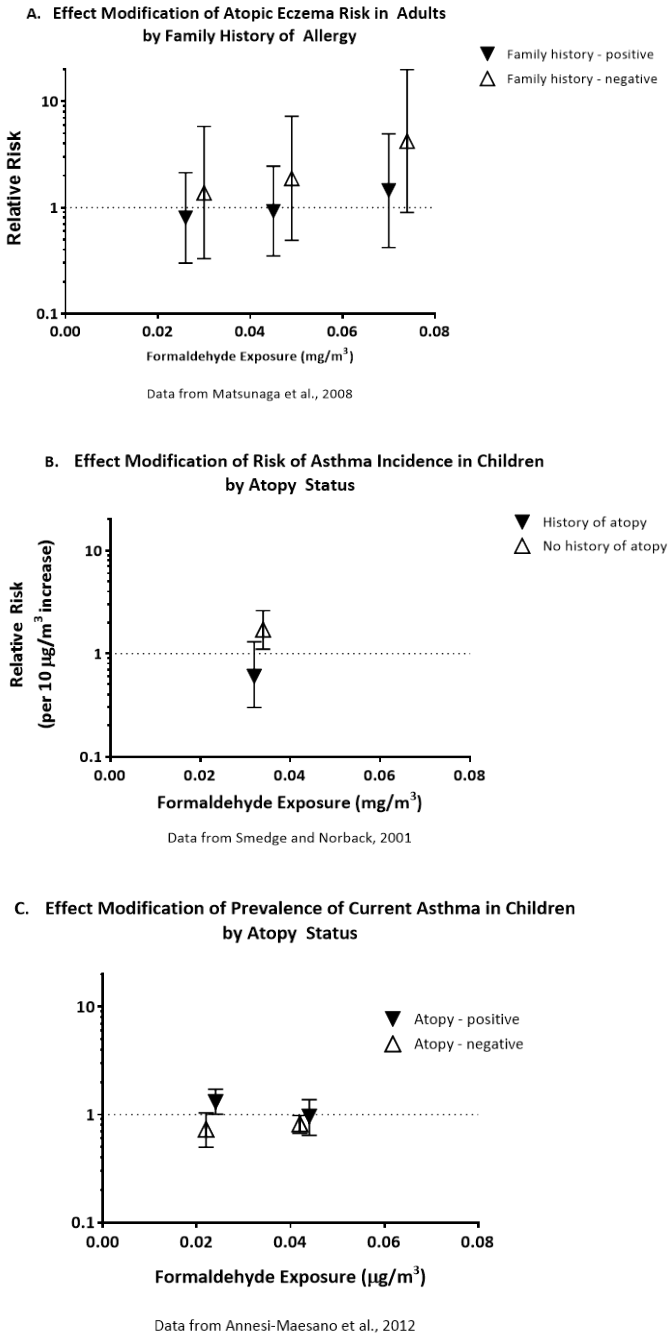


Figure 1-11. Examination of effect modification by family or personal history of atopy.

(A) Relative risk of prevalence of atopic eczema in adults (Matsunaga et al., 2008); study details in Table 1-12. Family history defined as parent or sibling with doctor-diagnosed asthma, atopic eczema, or allergic rhinitis. (B) Relative risk of incidence of asthma in children (Smedje and Norback, 2001); study details in Table 1-15. Atopy defined at baseline as a positive response to questions on childhood eczema, allergy to pollens, and allergy to pet dander. (C) Relative risk of prevalence of asthma in children (Annesi-Maesano et al., 2012); study details in Table 1-15. Atopy based on positive skin prick test (10 allergens).

Table 1-21. Effect modification by environmental tobacco smoke: results from studies in children and adults

Study and design[a]	Results

Palczynski et al. (1999) (Poland)
Prevalence survey, *n* = 278, ages 16–65 and *n* = 187, ages 5–15 years from 120 households with children (random selection, 10-year old apartments). Participation rate not reported.
Exposure: 24-hour household sample (area not specified)
Mean (±SD) (minimum, maximum) 0.026 (±0.011) (0.002, 0.067) mg/m^3
2% >0.050 mg/m^3
Outcome: Bronchial asthma diagnosed using American Thoracic Society criteria.
Evaluation[a]:

Uncertainty regarding asthma definition. Not informative above 0.050 mg/m^3 because of sample size (*n* = 4).

	N per group (Percentage with Current Asthma)	
	Environmental Tobacco Smoke	
Exposure (mg/m^3)	Positive	Negative
Children, IgE >100 kU/L		
<0.025	39 (38.5)	55 (29.1)
0.025–0.050	44 (52.3)	46 (23.9)
0.051–0.067	2 (0.0)	1 (100.0)
(Fisher's exact test *p*-value, children)	**(0.005)**	
Adults, IgE >100 kU/L		
<0.025	34 (23.5)	67 (29.9)
0.025–0.050	36 (22.2)	57 (26.3)
0.051–0.067	2 (0.0)	2 (0.0)
Children, Asthma		
<0.025	39 (6.9)	55 (5.4)
0.025–0.050	44 (2.3)	46 (6.5)
0.051–0.067	2 (0.0)	1 (0.0)
Adults, Asthma		
<0.025	34 (5.9)	67 (4.4)
0.025–0.050	36 (13.9)	57 (1.8)
0.051–0.067	2 (0.0)	2 (0.0)
(Fisher's exact test *p*-value, adults)	**(0.03)**	

Krzyzanowski et al. (1990) (United States, Arizona)
Prevalence survey, adults (*n* = 613 ages >15, mean 37) and children (*n* = 298 ages 5–15, mean 9.3) from 202 households (stratified sample from municipal employees). Participation rate not reported. 67% whites
Exposure: Two one-week samples (opposite seasons) in kitchen, living area, and bedroom (converted from ppb).
Household: mean 0.032 mg/m^3
<0.049 mg/m^3 83.7%
0.049–0.074 10.0%
0.074–0.172 6.3%
Only a few values above 0.111 mg/m^3.
Outcome: Asthma and symptoms based on Ferris (1978) (physician diagnosed)
Evaluation[a]:

For children, relatively small *n* in higher exposure categories; for adults, incomplete reporting.

N per group (Percentage with Current Asthma)

Children	Environmental Tobacco Smoke	
Exposure (mg/m^3)	Positive	Negative
<0.049	106 (15.1)	142 (8.5)
0.049–0.074	12 (0.0)	12 (8.3)
0.074–0.172	11 (45.5)	10 (0.0)
(trend *p*-value)	(<0.05)	(>0.50)

Log-linear models, stratified by environmental tobacco smoke, adjusted for socioeconomic status, ethnicity.
Adults: Results reported as "not significantly related" but rate of wheeze was "somewhat higher" with higher exposure; analyses stratified by environmental tobacco smoke exposure not reported.

Study and design[a]	Results
Related references: Quackenboss et al. 1989a); 1989c)	

Immune-mediated Conditions, Focusing on Allergies and Asthma, in Animal Studies

The animal studies most relevant to evaluating potential effects on allergy-related conditions and asthma, as well as a single study suggesting a potential increased vulnerability to respiratory infections, are discussed in the sections below.

Allergy-related conditions and asthma

There are currently no universally accepted animal models applicable to humans for determining dose-response relationships or the potency of low molecular weight chemicals to induce allergic symptoms via the inhalation route (IPCS, 2012). The majority of the experimental animal formaldehyde studies that are most relevant to interpreting these respiratory immune-mediated conditions used the ovalbumin (OVA) murine model, the best studied animal model of asthma. However, the OVA mouse model has several limitations relative to human data for hazard characterization. They include the following:

- Key features of human asthma are absent or minimal in the OVA model, including a lack of airway remodeling (Shin et al., 2009) and minimal airway hyperreactivity and eosinophilic inflammation (Mullane and Williams, 2014)
- OVA challenge models a small subset of endpoints and genes compared with those in humans (Mullane and Williams, 2014)
- The OVA model elicits an acute disease in contrast to the chronic condition in humans (Shin et al., 2009), and the antigen ovalbumin has questionable relevance and poor translatability for human asthma (Mullane and Williams, 2014; Bates et al., 2009)
- A standardized method for OVA administration is lacking; this precludes comparing results between laboratories and evaluating study protocols (Bates et al., 2009)
- There is uncertainty regarding the biological significance of airway hyperreactivity in mice (Bates et al., 2009)

In light of these limitations, EPA concluded for this assessment that the OVA model was more appropriate for examining mechanistic questions in support of hazard identification, based in part on the reasonably large number of well-conducted human studies on these endpoints. As such, the experimental animal studies were considered to be less informative than human studies for drawing interpretations regarding the potential for formaldehyde inhalation exposure to induce or exacerbate allergy-related conditions or asthma, and these studies are discussed below as mechanistic information that may add insight to the apical effects observed in exposed humans.

Other respiratory conditions

One experimental animal study of *medium* or *high* confidence evaluated endpoints related to the potential for formaldehyde exposure to cause other immune-mediated respiratory conditions, and reported a decrease in pulmonary antibacterial activity in mice exposed to 1.23 mg/m^3 formaldehyde for less than 1 day (Jakab, 1992). While such a finding could indirectly suggest that formaldehyde exposure might predispose animals to developing lower respiratory infections, this hypothesis was not specifically tested and other notable uncertainties with the study design exist (see Appendix A.5.6). Animal studies of long-term duration that are specifically designed to examine the functional capacity of the respiratory immune response would be informative.

Evidence on Mode of Action for Immune-mediated Conditions, Including Allergies and Asthma

An integrated evaluation of the abundant mechanistic information that might be relevant to the potential development of immune-mediated conditions following formaldehyde inhalation exposure is described in Appendix A.5.6, including evaluations of the individual mechanistic studies. The evaluation includes the somewhat heterogeneous data related (either directly or indirectly) to possible increases in respiratory infections after exposure, although those data are not discussed in detail in this section. Thus, this discussion focuses on mechanistic information that may inform the potential for formaldehyde to affect allergic conditions or asthma. This includes animal models using the allergen, OVA, which, although they do not fully capture the phenotype of human asthma or allergy-related conditions, can provide insight into some of the mechanistic changes that are relevant to these human conditions.

As shown in Figure 1-12, the integrated analysis identified several pathways describing potential associations between the most relevant mechanistic data available, with several of the initial or early events in these hypothesized pathways (e.g., oxidative stress and inflammatory changes) generally observed to occur at lower formaldehyde levels than other downstream changes (see Table 1-22). Overall, the mechanistic support for airway hyperresponsiveness was stronger (i.e., based primarily on moderate evidence of mechanistic events and their relationships). Although a definitive MOA(s) could not be defined, and it is unclear whether some important events would occur with chronic low-level formaldehyde exposure, the data were interpreted to identify an incomplete mechanism(s) by which formaldehyde exposure could cause this effect (see Figure 1-12), providing biological plausibility for inflammatory airway changes that could contribute to respiratory immune-mediated conditions. The mechanistic support for allergic sensitization was less clear (i.e., based on some potentially relevant events interpreted with moderate evidence and, in general, slight evidence for the relationships between events) because reliable data identifying mechanistic changes typically thought to be essential for sensitization, including changes in IgE, were lacking. However, moderate evidence for several mechanistic changes relevant to these responses was identified, providing some biological support.

Importantly, while many individual mechanistic events observed in animals are considered to be relevant to interpreting changes that may occur in the human airways, including potential amplified responses to inhaled materials, it is unclear how translatable these pathways are to interpreting complex human diseases like asthma, and notable key events have not been observed. Some of the data most informative to drawing conclusions for these health endpoints are described in greater detail below (see Tables 1-22 and 1-23).

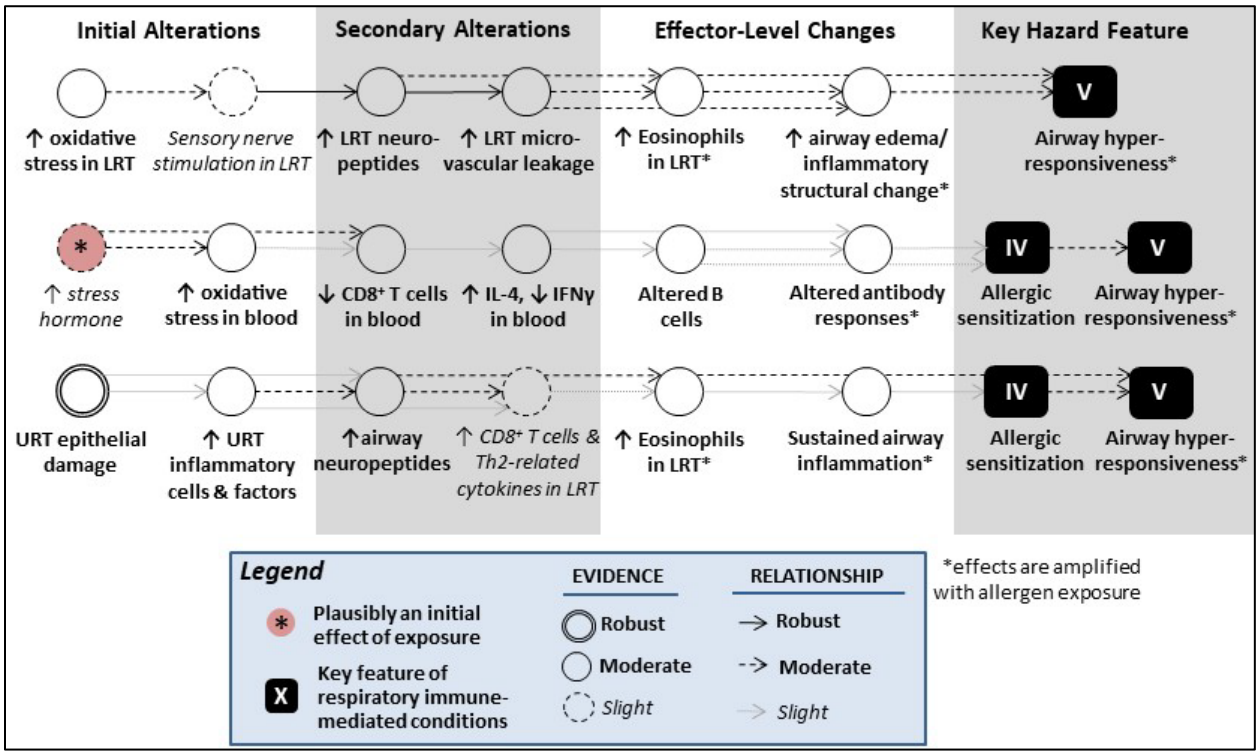


Figure 1-12. Possible mechanistic associations between formaldehyde exposure and immune-mediated conditions, including allergies and asthma.

An evaluation of the formaldehyde exposure-specific mechanistic evidence informing the potential for formaldehyde exposure to cause respiratory health effects (see Tables 1-22 and 1-23, and Appendix A.5.6) identified these mechanistic pathways as most relevant to interpreting effects on respiratory immune-related conditions such as asthma and allergic responses. Similar to effects on pulmonary function, events related to indirect stimulation of lower respiratory tract (LRT) sensory nerve endings (top pathway) were considered as likely to represent an incomplete mechanism by which formaldehyde inhalation could cause airway hyperresponsiveness, although whether certain events occur with chronic, low-level exposure remains unclear. While the observed alterations to circulating antibodies (i.e., primarily related to IgG and not IgE) following formaldehyde exposure might contribute to the development of both allergic sensitization and airway hyperresponsiveness (middle pathway), in the absence of additional clarifying data, this could not be identified as a likely mechanism for these effects. Likewise, the slight evidence of altered T cell-related airway responses and, secondarily, inflammatory eosinophil responses might be useful for explaining allergic sensitization (bottom pathway) if additional data were available to better explain the pattern and strength of these associations. Conversely, sustained airway inflammation, at least in animals previously sensitized to an allergen, was interpreted as likely to be an incomplete explanatory mechanism for airway hyperresponsiveness, although the sequence of events leading to

inflammation remain unclear. Interdependencies between the top and bottom pathways are likely to exist for airway hyperresponsiveness.

It is informative to consider the formaldehyde-specific mechanistic information in the context of the known pathogenesis of human asthma and related conditions. Asthmatic airways are characterized by an infiltration of eosinophils, plasma B cells, activated mast cells, and T cells that contribute to thickening of the airway wall, mucous secretion, airway remodeling, and airway hyperresponsiveness. Initiation and perpetuation of asthma are believed to be the result of T_H2 activity (Cohn et al., 2004). Specifically, T_H2 cells accumulate in the airway and secrete cytokines IL-4 and IL-13, which stimulate B cells to produce IgE (Barnes, 2008) (see Figure 1-13). Mast cells bind IgE and display this immunoglobulin as an allergen-specific receptor on their surfaces. When an allergen binds to this IgE, the mast cell is activated, triggering its release of several bronchoconstrictors (e.g., histamine, leukotrienes), which drive the disease state. T_H2 cells also release IL-5 that activates eosinophils following their migration into the airways. The precise role of eosinophils in asthma is unknown, but they are thought to contribute to inflammation (Barnes, 2008). Immune function and inflammatory responses do not fully explain the pathogenesis of asthma, particularly with respect to the varying phenotypes seen at a clinical level (Anderson, 2008). The interaction between nerve cells and the immune system also includes evidence that neuropeptide release may contribute to neurogenic inflammation and heightened airway responsiveness (Veres et al., 2009).

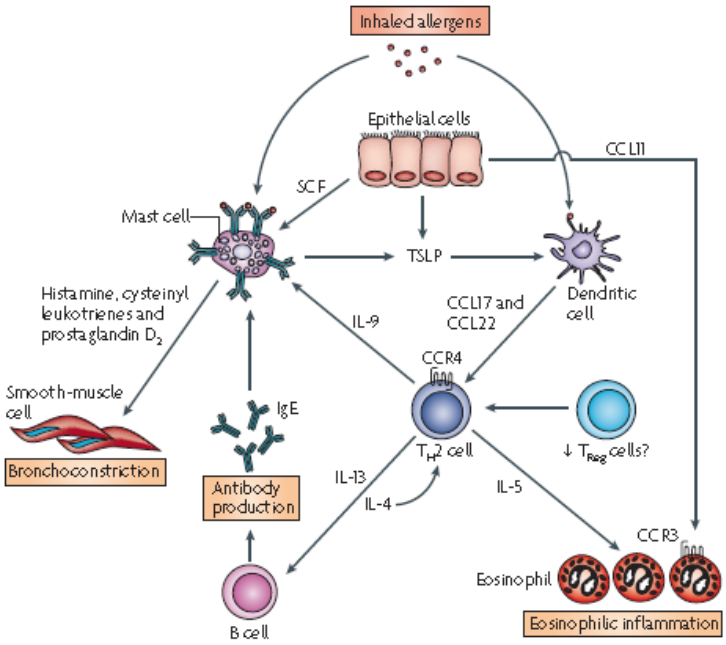


Figure 1-13. Inflammatory and immune cells involved in asthma

Inhaled allergens activate sensitized mast cells by crosslinking surface-bound IgE molecules to release prostaglandin D2. Epithelial cells release stem-cell factor (SCF), which is important for dendritic cells, which are conditioned by thymic stromal lymphopoietin (TSLP) secreted by epithelial cells and mast cells to release the chemokines CC-chemokine ligand 17 (CCL17) and CCL22, which act on CC-chemokine receptor 4 (CCR4) to attract T-helper 2 (T_H2) cells. T_H2 cells have a central role in orchestrating the inflammatory response in allergy through the release of interleukin-4 (IL-4) and IL-13 (which stimulate B cells to synthesize IgE), IL-5 (which is necessary for eosinophilic inflammation), and Il-9 (which stimulates mast-cell proliferation). Epithelial cells release CCL11, which recruits eosinophils via CCR3. Patients with asthma may have a defect in regulatory T (T_{reg}) cells, which may favor further T_H2-cell proliferation. Reprinted from Barnes (2008) with permission from Nature Publishing Group.

The mechanistic evidence that provides the most direct information regarding the potential role of formaldehyde in respiratory hypersensitivity responses consists of three *high or medium* confidence studies (Larsen et al., 2013; Fujimaki et al., 2004b; Ito et al., 1996; Riedel et al., 1996; Swiecichowski et al., 1993).[12] These studies all differed in the conditions under which formaldehyde affected asthma-relevant endpoints, specifically increased bronchoconstriction and airway hyperresponsiveness, using short-term and acute exposures in sensitized and nonsensitized animals. Formaldehyde exposure of 0.369 to 36.9 mg/m^3 increased bronchoconstriction in guinea pigs exposed for 2 to 8 hours (Swiecichowski et al., 1993). Both the in vivo and ex vivo data from this study indicate that smooth muscle airways are a (presumably indirect) target for formaldehyde. A 5-day formaldehyde exposure of 0.31 mg/m^3 prior to OVA sensitization increased OVA-induced bronchoconstriction in guinea pigs, indicating that formaldehyde exposure enhances reactivity to OVA sensitization (Riedel et al., 1996). Finally, a single 60-minute formaldehyde exposure of 7.0 mg/m^3 induced bronchoconstriction in OVA-sensitized mice housed only in humid, but not dry, environments, indicating that the bronchoconstrictive effects of formaldehyde may be impacted by humidity (Larsen et al., 2013). Taken together with supportive findings from a number of *low* confidence human and animal studies (see Appendix A.5.6), results across multiple species indicate that formaldehyde exposure is sufficient to trigger bronchoconstriction in both sensitized and nonsensitized animals, and that exposure appears to result in the development of hyperresponsive airways,[13] particularly in sensitized animals. This finding is consistent with the evidence supporting increases in microvascular leakage, edema, and other inflammatory airway changes with formaldehyde exposure after allergen sensitization (see Section 1.2.2 and Appendix A.5.6). Overall, the data do not indicate that formaldehyde is itself immunogenic, but instead suggest formaldehyde may augment immune responses to other allergens.

Other findings that may be relevant to asthma or allergic conditions with at least a moderate level of evidence include increases in airway eosinophils, increases in protein mediators

[12]Note: Swiecichowski et al. (1993) and Leikauf (1992) are interpreted to use the same cohort of animals.
[13]As the challenge stimuli used in the formaldehyde studies included allergens as well as nonimmunological stimuli, and because most experiments did not attempt to delineate the specifics of the functional changes, "airway hyperresponsiveness" or "hyperresponsive airways" encompasses any of a range of possible airway features: hyperreactivity (exaggerated response), hypersensitivity (lower dose to elicit response), altered ventilatory parameters (e.g., maximal response, resistance), recovery (longevity of response), or others.

of bronchoconstriction such as tachykinins, and changes in antibody titers (see Section 1.2.2 and Table 1-22). Although a precise role for eosinophils in asthma is unknown (i.e., eosinophilia is not necessary for the development of asthma), eosinophilic airway inflammation (presumably mediated by T_H2 lymphocytes) is a hallmark of asthma (George and Brightling, 2016); the formaldehyde-specific evidence indicates that eosinophils are increased in both the upper and lower airways following formaldehyde exposure, particularly with allergen sensitization (see Section 1.2.2). As activation of eosinophils can induce airway hyperresponsiveness and perpetuate further recruitment of inflammatory mediators into the airway (Cohn et al., 2004), these changes provide coherent biological support for the more apical immune-mediated conditions. In addition, as previously discussed (see Section 1.2.2), it appears that formaldehyde exposure mediates (at least in part) lung inflammation via tachykinins in rats and mice. For example, *high* or *medium* confidence studies show that substance P, a tachykinin and NK1 ligand, is dose-dependently increased in mice exposed for 12 weeks to 0.1 to 2.5 mg/m^3 formaldehyde (Fujimaki et al., 2004b), and that an antagonist of the NK1 receptor can completely abrogate formaldehyde-induced airway inflammation, at least following a 10-minute formaldehyde exposure at 18 mg/m^3 (Ito et al., 1996). Somewhat surprisingly, however, the formaldehyde-induced increases in substance P observed by Fujimaki et al. (2004b) were not observed in animals sensitized to OVA, despite the observation that airway eosinophils were increased at 2.5 mg/m^3 formaldehyde only in animals that were sensitized. Thus, some uncertainties remain. The results related to antibody production, although providing moderate evidence of an effect, were difficult to interpret in the context of their relevance to asthma. Specifically, while evidence from human and animal studies suggests that formaldehyde exposure modifies antibody responses, the most consistently observed responses were associated with changes in IgG, not IgE (see Table 1-22). The relevance of IgG-related responses to asthma or allergies is unclear.

Several other airway changes relevant to asthma or allergic conditions were not supported by moderate or robust evidence in the available studies. For example, slight evidence suggests changes in $CD8^+$ T cells or asthma-relevant T_H2 cytokines, including IL-4 [and, to a lesser extent, IL-5 and RANTES (regulated on activation, normal T cell expressed and secreted)], in the lungs after exposure to 0.5–12 mg/m^3 formaldehyde in both sensitized and nonsensitized rodents; however, no changes in IL-13 or histamine have been reported. At the cellular level, while slight evidence suggests that $CD8^+$ T cells might be increased in naïve rodents exposed to >7 mg/m^3 formaldehyde, mast cells or other T cell populations did not appear to be changed in the few studies that examined them, and none of the identified studies investigated other cells of interest (e.g., dendritic cells, smooth muscle cells).

Immune-related changes in the blood may also be relevant to interpreting the development of allergic conditions, and possibly asthma, albeit indirectly. A number of studies, across different human and animal populations, spanning an array of formaldehyde exposure scenarios, have reported changes in blood cell counts and secreted factors. Although some of the specific changes

vary across studies, taken together, the data provide robust evidence of an association between formaldehyde exposure and hematological effects. Interestingly, some changes noted in the blood of individuals exposed to formaldehyde are contrary to the cellular changes noted in the respiratory tract (e.g., $CD8^+$ T cells appear to be increased in the respiratory tract and decreased in the blood) (see additional discussion in Appendix A.5.6). Potential explanations could include recruitment of subsets of immunoresponsive cells from the circulation to the irritated and inflamed respiratory tract (e.g., due to a gradient of chemoattractants or other factors across tissue compartments, potentially resulting from sustained airway inflammation), or species differences in responses (i.e., LRT data are mostly from animal studies, while the data in blood are primarily from humans); however, none of the identified human studies report data across tissue compartments, and the animal data do not address such hypotheses. Overall, similar to the cellular changes in the LRT, no explanation exists for how formaldehyde exposure could affect blood immune cell counts.

One of the most consistent blood cell changes observed across studies was a decrease in the total number of white blood cells (WBCs), including moderate evidence of $CD8^+$ T cell decreases following formaldehyde exposure and a corresponding increase in the ratio of $CD4^+/CD8^+$ T cells (see Table 1-23). Depending on the specific stimuli, stimulated $CD8^+$ T cells can produce interferon-γ (IFN-γ) and inhibit production of IL-4 and immunoglobulin (i.e., IgE) responses (Holmes et al., 1997), or their phenotype can be driven toward production of excess IL-4, a situation hypothesized to be associated with atopic asthma (Lourenço et al., 2016). IL-4 can stimulate T cell receptors on $CD4^+$ and $CD8^+$ T cells (Serre et al., 2010), and can both drive $CD4^+$ T cells toward a T_H2 response (Kopf et al., 1993) and influence the activation and development of antigen-specific $CD8^+$ T cell immunity by shifting the phenotype of these cells from IFN-γ production to IL-4 production (Erb and Le Gros, 1996). Moderate evidence provides support for increases in blood IL-4 (slight evidence suggests similar increases in the LRT) and decreases in IFN-γ after formaldehyde exposure. Interestingly, several lines of evidence suggest a pattern of immune cell effects related to formaldehyde concentration, with potential stimulation at lower formaldehyde exposure levels and decreases at higher levels. This included slight evidence of changes in total T cells, NK cells, and IL-10. A complex relationship exists between IL-10, NK cells, and subsets of $CD4^+$ T cells (e.g., T_H1 and T_H2 cells), which can affect antibody responses (Moore et al., 2001). However, the potential effects of formaldehyde exposure on the specific phenotype of CD4+ or CD8+ T cells, or on the relationship between changes in lymphocyte populations or secreted factors and respiratory hypersensitivity, have not been well studied and remain to be elucidated.

Several other changes in the blood are of interest to the development of immune-mediated conditions (see Appendix A.5.6 for additional discussion). Moderate evidence indicates that formaldehyde exposure alters the percentage of B cells in the circulation. These cells produce antibodies upon stimulation with antigen (e.g., allergens) and can contribute to airway hyperresponsiveness (Hamelmann et al., 1997). While this finding, along with slight evidence of increased antigenic markers, suggests the potential for alteration of the adaptive immune response

after formaldehyde exposure, this observation alone is insufficient to indicate functional changes such as exposure-induced differences in clonal expansion and differentiation to antibody-producing cells, evidence of which would support a more convincing biological relationship. In addition, red blood cell counts were decreased in both human and animal studies (moderate evidence), generally at formaldehyde concentrations above 0.5 mg/m^3, although the relevance of these changes to respiratory system health effects is unknown. It is plausible that sustained increases in oxidative stress (markers for which are consistently elevated in blood and respiratory tissues after formaldehyde exposure), or other soluble factors that could segue from airway inflammation, might affect the viability of circulating erythrocytes and immune cells, or the circulating precursors for these cells; however, no evidence exists to substantiate this hypothesis. An increased level of the circulating stress hormone, corticosterone (the major animal glucocorticoid; in humans, it is cortisol), with short-term, but not acute, formaldehyde exposure is also suggested. Persistent increases in circulating glucocorticoids can also negatively impact the function and health of circulating immune cells, causing immunosuppression of most cell types (O'Connor et al., 2000). However, these potential linkages have also not been examined.

Overall, although additional studies clarifying inconsistencies across the studies would be informative, the available data support a conclusion that formaldehyde exposure can modify immune system function in the blood across a range of concentrations and exposure durations. Many of these observations would benefit from more specific studies on WBCs focused on understanding the phenotype of the modified cells, and the profile of secreted factors in the blood, particularly after formaldehyde exposures of varying duration and concentration. Taken together, the available mechanistic studies provide consistent evidence that formaldehyde may stimulate a number of immunological and neurological processes related to allergic or asthmatic responses; however, a molecular understanding of how formaldehyde exposure might favor asthmatic T_H2 responses has not been experimentally established and additional experimental support is necessary to interpret the translatability of these pathways to complex human airway diseases such as asthma. Importantly, the evidence supports that formaldehyde exposure induces bronchoconstriction with and without allergen sensitization, providing strong biological support for the development of hyperresponsive airways that could contribute to at least some of the observed respiratory immune-related symptoms. This heightened bronchoconstriction response may be due to a combination of neurogenic mechanisms through reduction of anti-inflammatory molecules or increased tachykinins, increased T_H2 cytokines and antibodies, and eosinophil recruitment and activation in the lung. Immune- and inflammatory-related changes in the blood provide additional support for exposure-induced alterations relevant to the development of these immune-mediated conditions. Additional studies are necessary to clarify the incomplete mechanisms that describe the association between formaldehyde exposure and these effects, as well as the exposure concentration and duration dependence of some of the more influential

findings from the current studies. Collectively, the available studies provide mechanistic support for the biological plausibility of the formaldehyde exposure-induced changes observed in humans.

Table 1-22. Mechanistic evidence most informative to the development of immune-mediated conditions after formaldehyde inhalation[a]

Endpoint	Endpoint-specific findings and confidence		Summary of evidence	Conclusion
Modifications in the upper or lower respiratory tract (URT or LRT)				
Some of these mechanistic changes have been discussed in previous sections. *See Section 1.2.2, Evidence on mode of action…, for presentation of the evidence for:* **↑ LRT oxidative stress** (moderate); **LRT sensory nerve activation** (slight); **↑ LRT neuropeptides** (moderate); **↑ LRT microvascular leakage** (moderate); **↑ LRT eosinophils** (moderate); **↑ airway edema or other inflammatory structural change**; and **URT epithelial damage** (robust)				
Upper airway indicators of altered immune function (inferred from URT infections)	*High or Medium*	*Human*: Increased frequency and duration of URT infections in symptomatic workers; increased chronic URT inflammation (and decreased function of blood neutrophils, but N/C in leukocyte counts) in exposed workers (Lyapina et al., 2004): chronic (yrs) exposure at 0.87 mg/m^3 (Note: recent URT infection was often an exclusion criterion in observational studies focusing on pulmonary function)	Indirect evidence of decreased immune capacity in a human study of long-term exposure at 0.87 mg/m^3 (note: mRNA changes were not necessarily indicative of a decreased immune response)	Slight (indirect evidence of ↑URT infection)
		Animal: mRNA changes suggestive of altered immune response (Andersen et al., 2010): short-term (≥1 wk) exposure at ≥12.3 mg/m^3		
	Low	*Human*: None	No evidence to evaluate	
		Animal: None		
Lower airway indicators of altered immune function (inferred from LRT infections)	*High or Medium*	*Human*: Increased LRT infections in infants (Roda et al., 2011): 32–41% increase in incidence per 0.0124 mg/m^3 increase in formaldehyde (LOD: 0.008 mg/m^3); ~1-year exposure at 0.020 mg/m^3 (median)	Indirect evidence in a single study of infants exposed to a median of 0.020 mg/m^3 observing an association between exposure and increased infections. One acute mouse study also provided indirect support for an increased likelihood of respiratory infections.	Moderate (indirect support for an increased propensity for LRT infections, particularly during development)
		Animal: Decreased antibacterial activity in mice (Jakab, 1992): acute exposure at 1.23 mg/m^3, noting that this finding appeared to be particularly sensitive to the pattern of formaldehyde exposure		
	Low	*Human*: Increased emergency room visits for episodes including LRT infections (Rumchev et al., 2002): children aged 6–36 months at mean levels 0.028–0.030 mg/m^3 (maximum 0.12–0.22)	Direct and indirect evidence of impaired LRT immune function in children and in a short-term rat study, respectively	
		Animal: Decreased expression of immune-related genes in rat lung (Sul et al., 2007), specifically HSP701a (involved in antigen presentation), complement four binding protein (binds necrotic or apoptotic cells for cleanup), and Fc portion of IgGiii (involved in leukocyte activation): 2 wk exposure at ≥6.15 mg/m^3		
Changes in pulmonary function with	*High or Medium*	*Human*: None	Acute and short-term studies in two animal species demonstrate that formaldehyde increases	Robust (↑ Hyper-responsive airways[b])
		Animal: [allergen challenge]: With ovalbumin [OVA] sensitization, increased airway obstruction in guinea pigs		

Endpoint	Endpoint-specific findings and confidence		Summary of evidence	Conclusion
challenge (e.g., with broncho-constrictor allergen) (Note: un-provoked responses are not included)		(Riedel et al., 1996): short-term exposure at 0.31 mg/m^3 and increased reactivity in mice (Larsen et al., 2013): acute exposure at ~5–7 mg/m^3 in humid or dry environments; [acetylcholine challenge]: Increased airway resistance and reactivity in guinea pigs (Swiecichowski et al., 1993; Leikauf, 1992): acute exposure at 1.23 mg/m^3	responsiveness to allergens and bronchoconstrictors, particularly with prior sensitization, at levels as low as 0.31 mg/m^3	
	Low	*Human*: [histamine challenge]: Hyperreactive airways with prolonged exposure (Górski and Krakowiak, 1991): ≥1 year exposure at ≤0.5 mg/m^3, but N/C after acute exposure (Krakowiak et al., 1998): at 0.5 mg/m^3; [allergen challenge]: hypersensitivity with acute exposure when exposure was restricted to mouth breathing in allergic asthmatics with a large allergen (mite) (Casset et al., 2006): acute exposure at 0.1 mg/m^3; N/C after oronasal exposure in allergic asthmatics using a different allergen (pollen), including a methacholine (MCh) responsiveness test after allergen exposure (Ezratty et al., 2007): acute exposure at 0.5 mg/m^3	Suggestive evidence of increases with prolonged exposure, and possibly acute mouth-breathing exposure when challenged with specific allergens, but not acute exposure alone, to ≤0.5 mg/m^3 in human adults; also, increased at ≥3 mg/m^3 in short-term or acute studies across three species, particularly with prior sensitization	
		Animal: [MCh challenge]: Hyperresponsive airways (increased reactivity and sensitivity) with exposure in mice and rats (Wu et al., 2013; Liu et al., 2011a; Qiao et al., 2009): short-term exposure at ≥3 mg/m^3, and in monkeys (Biagini et al., 1989): acute exposure at 3.1 mg/m^3; in mice and rats, this response was amplified with OVA sensitization; TRP antagonists reduced the hyperresponsiveness in mice (Wu et al., 2013)		
Sustained Inflam-mation	*High or Medium*	*Human*: Increased exhaled nitric oxide, a noninvasive and indirect marker of lower airway inflammation and oxidative stress, in healthy or asthmatic children (Flamant-Hulin et al., 2010; Franklin et al., 2000): unknown exposure duration (likely months to years; in classrooms or homes) at 0.04–0.06 mg/m^3	Immune cell counts are continually elevated in a subchronic mouse study with allergen stimulation at 2.46 mg/m^3; increased biomarkers (indirect evidence) of lower airway inflammation are observed in children with prolonged exposure.	Moderate (may require allergen sensitization)
		Animal: Eosinophils and monocyte counts remain elevated with continued exposure for subchronic duration with allergen (OVA) sensitization (Fujimaki et al., 2004b): 12 wk exposure at 2.46 mg/m^3		
	Low	*Human*: None	BAL cell counts and histologic evidence suggest that inflammation persists for several weeks with short-term exposure, and these effects are amplified by allergen	
		Animal: Immune cell counts were increased with short-term exposure in several studies at ≥0.5 mg/m^3 (see Table 1-23; histological evidence of inflammation without epithelial damage was noted in short-term exposure studies, typically at higher concentrations, which were amplified by allergen (e.g., ≥3 mg/m^3; (Wu et al., 2013; Kimura et al., 2010)		
↑ CD8+ T cells in LRT	*High or Medium*	*Human:* none	No evidence to evaluate	Slight (at >7 mg/m^3, but allergen
		Animal: none		

Endpoint	Endpoint-specific findings and confidence		Summary of evidence	Conclusion
	Low	*Human:* none *Animal*: Increased in short-term exposure studies in rats [at 7.4 mg/m^3; (Sandikci et al., 2007b)] and mice [at 12.3 mg/m^3; (Jung et al., 2007)]; no change with short-term exposure in a mouse study at ≥6.2-12.3 mg/m^3 (Kim et al., 2013a)	A study in rats and another in mice suggest that CD8+ T cells in the BAL might be increased after short-term exposure to high (>7 mg/m3) levels, although a second mouse study reported no changes	stimulus unstudied) (note: mixed, indeterminate evidence for B cells, and CD4+ cells; Appendix A.5.6)
↑ Th2-related (primarily) cytokines in LRT	*High or Medium*	*Human:* none *Animal*: none	No evidence to evaluate	Slight (↑ IL-4 at ≥0.5 mg/m^3 and IL-5 at >6 mg/m^3) (note: mixed, indeterminate evidence for IL-10, IL-6, IL-13, and for Th1 cytokines; see Appendix A.5.6)
	Low	*Human:* No change in IL-4 or IL-5 at 0.5 mg/m^3 after acute exposure and pollen coexposure (Ezratty et al., 2007) *Animal*: ↑ IL-4 in 4 studies in mice and one study in rats (all short-term exposure) testing exposures of 0.5-12.3 mg/m^3 and observing larger increases with antigen (OVA) administration (Wu et al., 2013; Liu et al., 2011a; Qiao et al., 2009; Jung et al., 2007; Lu et al., 2005) ↑ IL-5 in 2 short-term exposure studies in mice at ≥6.2 mg/m^3 (Jung et al., 2007; Sadakane et al., 2002) No change in IL-4 in a short-term exposure study in mice at >12.3 mg/m^3 with co-administered house dust mite antigen (Sadakane et al., 2002) [c]	IL-4 was increased in short-term studies of rats and mice at levels as low as 0.5 mg/m^3, with amplified increases with antigen; IL-5 was increased in 2 of 3 studies in mice only testing higher (>6mg/m^3) levels	
Modifications in the blood				
[[See Table 1-23 for cellular and cytokine responses in the blood]]				
Total IgE	*High or Medium*	*Human*: None *Animal*: No evidence suggesting changes (Fujimaki et al., 2004b): subchronic exposure at ≤2.46 mg/m^3	Slight (at ≥ 3 mg/m^3) Based on no changes in a *high or medium* confidence subchronic mouse study at ≤2.46 mg/m^3 and evidence of increased IgE in two short-term *low* confidence formalin studies in mice at ≥3 mg/m^3, but no evidence for changes in *low* confidence studies in mice or humans at <2 mg/m^3	Moderate for IgG Slight for IgE (only with specific exposure scenarios) Indeterminate for IgM or IgA (i.e., very little evidence; data not shown: see Appendix A.5.6)
	Low	*Human*: No evidence suggesting changes (Ohmichi et al., 2006; Erdei et al., 2003; Wantke et al., 2000; Palczynski et al., 1999; Wantke et al., 1996b): short-term exposure at ≤1.8 mg/m^3 (duration in Erdei et al. unknown) *Animal*: Evidence of increases in mice, which were increased further by OVA sensitization (Wu et al., 2013; Jung et al., 2007): short-term exposure at ≥3 mg/m^3; evidence of no changes in mice by FA alone (Kim et al., 2013b; Gu et al., 2008), although FA exacerbated house dust mite-induced IgE (Kim et al., 2013b): short-term exposure at 0.12–1.2 mg/m^3		
Formal-dehyde (FA)-Specific IgE	*High or Medium*	*Human*: Elevated in one study of children (Wantke et al., 1996a): years of exposure (assumed) at ~0.06 compared to ~0.03 mg/m^3 (note: elevations were unrelated to symptoms); N/C in adults (Kim et al., 1999): 4 years at 3.74 mg/m^3 *Animal*: None	Slight (in children) Based on increases in a *high or medium* confidence long-term study of children at <0.1 mg/m^3; although, no changes were observed in a	

Endpoint	Endpoint-specific findings and confidence		Summary of evidence	Conclusion
	Low	*Human*: No evidence of changes across multiple studies in adults (Ohmichi et al., 2006; Zhou et al., 2005; Wantke et al., 1996b; Górski and Krakowiak, 1991; Thrasher et al., 1987): short-term (weeks) or long-term (years) exposure at ~0.1–1.81 mg/m^3; however, findings were unclear in two adult studies of long-term exposure in which a small proportion of subjects did have FA-IgE (Dykewicz et al., 1991; Thrasher et al., 1990), and one study noted slight increases with longer exposure (Wantke et al., 2000): 10 wk, not 5 wk, at 0.265 mg/m^3	*high or medium* confidence long-term study of adults at 3.74 mg/m^3 and there was no clear evidence of changes across multiple *low* confidence short-term and long-term studies in adults at ≤1.81 mg/m^3	
		Animal: No change in guinea pigs with acute challenge (Lee et al., 1984) at 2.5 or 4.9 mg/m^3 after short-term exposure to 7.4 or 12.3 mg/m^3 (note: no measures without formaldehyde and isotype was unspecified)		
Antigen-Specific IgE (does not include FA-specific Ig)	*High or Medium*	*Human*: None	Slight Based on no changes in a *high or medium* confidence subchronic study with i.p. antigen sensitization and evidence in *low* confidence short-term studies in mice exposed to ≥1 mg/m^3 that appears to be highly situational (e.g., dependent on duration and periodicity of formaldehyde exposure, and antigen type and administration route)	
		Animal: N/C in OVA-IgE (Fujimaki et al., 2004b): 12 wk exposure at 0.1–2.46 mg/m^3 (OVA i.p.)		
	Low	*Human*: None		
		Animal: Increased OVA-specific IgE in mice in two short-term exposure studies (Gu et al., 2008; Tarkowski and Gorski, 1995): 10 d at 2 mg/m^3 (but not 1 d/wk for 7 wk, or when OVA sensitization i.p.) and 5 wk at 0.98 mg/m^3 with i.p. OVA (but not ≤4 wk), respectively; however, N/C in mice in three short-term (all 4-wk) exposure studies: (Wu et al., 2013) at 3 mg/m^3 with s.c. OVA sensitization, (Kim et al., 2013b) at 0.2–1.23 mg/m^3 with dermal house dust mite (HDM) sensitization, and (Sadakane et al., 2002) at >12.3 mg/m^3 with i.p. HDM sensitization [b]		
Total IgG	*High or Medium*	*Human*: Decreased in a single study of exposed workers (Aydın et al., 2013): 7 yr exposure at 0.264 mg/m^3	Moderate Based on decreased total IgG in a *high or medium* confidence long-term study in adult workers exposed to 0.264 mg/m^3, and a *high or medium* confidence short-term study in rats exposed to ≥6.15 mg/m^3. IgG isoforms were affected in 2 of 3 *low* confidence short-term mouse studies, but not a *low* confidence study of children at low levels	
		Animal: Decreased total IgG in rats (Sapmaz et al., 2015): short-term exposure at ≥6.15 mg/m^3		
	Low	*Human*: N/C in children at ~0.007–0.07 mg/m^3 (Erdei et al., 2003): unknown exposure duration (likely months-years)		
		Animal: IgG1 (N/C in IgG2a) increased by FA alone, whereas FA exacerbated IgG2a (N/C in IgG1) in atopic-prone mice (Kim et al., 2013b): short-term exposure at 0.25, but not 1.2, mg/m^3; increased IgG1 and IgG3, but decreased IgG2a and 2b, in C57 mice (Jung et al., 2007): short-term exposure at ≥6.15 mg/m^3; N/C in IgG Balb/c mice (Gu et al., 2008): short-term exposure at <1 mg/m^3		

Endpoint	Endpoint-specific findings and confidence		Summary of evidence	Conclusion
FA-Specific IgG	*High or Medium*	*Human*: Slight (i.e., <10%) increase in a single study of adults (Kim et al., 1999): years of exposure at 3.74 mg/m^3	Moderate Based on slight increases in a *high or medium* confidence long-term study of adults at 3.74 mg/m^3 and increases in *low* confidence studies of adults with long-term exposure at <1 mg/m^3, but not with short-term exposure at higher levels; studies in children were not identified	
		Animal: None		
	Low	*Human*: Increased in two studies (Thrasher et al., 1990; Thrasher et al., 1987) and unclear in one study in which 5/55 subjects did have FA-IgG (Dykewicz et al., 1991): all three studies examined years of exposure at <0.1–<1.0 mg/m^3; N/C in one study (Wantke et al., 2000): short-term exposure at 0.265 mg/m^3		
		Animal: No change in guinea pigs with acute challenge (Lee et al., 1984) at 2.5 or 4.9 mg/m^3 after short-term exposure to 7.4 or 12.3 mg/m^3 (note: the study did not present measures without formaldehyde exposure, and isotype was unspecified)		
Antigen-Specific IgG (does not include FA-specific Ig)	*High or Medium*	*Human*: None	Moderate (with inhaled antigen) Based on increased OVA-IgG1 in a *high or medium* confidence short-term study in guinea pigs at 0.31 mg/m^3 with inhaled allergen, but not a longer *high or medium* confidence mouse study at similar levels using injected allergen. Similarly, a long-term *low* confidence study observed increased IgG sensitization to airway antigens in children, whereas several *low* confidence studies in mice and rats suggest that IgG sensitization does not occur when antigen is injected.	
		Animal: Increased OVA-specific IgG1 in guinea pigs (Riedel et al., 1996): 5 d at 0.31 mg/m^3 with inhaled OVA; questionable decrease (i.e., effects were observed at 0.49, but not 2.46, mg/m^3) in OVA-IgG1 and OVA-IgG3 in mice (Fujimaki et al., 2004b): 12 wks exposure with i.p. OVA sensitization (N/C in OVA-IgG2)		
	Low	*Human*: Increased IgG against 2 bacterial pathogens by linear regression in 3rd grade children with respiratory complaints (Erdei et al., 2003): <0.1 mg/m^3, unknown exposure duration (likely years, home measures)		
		Animal: N/C in OVA-IgG or Der f-IgG1 in mice (Wu et al., 2013; Gu et al., 2008; Sadakane et al., 2002): up to 5 wk exposures at 0.123–3 mg/m^3 or >12.3 mg/m^3 [b]; N/C in IgG specific to vaccine antigens in rats (Holmstrom et al., 1989a): 22 months exposure at 15.5 mg/m^3. In all cases, s.c. or i.p. exposure was used for sensitization		
↑ **Circulating Stress Hormones**	*High or Medium*	*Human*: None	Increased at 3 mg/m^3 formaldehyde in a study in rats with short-term, but not acute, exposure	Slight
		Animal: Increased corticosterone in rats with short-term, but not acute, exposure (Sorg et al., 2001a): at ~3 mg/m^3		
	Low	*Human*: None	No evidence to evaluate	
		Animal: None		
Modifications in other non-Respiratory Tissues				
↑ **Oxidative stress in nonrespiratory tissues**	*High or Medium*	*Human*: Increased marker of lipid peroxidation in adult serum lymphocytes (Bono et al., 2010): likely months-to-years exposure (assumed) at ≥0.066 mg/m^3; Increased F2-Isoprostanes (suggested as the best in vivo biomarker of lipid peroxidation) in urine (Romanazzi et al., 2013): 0.21 mg/m^3 chronic occupational exposure (indirect for effects in blood), although smoking and formaldehyde were not additive, both were independently associated with	Two studies in adults indicate elevated oxidative stress markers at ≥0.066–0.21 mg/m^3 with long-term exposure. Given the uncertainty regarding use of urine to reflect associations in blood, one study	Moderate

Endpoint	Endpoint-specific findings and confidence		Summary of evidence	Conclusion
		ROS—Note: serum and urine IsoP measures are often correlated [e.g., (Rodrigo et al., 2007)], suggesting that urine levels may reflect similar serum changes	contributes as indirect evidence	
		Animal: None		
	Low	*Human*: Increased oxidative stress biomarkers (F2-Isoprostanes; malondialdehyde) in urine (Bellisario et al., 2016): work-shift exposure at ~0.034 mg/m^3 (indirect for effects in blood; responses likely reflect short-term exposure)	Several studies in three species suggest increases in markers of oxidative stress with acute or short-term exposure, even at formaldehyde levels ≤1 mg/m^3; it is not clear whether and to what extent this persists with long-term exposure	
		Animal: Increased oxidative stress markers in mice (Ye et al., 2013b; Matsuoka et al., 2010): acute or short-term exposures at as low as 0.12 mg/m^3; increased oxidative stress markers and protein indicators in rats (Aydin et al., 2014; Im et al., 2006): short-term exposure at 6.48–12.3 mg/m^3, although one study with a longer exposure (10 wk) observed a decrease in MDA in rats (Katsnelson et al., 2013): at 12.8 mg/m^3; other indicators in rodents included decreased GSH (Katsnelson et al., 2013; Ye et al., 2013b) and increased NO and SOD (Matsuoka et al., 2010): short-term exposure at ≥1 mg/m^3		
Cell counts in immune tissues (not including bone marrow)	*High or Medium*	*Human*: None	Suppression of CD8+ T cells in immune tissues (e.g., spleen) is indicated in one 8-wk mouse study, with indirect support from a second short-term mouse study, at around 2 mg/m^3 ; effects on CD4$^+$/CD8$^+$ ratio were mixed across 2 subchronic mouse studies	Moderate (for ↓ CD8+ T cell response in spleen and thymus) Slight NK cells (↑ at low level; ↓ at high level) Indeterminate for other cell counts
		Animal: Decreased CD8+ T cells and increased CD4$^+$/CD8$^+$ ratio in both thymus (immature immune cells) and spleen (mature immune cells) in male mice (Ma et al., 2020): Eight weeks of exposure at 2 mg/m^3; No change in splenic CD4$^+$/CD8$^+$ ratio in female mice (Fujimaki et al., 2004b): 12 wk at up to 2.46 mg/m^3; Increased splenic regulatory T cells (subset of CD4+) and indirect markers for suppression of effector T cell (CD8+) activity in female mice (Park et al., 2020): short-term exposure at ≥1.38 mg/m^3		
	Low	*Human*: None	Multiple short-term mouse studies suggest that overall splenic cell T and B cells are unchanged; however, 2 studies suggest that NK cells may be affected (1 study showed NK cells were stimulated at low formaldehyde levels, and another that high levels are inhibitory/toxic)	
		Animal: N/C in tissue weight, total cellularity or T or B cell counts in mice (Kim et al., 2013a; Gu et al., 2008; Dean et al., 1984); altered NK cell number and function was noted in mice, with one study showing decreases (Kim et al., 2013a): 2–3 wk at 12.3 mg/m^3, and another showing increases (Gu et al., 2008): 5 wk at up to 0.12 mg/m^3, and a third showing N/C in lymphocyte proliferation, functional parameters, IgM production, or NK cytotoxicity (Dean et al., 1984): 3 wk at 18.5 mg/m^3		
Systemic indicators of altered	*High or Medium*	*Human*: None	No evidence to evaluate	Indeterminate
		Animal: None		

Endpoint	Endpoint-specific findings and confidence		Summary of evidence	Conclusion
immune function	*Low*	*Human*: Increased autoantibodies in adults (Thrasher et al., 1990): long-term exposure at 0.06–0.95 mg/m^3 *Animal*: Improved cell-mediated immune response to bacteria challenge, but N/C against tumor challenge or delayed-type hypersensitivity response in mice (Dean et al., 1984): 3 wk exposure at 18.5 mg/m^3 (Note: N/C in vitro measures of immune cell function in the same study)	1 study in adults suggests that autoantibodies are elevated with low-level, long-term exposure; somewhat in contrast, one mouse study suggests short-term high-level exposure improves host response to bacteria	

[a]Several studies examining the lineage and maturity of immune and non-immune cells in the bone marrow and other systemic tissues (e.g., blood; spleen) are not discussed in this section. Although it is possible that differences in the maturation phenotype of cells could indirectly contribute to the immune changes of interest to this section, such alterations would be expected to cause functional or other detectable changes in more apical mechanistic events relevant to immune responses in the respiratory system. Thus, this discussion focuses on those mechanistic events considered more directly relevant to these POE outcomes. Please see Section 1.3.3 for a discussion of these cell lineage and maturation markers in the context of lymphohematopoietic cancer MOA.

[b]As the challenge stimuli used in the formaldehyde studies included allergens as well as nonimmunological stimuli, and because most experiments did not attempt to delineate the specifics of the functional changes, "airway hyperresponsiveness" or "hyperresponsive airways" encompasses any of a range of possible airway features: hyperreactivity (exaggerated response), hypersensitivity (lower dose to elicit response), altered ventilatory parameters (e.g., maximal response, resistance), recovery (longevity of response), or others.

[c]Reported as 0.5% formaldehyde solution; concentration assumed to be >12.3 mg/m^3 (Sadakane et al., 2002).

Table 1-23. Summary of changes in cell counts and soluble immunological factors in the blood following formaldehyde exposure

Endpoint			No changes observed (above dashed line= human studies; below dashed line= animal studies; *high or medium* confidence = *and bold)			Significant[a] increases (↑) or decreases (↓) (above dashed line= human studies; below dashed line= animal studies; *high or medium* confidence = *and bold)			Conclusion (notes)
			mg/m^3	Length[b]	References (details)	mg/m^3	Length[b]	References (details)	
White blood cells (WBCs)	**Total WBCs**		**0.87** **0.25** 0.018	**Years** **Years** Years[c]	(Lyapina et al., 2004)* (Aydın et al., 2013)* (Erdei et al., 2003) (asthmatic children)	**↓ 1.6** ↓ N/A[e] (≤1) ↓≤0.29	**Years (same cohort)** Yr vs. Mo Years	(Hosgood et al., 2013)*; (Zhang et al., 2010)*[d] (Bassig et al., 2016)* (Thrasher et al., 1990) (Kuo et al., 1997)	Moderate ↓ in WBCs [g]
			≥9.23	**8 wk**	(Morgan et al., 2017) **(mice)***	**≥2.46**[f] (indirect) ↓ 0.5–3	**Short** Short	(Rager et al., 2014)* **(rats)** (Zhang et al., 2013b) (mice)	
	Granulocytes	**All**				**↓ 1.6**	**Years (same cohort)**	(Hosgood et al., 2013)*; (Zhang et al., 2010)*[d] (Bassig et al., 2016)*	Slight ↓ in granulocytes (appears to reflect potential

Endpoint			No changes observed (above dashed line= human studies; below dashed line= animal studies; *high or medium* confidence = *and bold)			Significant[a] increases (↑) or decreases (↓) (above dashed line= human studies; below dashed line= animal studies; *high or medium* confidence = *and bold)			Conclusion (notes)
			mg/m³	Length[b]	References (details)	mg/m³	Length[b]	References (details)	
			18.5	Short	(Dean et al., 1984) (mice) [h]				changes in neutrophils at higher concentrations with short-term or longer exposure)
		Neutrophils	**0.25** ≤0.29 0.018	**Years** Years Years [c]	**(Aydın et al., 2013)*** (Kuo et al., 1997) (Erdei et al., 2003) (asthmatic children)	**↓ 0.87**	**Years**	**(Lyapina et al., 2004)* (i.e., function, in workers with URT dysfunction)**	
			≥9.23 0.5–3	**8 wk** Short	**(Morgan et al., 2017) (mice) (mice)** (Zhang et al., 2013b) (mice)	↓ 13	Short	(Katsnelson et al., 2013) (rats)	
		Eosinophils	≤0.29 0.018	Years Years [c]	(Kuo et al., 1997) (Erdei et al., 2003) (asthmatic children)				
			≥9.23	**8 wk**	**(Morgan et al., 2017) (mice) (mice)**				
		Basophils	≤0.29	Years	(Kuo et al., 1997)				
			No animal studies identified						
	Lymphocytes	All	**0.2 & 0.8** N/A[e] (≤1) 0.51 ≤0.29 0.018	**Months** Yr vs. Mo Weeks Years Years [c]	**(Jia et al., 2014)*** (Thrasher et al., 1990) (Ying et al., 1999) (Kuo et al., 1997) (Erdei et al., 2003) (asthmatic children)	**↓ 1.6** **↑ 0.25**	**Years (same cohort) Years**	**(Hosgood et al., 2013)*; (Zhang et al., 2010)* [d] (Bassig et al., 2016)* (Aydın et al., 2013)***	Indeterminate (multiple changes noted, but pattern is indiscernible)
			18.5 **≥9.23**	Short **8 wk**	(Dean et al., 1984) (mice) [h] **(Morgan et al., 2017)* (mice)**	↑ 13 ↓ 0.5–3	Short Short	(Katsnelson et al., 2013) (rats) (Zhang et al., 2013b) (mice)	

Endpoint		No changes observed (above dashed line= human studies; below dashed line= animal studies; *high or medium* confidence = *and bold)			Significant[a] increases (↑) or decreases (↓) (above dashed line= human studies; below dashed line= animal studies; *high or medium* confidence = *and bold)			Conclusion (notes)
		mg/m³	Length[b]	References (details)	mg/m³	Length[b]	References (details)	
	B Cells	**1.6** **0.25** 0.09–0.7	**Years (same cohort)** **Years** Years	(Hosgood et al., 2013)*; (Zhang et al., 2010)* (Bassig et al., 2016)* (Aydın et al., 2013)* (Thrasher et al., 1987)	**↑ 0.99** **↑ 0.2 & 0.8** ↑ N/A[e] (≤1) ↑ 0.51 **↓ 0.47** **↓ 0.36**	**Months** **Months** Yr vs. Mo Weeks **Years** **Years**	(Ye et al., 2005)* **(peak levels up to 1.69 mg/m³)** (Jia et al., 2014)* (Thrasher et al., 1990) (Ying et al., 1999) (Costa et al., 2019)* **(peak levels to 3.94 mg/m³)** (Costa et al., 2013)* **(peak levels to 0.69 mg/m³)**	Moderate for altered number of B cells (direction of change may differ by exposure levels or duration)
		No animal studies identified						
	T Cells (Total)	**0.2–0.8** N/A[e] (≤1)	**Months** Yr vs. Mo	(Jia et al., 2014)* (Thrasher et al., 1990)	**↓ 1.6** **↓ 0.99** **↑ 0.36** **↑ 0.25** ↓ 0.9 ↓ 0.51 ↓ ≥0.09	**Years (same cohort)** **Months** **Years** **Years** Years Weeks Years	(Hosgood et al., 2013)*; (Zhang et al., 2010)* [d] (Bassig et al., 2016)* (Ye et al., 2005)* **(peak levels to 1.69 mg/m³)** (Costa et al., 2013)* **(peak levels to 0.69 mg/m³)** (Aydın et al., 2013)* (Jakab et al., 2010) (Ying et al., 1999) (Thrasher et al., 1987) (levels up to 0.68 mg/m³)	Slight for altered total T cells (mixed results suggest dose-dependence, with ↓ at higher levels; possible ↑ at low levels, with longer duration)
					↑ 7.4	Short	(Sandikci et al., 2007a, b) (rats)	

Endpoint	No changes observed (above dashed line= human studies; below dashed line= animal studies; *high or medium* confidence = *and bold)			Significant[a] increases (↑) or decreases (↓) (above dashed line= human studies; below dashed line= animal studies; *high or medium* confidence = *and bold)			Conclusion (notes)
	mg/m³	Length[b]	References (details)	mg/m³	Length[b]	References (details)	
T Cells ($CD4^+$)	**1.6** **0.99** **0.47** **0.25** **0.2–0.8**	**Years (same cohort)** **Months** **Years** **Years** **Months**	(Hosgood et al., 2013)* **(note: ↓ T_{reg} cells)** (Zhang et al., 2010)* (Bassig et al., 2016)* (Ye et al., 2005)* **(peak levels up to 1.69 mg/m³)** (Costa et al., 2019)* **(peak levels to 3.94 mg/m³)** (Aydın et al., 2013)* (Jia et al., 2014)*	**↑ 0.36** ↓ 0.51	**Years** Weeks	(Costa et al., 2013)* **(peak levels to 0.69 mg/m³)** (Ying et al., 1999)	Indeterminate (mostly N/C, but variable and, considering also studies of spleen (above), suggests effects might exist for certain subsets of CD4 cells)
	No animal studies identified						
T Cells ($CD8^+$)	**0.36** **0.25** **0.2–0.8**	**Years** **Years** **Months**	(Costa et al., 2013)* **(peak levels to 0.69 mg/m³)** (Aydın et al., 2013)* (Jia et al., 2014)*	**↓ 1.6** **↓ 0.99** ↓ 0.51 **↑ 0.47**	**Years (same cohort)** **Months** Weeks **Years**	(Hosgood et al., 2013)*; (Zhang et al., 2010)* [d] (Bassig et al., 2016)* **(particularly memory cells)** (Ye et al., 2005)* **(peak levels to 1.69 mg/m³)** (Ying et al., 1999) (Costa et al., 2019)* **(peak levels to 3.94 mg/m³)**	Moderate ↓ CD8 and ↑ CD4/CD8 ratio (likely dose-dependence, as consistent observations are at higher levels)
	N/C CD4/CD8 ratio in these 3 studies (or in (Thrasher et al., 1990) comparing durations)			**↑ CD4/CD8 ratio in all but one of these studies**			
	No animal studies identified						
NK Cells				**↓ 1.6** **↓ 0.36** **↑ 0.25** **↑ 0.2** **N/C at 0.8**	**Years (same cohort)** **Years** **Years** **Months**	(Hosgood et al., 2013)*; (Zhang et al., 2010)* [d]; (Bassig et al., 2016)* (Costa et al., 2013)* **(peak levels to 0.69 mg/m³)** (Aydın et al., 2013)* (Jia et al., 2014)*	Slight for altered number of NK cells (mixed results suggest dose-dependence like total T cells)
	No animal studies identified						

Endpoint			No changes observed (above dashed line= human studies; below dashed line= animal studies; *high or medium* confidence = *and bold) mg/m³	Length[b]	References (details)	Significant[a] increases (↑) or decreases (↓) (above dashed line= human studies; below dashed line= animal studies; *high or medium* confidence = *and bold) mg/m³	Length[b]	References (details)	Conclusion (notes)
	Mono cytes		**1.6** **0.25**	**Years (same cohort)** **Years**	**(Hosgood et al., 2013)*; (Zhang et al., 2010)*[d]** **(Bassig et al., 2016)*** **(Aydın et al., 2013)***	↑ 0.018	Years[c]	(Erdei et al., 2003) (asthmatic children)	Indeterminate (data suggest N/C, at least in human adults)
			≥9.23	**8 wk**	**(Morgan et al., 2017) (mice)**	↓ 18.5 ↓ 0.5, not 3	Short Short	(Dean et al., 1984) (mice) (Zhang et al., 2013b) (mice)	
Red Blood Cells			**0.25** ≤0.29 0.018	**Years** Years Years[c]	**(Aydın et al., 2013)*** (Kuo et al., 1997) (Erdei et al., 2003) (asthmatic children)	**↓ 1.6** **↓ 0.87**	**Years** **Years**	**(Hosgood et al., 2013)*; (Zhang et al., 2010)*[d]** **(Lyapina et al., 2004)* (association with duration)**	Moderate ↓in RBCs[i] (suggests dose- and duration-dependence)
			≥9.23	**8 wk**	**(Morgan et al., 2017) (mice)**	↓ 0.5–3	**Short**	(Zhang et al., 2013b) (mice)	
Platelets			**0.87** ≤0.29 0.018	**Years** Years Years[c]	**(Lyapina et al., 2004)*** (Kuo et al., 1997) (Erdei et al., 2003) (asthmatic children)	**↓ 1.6**	**Years (same cohort)**	**(Hosgood et al., 2013)*; (Zhang et al., 2010)*[d]** **(Bassig et al., 2016)***	Slight ↓ in platelets[j] (possible dose-dependence as noted above)
			≥9.23	**8 wk**	**(Morgan et al., 2017) (mice)**	↑ 0.5–3	Short	(Zhang et al., 2013b) (mice)	
Secreted factors and immune markers	**Primarily Th1-related**	**TNF-α**	**1.8** **0.2–0.8**	**Years** **Months**	**(Seow et al., 2015)* (peak levels to 6.9 mg/m³)** **(Jia et al., 2014)***	**↑ 0.25**	**Years**	**(Aydın et al., 2013)***	Slight ↑ TNF-α and C3
			No animal studies identified						
		Complement	**0.25**	**Years**	**(Aydın et al., 2013)* (i.e., C3, C4)**				
						↑ 6.15	**Short**	**(Sapmaz et al., 2015)* (rats; i.e., C3)**	
		IFN-γ				**↓ 0.8**	**Months**	**(Jia et al., 2014)***	Moderate ↓ IFN-γ
						↓ 6.2–12.3	Short	(Im et al., 2006) (rats)	
	Primaril	**IL-4**				**↑ 0.8**	**Months**	**(Jia et al., 2014)***	Moderate ↑ IL-4
						↑ 6.2–12.3	Short	(Im et al., 2006) (rats)	

Endpoint		No changes observed (above dashed line= human studies; below dashed line= animal studies; *high or medium* confidence = *and bold)			Significant[a] increases (↑) or decreases (↓) (above dashed line= human studies; below dashed line= animal studies; *high or medium* confidence = *and bold)			Conclusion (notes)
		mg/m³	Length[b]	References (details)	mg/m³	Length[b]	References (details)	
	IL-10				**↓ 1.8** **↑ 0.2–0.8**	**Years** **Months**	**(Seow et al., 2015)* [d] (i.e., using less strict 20% FDR)** **(Jia et al., 2014)***	Slight IL-10 (suggests dose-dependence like total T cells)
		No animal studies identified						
	IL-6	**No human studies identified**						Indeterminate IL-6
		0.12	Acute	(Matsuoka et al., 2010) (mice)				
Chemoattractants	CXCL11 and CCL17				**↓ 1.8**	**Years**	**(Seow et al., 2015)* (i.e., using stringent 10% FDR)**	Slight ↓ (chemo-attractants for neutrophils: IL-8, and lymphocytes: Cxcl11, Ccl17)
		No animal studies identified						
	IL-8				**↓ 0.2–0.8**	**Months**	**(Jia et al., 2014)***	
		No animal studies identified						
Other	Ta1 and IL-2R				↑ N/A[e] (≤1)	Yr vs. Mo	(Thrasher et al., 1990) (antigen reactivity markers)	Indeterminate (data suggest N/C in B cell activation markers)
		No animal studies identified						
	CD27 and CD30	**1.6**	**Years**	**(Bassig et al., 2016)* (B cell activation markers)**				
		No animal studies identified						

Abbreviations and definitions: Der f = *Dermatophagoides farina* (house dust mite) and OVA = ovalbumin (major protein of chicken egg whites): both immunogenic materials used to stimulate an allergy-like response; FDR = false discovery rate; N/C = no change; T_{reg} = T regulatory cells, a subset of helper T cells; short = short-term.

Notes: Formaldehyde concentrations typically reflect average or median levels in human studies (e.g., when effects were not observed); Gray shading = no data meeting the inclusion criteria were available (see Appendix A.5.6); one study observing increased substance P and related changes in the serum (Fujimaki et al., 2004b) is presented in the context of changes in the respiratory system (see Section 1.2.2).

[a]Primarily, this reflects reporting of a statistically significant change; in rare instances where a *p*-value was not given, changes are indicated if the authors discussed the change as a significant effect.

[b]Human study exposure durations are indicated as "years," "months," "weeks," "acute," or "Yr vs. Mo" (see footnote d) and defined based on the anticipated exposure duration for the majority of the exposed population(s); these durations are interpreted to approximate animal study exposure durations of chronic (>1 year), subchronic (several months), short term ("Short" in table; <30 days), and acute (1 day or less).

[c]Erdei et al. (2003) studied 9- to 11-year-old students symptomatic with respiratory issues, so duration of exposure was presumed to be years in schools (average exposure concentration is indicated).

[d]The differences in lymphocyte subset levels between exposed and unexposed workers reported by Zhang et al. (2010) were challenged by Mundt et al. (2017) in a reanalysis who did not find evidence of an exposure-response trend within the exposed group, although the difference between unexposed and exposed subjects was reconfirmed. The critique by Mundt was responded to in a letter to the editor by the study investigators who explained that the study was not designed to provide a range of exposures wide enough to evaluate exposure-response relationships given the expected effect size and sample size in the study (Rothman et al., 2017).

[e]The exposure level is, in general, considered not applicable (N/A), as the comparison presented by Thrasher et al. (1990) reflected differences in exposure duration (i.e., years of exposure [Yr], as compared to weeks or months [Mo] of exposure), but there appeared to be minimal differences in concentration from the controls.

[f]The studies by Rager et al. (2014; 2013) were molecular studies (e.g., miRNA) interpreted as *high* or *medium* confidence that provide some indirect evidence of inflammatory changes.

[g]This finding (decreased total WBCs) is supported by three studies in humans based on an evaluation by NRC (2014b): [(Tong et al., 2007; Cheng et al., 2004; Tang and Zhang, 2003)], but these studies were not evaluated in this analysis (i.e., they were not indexed in any of the searched databases); additionally, this finding is supported by a study in mice (Yu et al., 2014) and a study in rats (Brondeau et al., 1990), which are not included above as they only tested excessive formaldehyde levels (i.e., ≥20 mg/m^3).

[h]The authors indicated no changes in "WBC differentials" other than decreased monocytes, but further details NR (Dean et al., 1984). This test was assumed to include basic granulocyte and lymphocyte counts.

[i]This finding (decreased erythrocytes) is supported by one study in humans based on an evaluation by the NRC (2014b): [(Yang, 2007)], but this study was not evaluated in this analysis.

[j]This finding (decreased platelets) is supported by two studies in humans based on an evaluation by NRC (2014b): (Tong et al., 2007; Yang, 2007), but these studies were not evaluated in this analysis. The finding is also supported by a mouse study testing excessive formaldehyde levels (Yu et al., 2014).

Integrated Summary of Evidence on Immune-mediated Respiratory Conditions, Focusing on Allergies and Asthma

The general population studies in children and adults provide *moderate* evidence of an association between formaldehyde exposure and prevalence of rhinitis or rhinoconjunctivitis, with a relative risk of approximately 1.2 for formaldehyde exposures of around 0.04–0.06 mg/m^3. Although the effect size is small, these are relatively common conditions. The observation of an increase in the magnitude of the odds ratio with increasing severity of rhinitis provides coherence and greater certainty in the evidence (Yon et al., 2019). A stronger association (two-fold risk) was seen in the only study of eczema and a 3-fold odds of experiencing allergy-like symptoms involving the eyes, nose and skin within the past week was observed for students exposed to formaldehyde concentrations in classrooms >0.035 mg/m^3 (median 0.045 mg/m^3) compared to <0.035 mg/m^3 (OR 3.23, 95% CI 1.31, 8.00).

The available general population and occupational studies also provide a *moderate* level of evidence of an association between formaldehyde exposure and prevalence of current asthma, as determined by symptoms or medication use in the past 12 months for asthma in studies with exposures above 0.05 mg/m^3 Notably, a study using an intervention to increase ventilation in participants' residences observed a decrease of 14–20% in asthma symptoms and medical care needed during the following year among asthmatic children associated with a 50% reduction in formaldehyde concentration (Lajoie et al., 2014). However, confounding by coexposures cannot be excluded. Geometric mean formaldehyde concentrations at baseline were 0.035 mg/m^3 and 0.057 mg/m^3 in fall/winter and summer, respectively. The two studies examining asthma control or severity among children with asthma suggest associations may be seen at lower exposures (e.g., 0.04 mg/m^3) in this potentially susceptible population. Relatively strong associations were seen in studies examining prevalence of current asthma in relation to higher levels of formaldehyde exposure in occupational settings (exposures above 0.10 mg/m^3).

Sensitivity may also be increased by other attributes as well disease severity. Although associations with either eczema, prevalence of asthma, or asthma control were either increased or decreased by a positive atopy status in studies of adults or children, studies in allergen-sensitized animals suggest that atopy may increase sensitivity to formaldehyde-related asthma endpoints. In addition, associations with IgE levels or prevalence of asthma symptoms were stronger among groups exposed to environmental tobacco smoke, although inconsistencies by lifestage were reported. Relatively strong associations were seen in studies examining prevalence of current asthma in relation to higher levels of formaldehyde exposure in occupational settings (exposures above 0.10 mg/m^3). Mechanistic studies in animals indicate that formaldehyde exposure can induce bronchoconstriction with and without allergen sensitization. This heightened bronchoconstriction response may be due to a combination of increased tachykinins, increased T_H2 cytokines and antibodies, and eosinophil recruitment and activation in the lung. Mechanistic studies of respiratory tissues and the blood provide consistent evidence that formaldehyde exposure can stimulate a number of immunological and neurological processes that may drive asthmatic responses; however, a molecular understanding of how formaldehyde exposure favors asthmatic T_H2 responses has not been experimentally established. Separately, the possibility that formaldehyde exposure might increase the risk or severity of respiratory infections, particularly in young children, has not been well studied.

Overall, based primarily on a *moderate* level of human evidence supporting an association from the available epidemiology studies, with corresponding *slight* evidence for an effect in animals based on mechanistic studies in animals supporting biological plausibility, the **evidence indicates** that inhalation of formaldehyde likely causes an increased risk of prevalent allergic conditions and prevalent asthma symptoms, as well as decreased control of asthma symptoms, given appropriate exposure circumstances (see Table 1-24). The primary basis for this conclusion involves studies of occupational settings (>0.1 mg/m^3) and population studies where formaldehyde concentrations measured in schools and homes averaged between 0.03 and <0.1 mg/m^3.

Table 1-24. Evidence integration summary for effects on immune-mediated conditions, including allergies and asthma

Evidence	Evidence judgment	Hazard determination
Allergic Conditions		
Human	*Moderate for* Allergic Conditions, based on: *Human health effect studies*: Small elevated risks in five out of six *high* and *medium* confidence studies of prevalence of rhinitis, conjunctivitis, and eczema among adults and children in residential and school settings with exposures in the range of 0.04–0.06 mg/m^3 formaldehyde. Very low formaldehyde concentrations were measured in the one insensitive null study. *Biological Plausibility (both conditions)*: Studies in humans do not provide robust or moderate evidence for mechanistic events that clearly support the	The **evidence indicates** that inhalation of formaldehyde likely increases the prevalence of allergic conditions in humans, given the appropriate exposure circumstances[a] This judgments is primarily based on studies of occupational

	development of asthma, although effects in the blood, such as cytokine, cell, and antibody changes, might contribute	settings (>0.1 mg/m^3) and population studies where mean formaldehyde concentrations measured in schools and homes were between 0.03 and 0.1 mg/m^3 *Potential Susceptibilities*: Variation in sensitivity is anticipated depending on respiratory health, physiologic changes during pregnancy, age, and exposure to tobacco smoke
Animal	*Slight for* Immune-Mediated Respiratory Effects based on: *Biological Plausibility*: Robust evidence for mechanistic events exists in relation to formaldehyde-induced augmentation of responses to allergens and airway bronchoconstrictor effects in animal models. Although several events typically associated with asthma were not corroborated (i.e., slight or inadequate evidence exists for these events), moderate evidence for mechanistic events exists for stimulation by formaldehyde of important immunological and neurological processes. These include airway eosinophil increases and other inflammatory changes in the airways and systemic circulation that can be reasonably associated with effects on airway hyperreactivity or other responses relevant to the development of allergic conditions and, potentially, asthma. *Animal health effect studies:* Experimental animal models are generally considered to be unable to reproduce the overt manifestations of allergic conditions and are not interpreted to provide direct support.	
Other inferences	• *Relevance to humans*: The most relevant mechanistic findings in animals involve neurological and immunological constituents present in both human and rodent airways. • *MOA*: Several incomplete MOAs involving airway inflammatory changes are considered likely to be involved.	
Prevalence of Current Asthma		
Humans	*Moderate for* Asthma, based on: *Human health effect studies*: • Elevated risks in eight *medium* confidence studies of prevalence of current asthma in adults and children, change after an intervention to reduce exposure, or reduced symptom control in children in residential settings including homes with >0.05 mg/m^3 formaldehyde; greater susceptibility among children • Inconsistencies in study results appear to be explained by exposure levels. No elevated risk of current asthma in six *high* and *medium* confidence studies with relatively low exposures (<0.05 mg/m^3), but associations with adequacy of asthma control were observed in one study at this lower exposure level • Strongly elevated risks in three *medium* confidence studies in occupational settings with exposures from 0.100 to >0.500 mg/m^3 *Biological Plausibility (both conditions)*: Studies in humans do not provide robust or moderate evidence for mechanistic events that clearly support the development of asthma, although effects in the blood, such as cytokine, cell, and antibody changes, might contribute	The **evidence indicates** that inhalation of formaldehyde likely increases the prevalence of asthma symptoms in humans, as well as decreased control of asthma symptoms, given appropriate exposure circumstances[a] This judgment is primarily based on studies of occupational settings (>0.1 mg/m^3) and population studies where mean formaldehyde concentrations measured in schools and homes were between 0.03 and 0.1 mg/m^3 *Potential Susceptibilities*: Variation in sensitivity is anticipated depending on respiratory health, physiologic changes during pregnancy, age, and exposure to tobacco smoke
Animals	*Slight for* Immune-Mediated Respiratory Effects based on: *Biological Plausibility*: In the same way the available mechanistic data are interpreted to provide *slight* animal evidence supporting the development of allergic conditions in humans, this evidence provides *slight* evidence supportive of asthma. *Animal health effect studies:* Experimental animal models are generally considered to be unable to reproduce the overt manifestations of asthma and are not interpreted to provide direct support.	

Other Inferences	• *Relevance to humans*: For the animal mechanistic data, while several events (e.g., amplified bronchoconstriction; eosinophil increases) have an unclear direct linkage to complex human diseases like asthma, these findings inform the potential for exposure to result in changes to relevant neurological and immunological constituents present in both human and rodent airways. • *MOA*: Several incomplete MOAs involving airway inflammatory changes are considered likely to be involved.	

[a]The "appropriate exposure circumstances" are more fully evaluated and defined through dose-response analysis in Section 2

1.2.4. Respiratory Tract Pathology

This section describes research on formaldehyde inhalation and pathology endpoints in the respiratory system. Numerous well-conducted experimental animal studies consistently demonstrate concentration- and, to a lesser extent, duration-dependent URT hyperplasia and metaplasia after formaldehyde exposure. Supporting these observations, a set of four studies in formaldehyde-exposed workers provides consistent findings of an elevated prevalence of nasal lesions such as hyperplasia and metaplasia. The workers were generally exposed to lower levels of formaldehyde than those eliciting changes in experimental animals. While the evidence for both of these nonneoplastic lesions indicates that formaldehyde exposure changes the morphology and function of the URT tissue, the evidence for metaplasia, in particular, is considered to be the best representation of a potential health hazard.

In the URT, both hyperplasia and metaplasia are adaptive tissue responses. These cellular responses help reduce the impact of stressors by changing the structure or function of the locally affected tissue (Harkema et al., 2013). Hyperplasia, generally a response to cell injury, involves an increase in the population of resident cells that results in additional cell layers noticeable by histology, whereas metaplasia, which typically occurs following prolonged or repeated insults, results in the replacement of one differentiated cell type with another more resilient cell type (Harkema et al., 2013). While hyperplasia and metaplasia may also be relevant, but not necessary, to the development of cancer (see Section 1.2.5), they are, by themselves, nonneoplastic lesions. Importantly, metaplasia results in a hardened, drier, and nonciliated skin-like layer (Tomashefski, 2008). Along with the acquisition of a protective, barrier-type phenotype, this metaplastic change causes a loss of normal tissue function, including reduced mucous secretion and ciliary clearance. Thus, this loss of normal function is judged to be an adverse outcome in and of itself (i.e., independent from its potential role in progression to cancer). As an interpretation regarding adversity is less clear for hyperplasia, this discussion emphasizes the data on squamous metaplasia.

Both hyperplasia and metaplasia are typically associated with cellular proliferation (Harkema et al., 2013). As compared to transient increases in cell number, sustained cell proliferation is required for the formation of hyperplasia. This type of change can be precipitated by damage to the nasal epithelium, which is evaluated histologically by measures of, for example, cell loss or necrosis, epithelial degeneration, and erosions. Relatedly, squamous metaplasia is an

adaptive response to continued toxic insult that involves cellular substitution. Thus, it is useful to consider these cellular damage-related endpoints in the context of hyperplasia and metaplasia. While evaluations of necrosis- and cytotoxicity-related pathology are informative to this section, these endpoints were generally inconsistently measured or poorly reported across the available studies and are therefore are only summarily discussed. Although hyperplasia and metaplasia might have been underevaluated or underreported for similar reasons (e.g., most studies focus on carcinogenic lesions), the potential development of these lesions appears to have been considered and documented in nearly all the long-term formaldehyde inhalation studies examining URT histopathology.

Studies that evaluated related outcomes, such as mucociliary flow rates, cellular proliferation counts based on DNA labeling, and mucosal swelling, are summarized in Appendix A.5.6). These types of effects were generally evaluated after acute or short-term exposure and typically represent immediate response repair mechanisms rather than tissue remodeling (e.g., hyperplasia, metaplasia), the latter of which is often a consequence of longer-term exposure or sustained injury. Accordingly, those related outcomes are interpreted to be most relevant to the mechanistic progression of the more overt URT lesions considered in this section, and they are discussed as such in the MOA analysis. Overall, mechanistic insights from the human and animal data indicate a clear role for altered mucociliary function or cellular proliferation in the occurrence of the more overt lesions. Consistent with some of the animal health effect studies, these mechanistic data also suggest that concentration is likely to be more of a driver of these effects than duration (noting that duration still contributes).

Given the large number of long-term exposure studies with information on URT pathology and the focus of the assessment on the effects of lifetime formaldehyde exposure, this section generally focuses on animal studies of subchronic or chronic exposure, and on human studies of occupational exposure where exposed employees were generally employed for longer than 5 years. Exceptions include discussion of shorter-term studies that might inform the potential for relationships between lesion types and studies specifically considering differences in the exposure paradigm (e.g., intermittent versus constant exposures) for lesion induction. Dysplastic lesions and other evidence of carcinogenicity, which are examined in many of the same studies addressed in this section, are discussed in Section 1.2.5.

Overall, the strength of the evidence for hyperplasia and squamous metaplasia includes *robust* evidence from animal studies and *moderate* human evidence from observational epidemiology studies, and strong support for a plausible MOA based largely on mechanistic evidence in animals (supported by more limited, coherent findings in human mechanistic studies). Therefore, the **evidence demonstrates** that inhalation of formaldehyde causes respiratory tract pathology in humans given the appropriate exposure circumstances. The primary support for this conclusion is based on rat bioassays of chronic exposure, which consistently observed squamous metaplasia at formaldehyde exposure levels ≥2.5 mg/m^3.

Literature Search and Screening Strategy

Systematic literature searches were conducted separately to identify health effect studies in humans and in experimental animals. The identification of relevant studies on respiratory tract pathology in humans and laboratory animals included literature searches in PubMed, Web of Science, and ToxNet through September 2016 (see Appendix A.5.5 for search details), and a systematic evidence map updating the literature through 2021 (see Appendix F). Primary research studies using measurements of formaldehyde in workplace air and histopathological endpoints in nasal tissue in humans were identified and included. Studies reporting primary research on formaldehyde exposure and measures of respiratory pathology in several animal species were identified and included. As stated above, subchronic and chronic exposure durations in either animals or humans were preferred. The mechanistic evidence informing this health effect was identified and evaluated as part of the overarching review of mechanistic data relevant to potential respiratory health effects (see Appendix A.5.6 for details). The bibliographic databases, search terms, and specific strategies used to search them are provided in Appendix A.5.5 and A.5.6, as are the specific PECO criteria. Literature flow diagrams summarize the results of the sorting process using these criteria and indicate the number of studies that were selected for consideration through 2016 (see Appendix F for the identification of newer studies through 2021). The relevant health effect studies in animals and humans, and the mechanistic data informative to respiratory tract pathology, were evaluated to interpret the quality and relevance of the study results in regard to hazard identification (see Appendix A.5.5 and A.5.6).

Methodological Issues Considered in Evaluating Studies

Cross-sectional studies among occupational cohorts were likely influenced by the selection of the workforce in favor of individuals less responsive to the irritant properties of formaldehyde, with resulting bias toward null results. Despite this methodological limitation and subsequent reduction in sensitivity, most of the studies observed increases in histopathological outcomes among exposed workers, and therefore, confidence in these studies was increased. Nasal biopsies were taken in four occupational studies; tissues were subsequently stained and cell structure examined according to variations of the Torjussen et al. (1979) method. The original Torjussen method scored morphological characteristics of the nasal epithelium using a whole number between 0 and 8, with 0 indicating normal epithelium and 8 indicating carcinoma and the midpoint of four signifying stratified squamous epithelium with a horny layer. Despite the variations of this scale, in each study the lowest numbers (0 or 1) always indicated normal cell structure while increasingly higher numbers indicated more disruptive cellular changes. Although the focus of this section is nonneoplastic histopathologic lesions, the studies compared the means of the total score between exposed and referent groups. Therefore, the prevalence of dysplasia is presented in the evidence tables when it was reported. Information regarding workplace temperature and

humidity, or home environment, all of which may affect nasal pathology, was rarely reported (Arundel et al., 1986).

Most studies of respiratory pathology in experimental animals used paraformaldehyde or freshly prepared formalin as the test article, but some studies tested commercial formalin, an aqueous solution containing both formaldehyde and methanol. The toxicokinetics of these two chemicals are vastly different, and their toxicities are likely to vary as well. Highly reactive formaldehyde is mostly captured in the nose, the main site of formaldehyde-induced lesions, and very little enters the blood stream. Conversely, methanol mostly bypasses the nose but is readily absorbed in the lungs and then distributed to distal sites, including the blood and other nonrespiratory tissues, where it can be metabolized to formaldehyde. Inhalation studies of methanol suggest that URT effects occur at concentrations many times higher than estimates of methanol concentrations in air, at least those generated from spraying formalin solutions onto heated glass[14] (e.g., >650 mg/m^3 in methanol studies by Poon et al. (1995) and Andrews et al. (1987) versus 5.5 mg/m^3 methanol reported by Kamata et al. (1997) in a formalin study testing formaldehyde levels of 0 and 18.27 mg/m^3). Thus, in general, the levels of methanol in formalin studies are considered unlikely to cause substantial increases in URT lesion severity. While coexposure to methanol in formalin studies may be a significant confounding factor for systemic effects, it is not expected to have a substantial influence on formaldehyde-induced respiratory effects. However, it does introduce the possibility that effective respiratory tract tissue concentrations of formaldehyde might be slightly higher after inhalation of formalin (due to some methanol conversion to formaldehyde within the tissue) than after exposure to the same concentrations of formaldehyde from sources without methanol, which would result in an overestimate of the effect of formaldehyde exposure. A discussion of the different test articles (e.g., paraformaldehyde, formalin) used for formaldehyde inhalation studies can be found in Appendix A.5.1.

For assessing histopathological changes for the different regions of rodent nasal passages, standard cross-section levels (e.g., Levels I–V) have generally been adopted for consistent analysis across studies (Mery et al., 1994; Young, 1981). Although the number and naming of cross-section levels varied from study to study, the levels always progressed through the nasal cavity from the area posterior to the nostrils (e.g., Level I or A) to areas anterior to the nasopharynx. Two different examples of the cross-sectioning procedures in rats are illustrated in Figure 1-14, with other studies of rats and other rodents employing similar procedures; however, illustrations of the specific cross-section levels used in each individual study are not included in the evidence tables.

[14]Even though methanol levels in the air using the generation methods in the other available formalin studies may be quite different, and possibly significantly higher, than the levels estimated by Kamata et al. (1997) (see Preface for discussion), given the relative insensitivity of the URT to methanol, these crude comparisons were considered sufficient for interpretations drawn in the context of these URT effects.

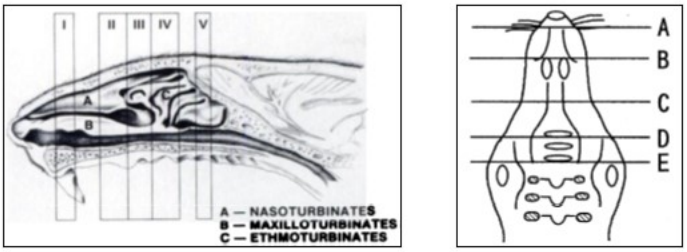


Figure 1-14. Example cross-section levels in rat nasal passages used for histopathological evaluations from Kerns et al. (1983) (left; Levels I-V) and Kamata et al. (1997) (right; Levels A-E).

It is preferred that studies assessed multiple tissue sections across multiple cross-section levels to allow for reasonable sampling of the nasal mucosa. Where applicable, histopathological findings in the nasal mucosa are discussed with reference to these sections, and the specific structures examined are stipulated in the evidence tables (e.g., nasoturbinates, maxilloturbinates, or ethmoid turbinates). When data were available, the type of epithelium affected (e.g., respiratory epithelium) was also noted. Only a few studies evaluated sections of the URT distal to the nasal cavity, and these evaluations were generally less rigorous (e.g., examining only a single tissue section) than evaluations of the nasal mucosa and tested much higher formaldehyde concentrations. Pathological findings in the LRT were generally not identified in higher confidence studies and are not discussed.

Based on the considerations described above, as well as other potential methodological issues, the experimental animal studies were evaluated with regard to the utility of their study results for characterizing hazard (see Appendix A.5.5 for details). Because of the abundance of studies of respiratory pathology, this section focuses on longer duration (i.e., chronic and subchronic) studies interpreted with *high* or *medium* confidence. Unlike some other sections, this includes well-performed formalin studies (see above.)

Some studies reported multiple endpoints (e.g., pathological effects and cell proliferation), which were individually considered. Overall, 22 controlled exposure studies were identified as *high* or *medium* confidence for characterizing respiratory pathology. Studies that reported URT pathology-related mechanistic information relevant to interpreting the progression of events leading to overt respiratory tract pathology, including cell proliferation and mucociliary function, are also discussed (see Appendix A.5.6).

Respiratory Tract Pathology Studies in Humans

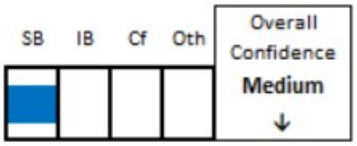
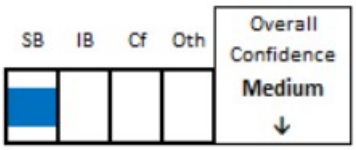
A small number of studies were available that reported the results of histological examinations of nasal tissues from formaldehyde-exposed occupational groups. These are described in Table 1-25, organized by publication year. Although the evidence was more equivocal in one study (Boysen et al., 1990), the four *medium* confidence studies examining histopathology found that exposed participants had a higher average histopathological score than their respective

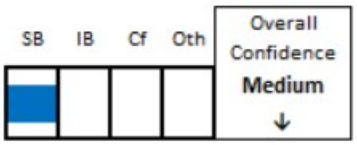
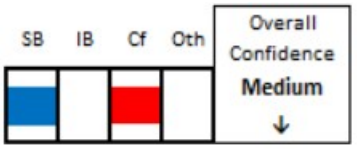
comparison group (Ballarin et al., 1992; Holmstrom et al., 1989c; Edling et al., 1988). Average formaldehyde levels ranged from 0.05 to 0.6 mg/m^3. These were cross-sectional studies of current workers who likely were less sensitive "survivors" of the long-term respiratory irritant effects of formaldehyde, which would cause survival bias and an attenuation of comparisons between exposed and comparison groups. Although the studies were limited by probable survival bias, and in some cases, other limitations resulting in a bias toward the null, a consistent association with histopathological endpoints was observed. Edling et al. (1988) did not adjust analyses for differences in smoking prevalence between the exposed and referent groups; smoking prevalence was higher among participants in the referent group. Therefore, the expected effect on the association with formaldehyde exposure would again be toward the null. However, the association observed by Edling et al. (1988) was consistent with those reported by the other studies that did address potential confounding by smoking status. There was no evidence of a time-dependent relationship with formaldehyde. Additionally, there was no indication that coexposure with wood dust or smoking modified the pathological effects of formaldehyde.

The preponderance of evidence shows that the increases in histopathological score levels were due to a high level of squamous metaplasia among participants exposed to formaldehyde levels ranging from 0.1 to 2.5 mg/m^3. Squamous metaplasia was seen in 32–67% of exposed participants (Ballarin et al., 1992; Boysen et al., 1990; Edling et al., 1988).

Table 1-25. Formaldehyde effects on respiratory pathology in occupational settings

Study and design and exposure	Results
Histological analyses	
Ballarin et al. (1992) Italy Prevalence study **Population:** 15 plywood factory workers (mean age 31 yrs, employment duration 6.8 yrs) compared to 15 university or hospital clerks matched for age and sex. All nonsmokers. **Exposure:** Personal sampling; 8-hr TWA Kominsky and Stroman (1977) Warehouse (N = 3), 0.39 ± 0.20 mg/m^3, range 0.21–0.6 mg/m^3 Shearing-press (N = 8), 0.1 ± 0.02 mg/m^3, range 0.08–0.14 mg/m^3 Sawmill (N = 1), 0.09 mg/m^3 Inspirable wood dust: 0.11–0.69 mg/m^3, 0.73 in sawmill **Methods:** Cytopathology analysis of nasal respiratory mucosa cells blinded by two readers, scoring and classification analogous to Torjussen et al. (1979) and Edling et al. (1988); most severe score present assigned. Mean histological scores exposed compared to referent using Mann-Whitney U test; difference by exposure group for classification of pathology, χ^2 test. **Evaluation:**[a]	**Distribution of histological scores of nasal respiratory mucosa cells** Description / Exposed / Referent Normal: 0 / 4 (26%) Loss of ciliated cells: 15 (100%) / 10 (67%) Hyperplasia: 6 (40%) / 5 (33%) Squamous metaplasia: 10 (67%)* / 1 (6%) Mild dysplasia: 1 (6%) / 0 **Score (Mean (SD))**: 2.3 (0.5)* / 1.6 (0.5) *Mann-Whitney U test (p < 0.01) or χ^2 test (p < 0.01)

Study and design and exposure	Results
 Inclusion only of current workers raises possibility of healthy worker survival effect due to irritation effects.	
Boysen et al. (1990) *Prevalence survey* *Oslo, Norway* **Population:** 37/74 exposed volunteers from a chemical company producing formaldehyde (50% of exposed workforce). Mean age 51, range 27–66 years. Mean years employed 20, range 3–36 years. 37 age-matched referent subjects without overt nasal disease or occupations associated with nasal cancer. Office staff at two Oslo chemical companies, hospital laboratory personnel, and outpatients at the ear, nose, and throat department of hospital. Mean age 49, range 35–66 years. **Exposure:** Systematic formaldehyde monitoring after 1980. Before 1980, exposure assessed by plant health officer with knowledge of the production process, recent measurements, and worker sensations. Range of formaldehyde 0.5 ppm to >2 ppm. **Methods:** Scoring and classification of histologic samples per Tojussen, 1979 protocol but on a 0–5-point scale by two authors blinded to clinical or occupational status. Wilcoxon rank sum test used to compare histological findings in the two groups. χ^2 test used to compare the rhinoscopical findings and subjective complaints. **Evaluation:**[a]  Inclusion only of current workers and long duration of employment raises possibility of healthy worker survival effect due to irritation effects.	Rhinoscopy: 75% of exposed workers and 89% of controls had normal mucosa. 24% of the exposed and 8% of the unexposed had hyperplastic nasal mucosa (difference not statistically significant). Degree of metaplastic alterations more pronounced among the exposed workers than in controls (difference not statistically significant). Higher prevalence of subjective nasal complaints in formaldehyde-exposed workers (43%) compared to 5% in unexposed controls ($p < 0.01$). **Distribution of histological scores** 0 Columnar epithelium: Exposed 3, Referent 5 1 Stratified cuboidal epithelium: Exposed 16, Referent 17 2 Mixed stratified cuboidal/stratified squamous epithelium: Exposed 5, Referent 10 3 Stratified squamous epithelium, nonkeratinizing: Exposed 9, Referent 5 4 Stratified squamous epithelium, keratinizing: Exposed 1, Referent 0 5 Dysplasia: Exposed 3, Referent 0 Exposed 1.9/5, Referent 1.4/5
Holmstrom et al. (1989a); Holmström and Wilhelmsson (1988) *Sweden* *Prevalence study* **Population:** Two exposed groups 170 total; 70 formaldehyde production workers, Mean age 36.9 years, 87% male, mean duration employment 10.4 yr. 100 workers exposed to wood dust and formaldehyde at five furniture factories. Mean age 40.5 years, 93% male, mean duration employment 16.6 yr. Referent: 36 persons from local government in the same village as the furniture workers, with no history of occupational exposure to formaldehyde or wood dust. Mean age 39.8 years, 56% male, mean duration employment 11.4 yr. "Slightly" larger number of smokers in the exposed group than control group, but difference not statistically significant (data not provided). **Exposure:** Personal sampling in breathing zone for 1–2 hours in 1985. Total dust and respirable dust also measured.	Formaldehyde-only nasal specimens had higher mean score of 2.16 (range 0–4) ($p < 0.05$, comparison to referent) while formaldehyde-dust group had mean score of 2.07 (range 0–6) ($p > 0.05$, comparison to referent). Referent group score was 1.56 (range 0–4). Combining formaldehyde-only and formaldehyde-dust group mean score of 2.11 ($p < 0.05$). No correlation observed between smoking habits and biopsy score, nor was a correlation found between the duration of exposure and any histological changes.

<table>
<tr><th>Study and design and exposure</th><th>Results</th></tr>
<tr><td>Previous measurements 1979–1984 in chemical company combined with 1985 values to estimate average annual values for each participant. Only 1985 values available for wood factories. Formaldehyde concentration: Chemical Plant: 0.05–0.5 mg/m^3, mean 0.26 [SD 0.17 mg/m^3]. Furniture Factory: 0.2–0.3 mg/m^3, mean 0.25 [SD 0.05 mg/m^3]. Referent mean 0.09 mg/m^3 (based on four measurements in four seasons).
Methods: Pretesting questionnaire, histological changes in nasal mucosa graded by a pathologist blind to exposure according to Torjussen et al. (1979) grading scale of 0–8. 2 tailed *t*-test for group comparisons.
Evaluation:[a]
 
Inclusion of only current workers and long duration of employment raises possibility of healthy worker survival effect due to irritation effects.</td><td></td></tr>
<tr><td>Edling et al. (1988, 1987a)
Prevalence Study
Sweden
Population: 75 of 104 exposed male factory workers from three plants (2 particle board plants and one laminae-processing). Mean duration of employment: 10.5 years. Mean age: 38 years; range 22–63 years. 35% smokers and 9% ex-smokers. Referents: 25 men with similar age and smoking habits and no known industrial exposures to formaldehyde. Mean age: 35 years, range 25–60. 48% smokers and 10% ex-smokers.
Exposure: Past TWA formaldehyde measurements made by plant industrial hygienists sporadically between 1975 and 1983. Levels of formaldehyde in air ranged from 0.1 to 1.1 mg/m^3, with peaks up to 5 mg/m^3. No measurements available before 1975 but estimated levels higher during the 1960s and early 1970s. Particle board plants contained low concentrations of wood dust at 0.6–1.1 mg/m^3.
Methods: Nasal mucosa histological grading by pathologist blinded to exposure using Torjussen et al. (1979) grading system with 0–8 ranking.
Compared differences in nasal mucosa histological score using Wilcoxon nonparametric test.
Evaluation:[a]
 
Inclusion of only current workers and long duration of employment (mean 10.5 years) and high prevalence of symptoms raises possibility of healthy worker survival.</td><td>Prevalence in exposed of normal nasal mucosa, 75%; prevalence swollen or dry or both changes, 25%. Histological scores higher in exposed compared to referents, mean 2.9 vs. 1.8; ($p < 0.05$) (Wilcoxon). No association with years of exposure.

Histological scores in exposed[a]
<table><tr><th>Characteristics</th><th>Score</th><th>#</th><th>%</th></tr><tr><td>Normal respiratory epithelium</td><td>0</td><td>3</td><td>4</td></tr><tr><td>Loss of ciliated cells</td><td>1</td><td>8</td><td>11</td></tr><tr><td>Mixed cuboid/squamous epithelium, metaplasia</td><td>2</td><td>24</td><td>32</td></tr><tr><td>Stratified squamous epithelium</td><td>3</td><td>18</td><td>24</td></tr><tr><td>Keratosis</td><td>4</td><td>16</td><td>21</td></tr><tr><td>Budding of epithelium</td><td>5</td><td>0</td><td>0</td></tr><tr><td>Mild or moderate dysplasia</td><td>6</td><td>6</td><td>8</td></tr><tr><td>Severe dysplasia</td><td>7</td><td>0</td><td>0</td></tr><tr><td>Carcinoma</td><td>8</td><td>0</td><td>0</td></tr></table>[a]Data for referent group were not reported</td></tr>
</table>

[a]Evaluation of sources of bias or study limitations (see details in Appendix A.5.1 and A.5.5. SB = selection bias; IB = information bias; Cf = confounding; Oth = other feature of design or analysis. Extent of column shading reflects degree of limitation. Direction of anticipated bias indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be

toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact would be likely to be away from the null (i.e., spurious or inflated effect estimate).

Respiratory Tract Pathology Studies in Animals

A large database of well-designed studies has characterized formaldehyde-induced respiratory tract pathology in mice, hamsters, and monkeys, but primarily in rats. The durations of these studies range from a few hours to longer than 2 years, and several studies included recovery periods that explored the reversibility of lesions. While a few studies include the examination of tissues in other areas of the respiratory tract, most studies focus on pathology in the nasal mucosa. This synthesis focuses on the incidence of hyperplasia and metaplasia formed after inhaled formaldehyde exposure. To the extent the available data allow, the discussion separately addresses the lesion locations along the URT and specifically within the nasal mucosa, the influence of concentration and exposure duration on lesion formation and lesion persistence, and sex and species differences in pathology. Because of the abundance of studies that evaluated respiratory tract pathology, only those studies judged to be of *high* and *medium* confidence (see Appendix A.5.5) are presented in detail in the synthesis and evidence tables below. Likewise, as animal studies of effects from long-term exposure are most pertinent to lifetime human exposure, and because some of these lesions can be very slow to develop, long-term studies (preferably ≥52 weeks of exposure and follow-up) were generally considered to be more informative. Accordingly, evidence tables of the experimental animal studies are organized by study duration, with chronic and subchronic respiratory pathology studies ordered according to species and study confidence in Tables 1-26 and 1-27, respectively. Short-term studies, generally ≤1−4 weeks long, are sometimes discussed in the synthesis, but are only described in detail if they provide insights unavailable in the longer-term studies, specifically including information on potential species differences or the relationship between the concentration and duration dependency of lesion formation (see Appendix A.5.5 for evidence tables of the other short-term studies).

Nasal lesions (i.e., cytotoxicity, hyperplasia, and metaplasia) have been consistently reported in multiple rodent species and strains, and in monkeys. For hyperplasia and metaplasia, there were consistent indications of a concentration-response, and to a somewhat lesser extent, exposure duration-dependent relationships with inhaled formaldehyde. Somewhat surprisingly, multiple studies report that metaplasia appeared to be more sensitive, prevalent or extensive than hyperplasia (sometimes pronounced metaplasia was observed in the absence of hyperplasia), reducing support for a strictly sequential progression of these lesions. The most informative data on squamous metaplasia (i.e., from long-term *medium* or *high* confidence studies), which is considered to be an adverse effect independent of its potential role in cancer progression, are illustrated in Figures 1-15 and 1-16.

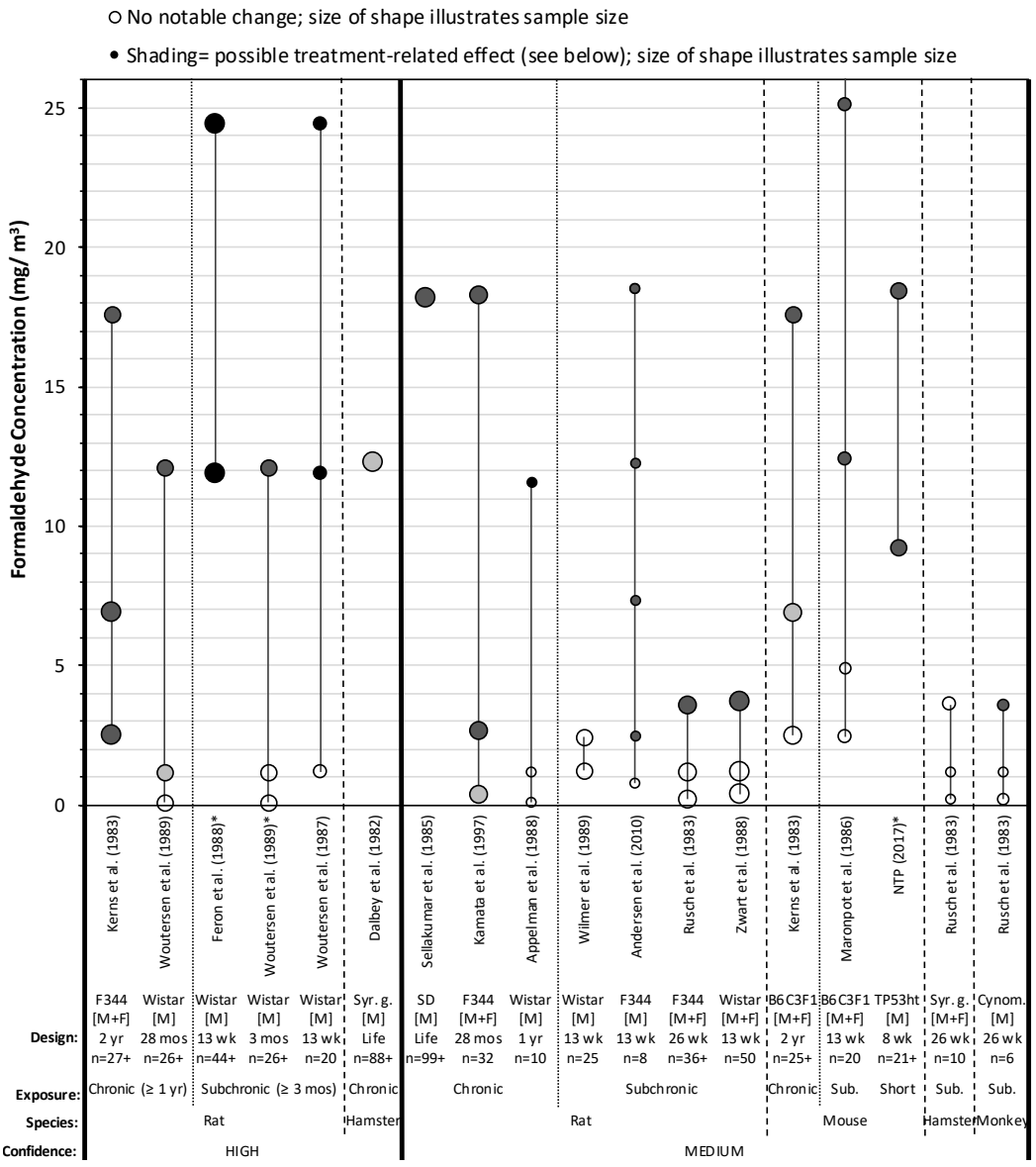


Figure 1-15. Squamous metaplasia in *medium* and *high* confidence chronic and subchronic respiratory pathology studies of inhaled formaldehyde.

Studies are organized by study evaluation confidence (see Appendix A.5.5), species, and then duration of exposure. Shading is indicated as follows: black = statistically significant effects, as indicated by study authors; gray = increases in incidence in studies without statistical analyses, with dark gray indicating pronounced changes (incidences of 50–100% were noted for many of these groups) and light gray indicating subtle changes (generally <25% change compared to controls); see Tables 1-26 through 1-28. Exposure groups with larger sample sizes are depicted as larger circles. Abbreviations: Syr. g. = Syrian golden; ht = heterozygotes; Sub. = subchronic; M + F = male and female; wk = week, mos = months, yr = year.

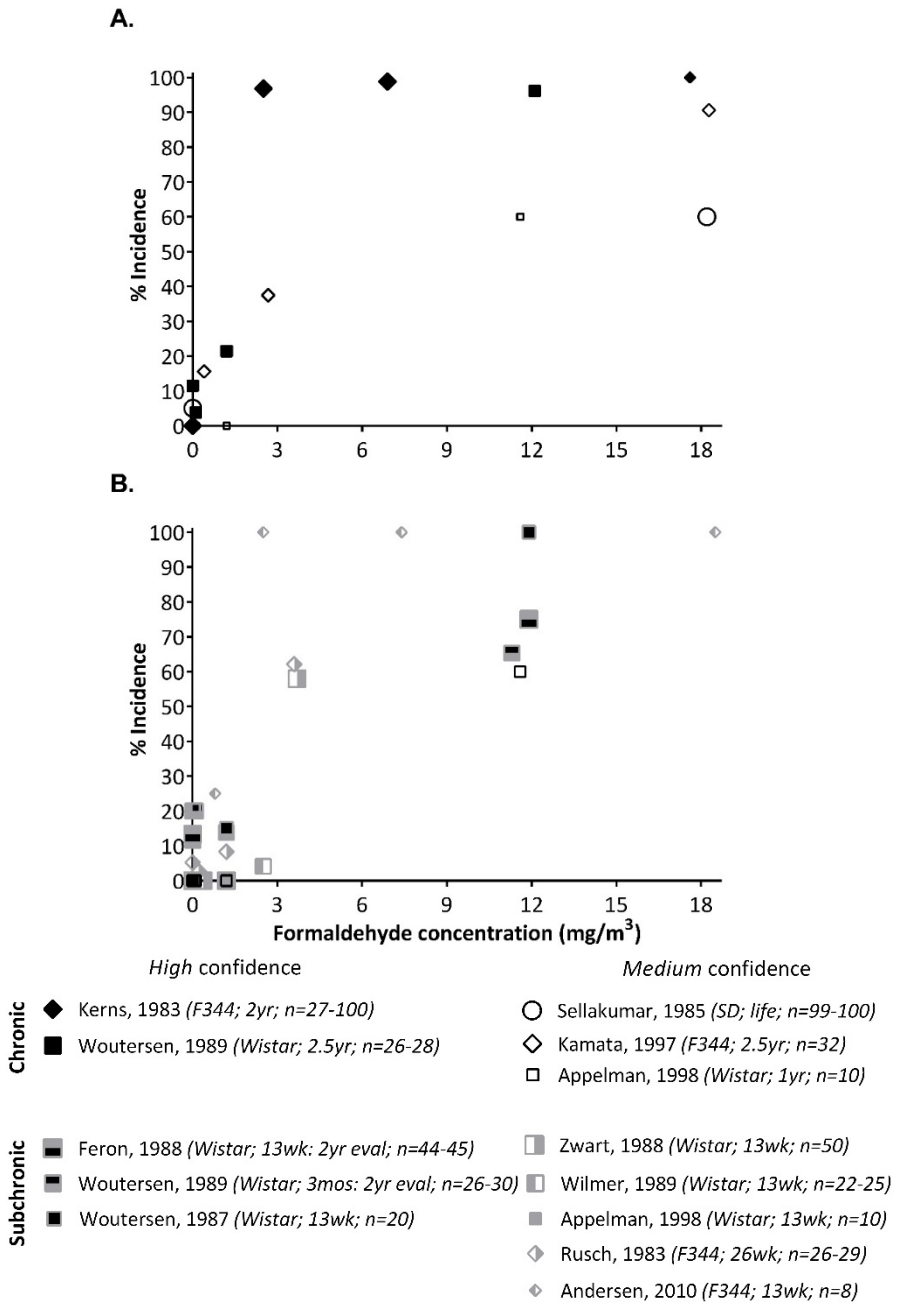


Figure 1-16. Squamous metaplasia incidence in *high* and *medium* confidence rat studies of chronic and subchronic formaldehyde exposure duration.

Incidence data for squamous metaplasia (i.e., of any severity) from the *high* and *medium* confidence studies with ≥1 year of formaldehyde exposure (Panel A, chronic exposure) or with ≥3 months of exposure (Panel B, subchronic exposure). Symbols for chronic studies are outlined in black, while subchronic studies are outlined in gray. In addition, *high* confidence studies include black fill, while *medium* confidence studies are filled in either white or a combination of white and gray. The size of the points reflects sample size for that particular exposure group (i.e., larger size = larger *n*). Notes: this figure does not present statistical significance; data points at 24.2 mg/m^3 (Woutersen et al., 1987) and 24.6 mg/m^3 (Feron et al., 1988) formaldehyde are not shown (the incidence of squamous metaplasia was approximately 100% at these levels).

Anatomical location of lesions in the upper respiratory tract

As previously mentioned, the majority of evidence for formaldehyde exposure-induced pathology in the URT of experimental animals is confined to the nasal cavity, which is discussed in greater detail in the sections below. This focus on the nasal cavity can be explained, at least in part, by the historical interest in nasal carcinogenesis.

The evidence for lesions beyond the nasal cavity in rats suggests that concentration is an important variable in long-term studies. Laryngeal lesions, including hyperplasia and squamous metaplasia, were observed in Sprague Dawley rats exposed to 18.2 mg/m^3 for a lifetime (Sellakumar et al., 1985) and in male Wistar rats exposed to 24.4 mg/m^3, but not to ≤11.9 mg/m^3, for 13 weeks (Woutersen et al., 1987). Tracheal lesions (metaplasia and hyperplasia) were reported in F344 rats after chronic exposure to 17.6 mg/m^3 formaldehyde (Kerns et al., 1983). Similar results were observed in Sprague Dawley rats in a single concentration (18.2 mg/m^3) lifetime study (Sellakumar et al., 1985). However, no laryngeal or tracheal lesions were observed in rats exposed to 11.6 mg/m^3 for 1 year (Appelman et al., 1988).

As reported in three studies, even higher concentrations of inhaled formaldehyde may be necessary for effects beyond the nose in mice. Histopathological changes were not observed in the trachea or lungs of B6C3F1 mice exposed to 17.6 mg/m^3 for 104 weeks in a study that did not provide quantitative incidence or severity information (Kerns et al., 1983), nor in the larynx of mice exposed to up to 18.5 mg/m^3 for 8 weeks and evaluated at 1 year (Morgan et al., 2017). However, a subchronic formalin study observed increases in metaplasia and hyperplasia in the trachea at ≥25.1 mg/m^3 and in the lung at ≥49.6 mg/m^3 (Maronpot et al., 1986). These high-concentration changes were also observed in a *low* confidence study with limited severity information that observed squamous metaplasia and hyperplasia in the tracheobronchial epithelium of C3H mice exposed to ≥50 mg/m^3 for 35 weeks (Horton et al., 1963).

While it is difficult to draw mechanistic inferences with confidence, these studies suggest that, in rodents, high levels of formaldehyde might be necessary to exceed the ability of the nose to scrub formaldehyde from inhaled air and allow formaldehyde to reach sites farther down the respiratory tract, which would be consistent with rodent toxicokinetic data (Appendix A.2).

Somewhat in contrast to the rodent studies, a single *medium* confidence study in rhesus monkeys, which failed to report lesion severity or incidence, observed a loss of goblet cells, hyperplasia, and metaplasia in the larynx, trachea, and carina, but not in the lungs, after exposure for ≤6 weeks to 7.4 mg/m^3 formaldehyde (Monticello et al., 1989). This might suggest that the monkey nose is less efficient than the rodent nose at scrubbing formaldehyde from inhaled air.

Overall, the evidence indicates the potential for lesions in the larynx and trachea of rats at sustained high formaldehyde concentrations and in rhesus monkeys at sustained moderate concentrations. These findings are particularly interesting in the context of future research into anatomical lesion location following formaldehyde inhalation in nonrodent animal models. The

remainder of this section will highlight the far more robust evidence of respiratory tract pathology localized to the nasal cavity.

Duration dependency of nasal lesions

Data from exposed rats, supported by findings in other species, identify a clear relationship between formaldehyde exposure duration and the development of squamous metaplasia and, to a lesser extent, hyperplasia. These lesions appear to be at least partially reversible after exposure ceases (see Tables 1-26 through 1-28 for study details).

As shown in Figure 1-17, the nasal cavities of monkeys and rats are lined with four types of epithelia—squamous, transitional, respiratory, and olfactory—and there are unique structures that may be susceptible to pathological change (Renne et al., 2009; Harkema et al., 2006; Renne and Gideon, 2006; Monticello et al., 1989; Young, 1981). Due to the high reactivity and water solubility of formaldehyde, nasal metaplasia and hyperplasia have primarily been assessed (and subsequently observed) in the epithelium lining the anterior regions of rodent nasal passages (typically Levels I, II, and III) following formaldehyde inhalation exposure, mostly in regions containing respiratory epithelium.

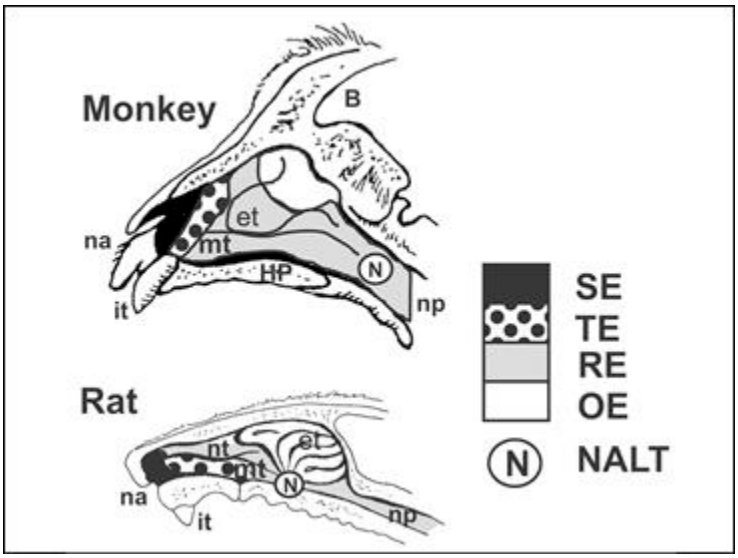


Figure 1-17. The four epithelial cell populations that line the nasal lateral wall in monkeys and rats are portrayed in this image.

The cell populations are SE = squamous epithelium, TE = transitional epithelium, RE = respiratory epithelium, OE = olfactory epithelium. Note that considerably more olfactory epithelium (OE) lines the intranasal surface in rats than in monkeys. Other abbreviations used in this image are NALT = nasal-associated lymphoid tissue, et = ethmoturbinate, mt = maxilloturbinate, nt = nasoturbinate, na = naris, it = incisor tooth, B = brain. Source: Harkema et al. (2006).

Squamous metaplasia

Squamous metaplasia has been observed to occur after chronic, subchronic, and short-term exposure to inhaled formaldehyde. Overall, the most robust responses (i.e., higher incidence or severity at lower formaldehyde concentrations) occur following chronic exposure.

Multiple chronic rat studies have reported robust increases in squamous metaplasia following exposures of approximately 2.5–2.7 mg/m^3 (Kamata et al., 1997; Kerns et al., 1983; Battelle, 1982) or 11.3–11.6 mg/m^3 (Woutersen et al., 1989; Appelman et al., 1988), although some data suggest that slight increases might be present at lower levels (i.e., 0.4–1.2 mg/m3, Kamata et al., 1997; Woutersen et al., 1989). In studies that compared changes in respiratory and olfactory epithelia (Woutersen et al., 1989; Appelman et al., 1988), squamous metaplasia was observed almost exclusively in the respiratory epithelium, except perhaps at the highest formaldehyde levels and with the longest exposure durations [i.e., slight increase in metaplasia at 12.1 mg/m^3 after 28 months of exposure in Woutersen et al. (1989)]. With subchronic exposure, squamous metaplasia is observed in rat noses at higher concentrations (i.e., ≥11.3 mg/m^3) in *high* confidence studies by Appelman et al. (1988), Woutersen et al. (1987), and Feron et al. (1988), the results of which are supported by consistent observations in two *medium* confidence studies (Andersen et al., 2010; Zwart et al., 1988), although these latter studies observed increases at lower exposure levels (i.e., 2.5–3.7 mg/m^3). With short-term exposures ranging from 4.4 to 18.4 mg/m^3, observations of squamous metaplasia in rats across several studies with various methodological limitations provide supporting evidence (Speit et al., 2011; Andersen et al., 2008; Cassee and Feron, 1994; Wilmer et al., 1987), although some findings were not completely consistent with a straightforward duration-dependency (e.g., Andersen et al. (2008) observed squamous metaplasia with 5 days of exposure, but not with shorter or longer exposure durations, at 7.4 mg/m^3).

The duration-dependency of these lesions in rat studies also appears to be reflected by the locations at which lesions develop, as well as their severity, possibly in parallel with the increases resulting from increasing formaldehyde concentration (see additional discussion below). The association with lesion location is demonstrated by the results of Kerns et al. (1983) which showed that, in anterior nasal regions (i.e., Level I and II) of F344 rats exposed to ≥2.5 mg/m^3, the incidence of squamous metaplasia increased from ≤20 to 100% with increasing duration (i.e., 6–24 months); however, in posterior nasal regions (i.e., Levels III–V), a duration-dependent increase in incidence was only observed at 17.6 mg/m^3 (Battelle, 1982). In some instances, noted by Kerns et al. (1983), more posterior lesions were entirely unique to longer exposure durations as compared to shorter exposures (e.g., Level III at 6.9 mg/m^3 only with 24 months of exposure). Regarding severity, squamous metaplasia was observed to increase (i.e., from slight focal lesions to metaplasia with keratinization) with exposure duration increases from 13 to 52 weeks of exposure to 11.6 mg/m^3 in Wistar rats (Appelman et al., 1988). Similarly, at ≥11.6 mg/m^3 in Wistar rats, an increase in the severity of squamous metaplasia in respiratory epithelium occurred as exposure duration increased from 4–8 to 13 weeks (Feron et al., 1988), and at very high formaldehyde levels

(24.2 mg/m^3), exposure duration was associated with an increase in the severity of focal replacement of olfactory epithelium with respiratory epithelium.

Several studies in rats confirm the important role of exposure duration in lesion development by demonstrating that the increases in lesions observed with longer-term exposure, as compared to shorter-term exposure, were not attributable to longer latencies after formaldehyde exposures began in the studies of longer-term exposure (i.e., since metaplasia, in particular, is expected to take several weeks to months to develop). In these studies of Wistar rats, nasal lesions including metaplasia and hyperplasia were consistently investigated at approximately 2 years of age following formaldehyde exposures of different durations (which began at the same ages, thus requiring longer periods of nonexposure in the shorter-term studies) (Woutersen et al., 1989; Feron et al., 1988). When animal ages at evaluation and formaldehyde exposure levels were matched, comparisons of subchronic exposure to chronic exposure (Woutersen et al., 1989) and of short-term exposure to subchronic exposure (Feron et al., 1988) revealed greater incidences or severity of these lesions with the longer exposure durations.

Rodent species other than rats also exhibit squamous metaplasia, although the duration-dependence of these lesions has not been as well established. Additionally, compared to rats, other laboratory rodents may require higher levels (i.e., mice) or exhibit a substantially reduced response (i.e., hamsters), suggesting that there may be differences in species sensitivity to formaldehyde-induced squamous metaplasia. Following chronic exposure, slight increases in the number of mice with metaplasia were observed at 6.9 mg/m^3, with more pronounced changes at 17.6 mg/m^3 (Kerns et al., 1983); however, the incidence and severity of these lesions were not quantified. Similarly, in a subchronic formalin study, squamous metaplasia was observed in all mice exposed to 12.4 mg/m^3 (Maronpot et al., 1986). Two strains of p53 deficient mice (*Trp*53 heterozygotes) also developed pronounced metaplasia at both tested concentrations (i.e., 9.23 and 18.45 mg/m^3) after only 8 weeks of exposure (Morgan et al., 2017), with changes that were dose dependent and exhibited an anterior-to-posterior gradient, similar to findings in rats. Squamous metaplasia was observed only in 5% of Syrian golden hamsters exposed to 12.3 mg/m^3 for a lifetime (Dalbey, 1982), and no changes were observed after subchronic exposure to 3.6 mg/m^3 in the same strain (Rusch et al., 1983), although these studies did not provide lesion severity.

Although the few available monkey studies did not report detailed endpoint information, squamous metaplasia was observed at 3.6 mg/m^3 in cynomolgus monkeys following subchronic, near-constant exposure (i.e., 22 hr/day for 7 d/week), and in rhesus monkeys after short-term (i.e., 1 or 6 weeks) exposure to 7.4 mg/m^3 (Monticello et al., 1989). The latter study in rhesus monkeys also supports the findings in rats of an anterior-to-posterior gradient of lesions with increasing exposure duration, and the general susceptibility of respiratory epithelium. After exposure to 7.4 mg/m^3 for 1 week, mild squamous metaplasia was observed in the respiratory epithelium of anterior regions (i.e., primarily Level A, the nasal atrium, but also including Levels B and C); however, with exposure to the same concentration for 6 weeks, the lesions were more

developed and had progressed to more posterior regions of the nasal cavity (i.e., regions of olfactory epithelium close to the olfactory/respiratory epithelial interface, and including Levels D and E) (Monticello et al., 1989). In another study (Rusch et al., 1983), monkeys exposed to formalin for 26 weeks had both squamous metaplasia and hyperplasia (these lesions were reported together) in the middle region of the nasal turbinates, with incidences of 17% at 0.23 mg/m^3 and 100% at 3.6 mg/m^3. No exposure-related effects were reported for the anterior and posterior nasal turbinates.

Although uncertainties remain, the reversibility of metaplasia may depend more on formaldehyde concentration than the duration of exposure. In general, increases in squamous metaplasia incidence appeared to be a persistent effect at higher levels of exposure (i.e., >11 mg/m^3 in rats and >9 mg/m^3 in mice), as these lesions were observed many months after formaldehyde exposure in rat recovery study comparisons by Woutersen et al. (1989) and Feron et al. (1988), and in two transgenic mouse strains (Morgan et al., 2017). However, it appears that the magnitude of this effect, particularly at lower formaldehyde levels (e.g., ≤6.9 mg/m^3), decreases with a recovery period, as evidenced by significant declines in the incidences of squamous metaplasia (and rhinitis) in F344 rats and B6C3F1 mice 3 or 6 months after 24 months of exposure (Kerns et al., 1983; Battelle, 1982).

In summary, experimental studies, primarily in rats, have demonstrated that formaldehyde exposure duration clearly influences the incidence, severity, or anatomical location of squamous metaplasia.

Hyperplasia

As with metaplasia, hyperplasia of the nasal epithelium has been observed across various durations of exposure. In some studies, hyperplasia was reported as a concurrent lesion with metaplasia (Kamata et al., 1997; Cassee and Feron, 1994; Reuzel et al., 1990; Rusch et al., 1983).

Reliable results from several studies show that chronic formaldehyde exposure of approximately 11.6–12.1 mg/m^3 induces hyperplasia in the nasal epithelium of rats (Woutersen et al., 1989; Appelman et al., 1988). Studies with more limited endpoint information also reported the formation of hyperplasia following exposure to 7.4–18.2 mg/m^3 (Monticello et al., 1996; Sellakumar et al., 1985). Subchronic exposure to formaldehyde also leads to hyperplasia in rat nasal passages after exposure to 11.9 mg/m^3 (Woutersen et al., 1987) and after exposure to approximately 3.7 mg/m^3 as reported in two studies with limited endpoint information (Zwart et al., 1988; Rusch et al., 1983). Following short-term exposures in rats to 4.4–18.5 mg/m^3, studies with methodological shortcomings also report the formation of nasal epithelium hyperplasia (Andersen et al., 2008; Cassee and Feron, 1994; Wilmer et al., 1987; Chang et al., 1983), adding support. While in nearly all cases, hyperplasia was observed in respiratory or transitional epithelium (or, in a few cases, isolated regions of olfactory epithelium), a single *high* confidence, short-term study reported that after 4 weeks of exposure to 18.4 mg/m^3, hyperplasia of the epithelium surrounding NALT (nasal-associated lymphoid tissue) was observed in a majority (87.5%) of F344 rats, but not

B6C3F1 mice (Kuper et al., 2011). Overall, comparisons of the formaldehyde concentrations at which significant increases in hyperplasia are observed across studies of differing exposure duration do not provide a clear picture of the potential duration dependence of formaldehyde-exposure-induced hyperplasia.

However, like the results for metaplasia, several rat studies comparing exposures of differing exposure duration (e.g., chronic versus subchronic) demonstrate that increasing exposure duration results in increases in the incidence and/or severity of hyperplasia in the respiratory epithelium when testing the same formaldehyde concentrations and anatomical levels (Woutersen et al., 1989; Appelman et al., 1988; Feron et al., 1988; Kerns et al., 1983). This included two *high* confidence studies matching the age of the animals at assessment (Woutersen et al., 1989; Feron et al., 1988) to allow identical amounts of time for lesions to develop after the exposures began. Similarly, some data also indicate that duration can influence the location of the observed hyperplasia, with an increased frequency of lesions in more posterior locations (i.e., at more posterior nasal levels or in more posterior structures, such as the trachea) with longer-term exposure (Woutersen et al., 1989; Kerns et al., 1983). However, in the identified rat studies, the within-study increases in incidence or posterior location with comparatively longer exposures were generally only observed at high levels of formaldehyde (i.e., >10 mg/m^3), preventing clear interpretations regarding the duration dependence of hyperplasia at lower formaldehyde levels.

The role for duration in the development of hyperplasia in other laboratory animal species is less clear. Hyperplasia was reported in a chronic mouse study with limited endpoint information following exposure to 2.5 mg/m^3 (Kerns et al., 1983), with consistent findings in a *low* confidence, short-term study at 18.5 mg/m^3 (Chang et al., 1983); however, a *medium* confidence, short-term study in transgenic mice failed to observe significant increases in hyperplasia after exposure to 9.23–18.5 mg/m^3, despite the presence of pronounced metaplasia (Morgan et al., 2017). Interestingly, however, this short-term mouse study did observe increases in nasal osteogenesis (evidence of bone proliferation in the nasal turbinates) at 18.45 mg/m^3 in both strains tested (Morgan et al., 2017). In a lifetime study by Dalbey (1982), 5% of hamsters had hyperplasia following exposure to 12.3 mg/m^3; however, hyperplasia did not appear to develop in hamsters exposed to 3.6 mg/m^3 for 26 weeks, although hyperplasia was not specified (i.e., the authors reported no treatment-related histopathology) (Rusch et al., 1983). In cynomolgus monkeys, hyperplasia along with metaplasia was reported following subchronic exposure to 3.6 mg/m^3 (Rusch et al., 1983), and hyperplasia was also found in rhesus monkeys exposed to 7.4 mg/m^3, although lesion incidence or severity was not reported (Monticello et al., 1989). When specified, the hyperplasia observed in mice (Kerns et al., 1983) and rhesus monkeys (Monticello et al., 1989) was generally identified in the anterior nose.

Hyperplasia in rats and mice appears to persist, at least in part (Woutersen et al., 1989; Feron et al., 1988; Kerns et al., 1983; Battelle, 1982), as with observations of squamous metaplasia. However, hyperplasia generally appears to be more reversible than metaplasia, even at higher

formaldehyde concentrations, as evidenced by smaller increases in incidence with a prolonged recovery following exposure to ~11 mg/m^3 formaldehyde (Woutersen et al., 1989; Feron et al., 1988). Findings in a short-term recovery study in rats (Andersen et al., 2008), with similar results observed in a *low* confidence study in mice (Chang et al., 1983), suggest that hyperplasia may take some small amount of time to develop, as lesions progressed in incidence or severity with 18 hours of recovery after very brief (i.e., days) exposures.

Taken together, formaldehyde exposure duration does appear to have some influence on the development of hyperplasia, primarily based on studies in rats. However, considering the notable influence of exposure duration on metaplasia at formaldehyde levels ranging from 2.5 to 2.7 mg/m^3 in rat studies (Kamata et al., 1997; Kerns et al., 1983), the easier reversibility of hyperplasia, as well as the generally more robust effects of duration on the incidence of metaplasia as compared to hyperplasia across species, exposure duration appears to be more important to the development of metaplasia in laboratory animals than to the development of hyperplasia. Overall, uncertainties remain regarding the relative impact of duration on the development of hyperplasia (particularly in species other than rats), as compared to the pronounced role for concentration, particularly at low formaldehyde levels (see additional discussion below).

Necrosis, nasal damage, and cytotoxicity

Although possessing methodological limitations, numerous short-term studies and three long-term studies in rats report overt damage to the nasal epithelium following exposure to 3.9–7.4 mg/m^3 (Andersen et al., 2010; Cassee et al., 1996; Cassee and Feron, 1994), 12 mg/m^3 (Wilmer et al., 1987), or approximately 18.5 mg/m^3 (Speit et al., 2011; Chang et al., 1983), with supporting evidence from ultrastructural analyses in a short-term study (Monteiro-Riviere and Popp, 1986). Consistent observations of nasal tissue damage were reported in rhesus monkeys (Monticello et al., 1989) and in a *low* confidence, mouse study with methodological limitations (Chang et al., 1983) following short-term exposure to ≥7.4 mg/m^3. In rhesus monkeys (Monticello et al., 1989), loss of cilia and goblet cells was more severe and covered a greater surface of respiratory epithelium (including extranasal respiratory tract regions), as duration of exposure increased. As these observations of tissue cytotoxicity generally appear to occur following exposures of shorter duration than in many of the studies reporting metaplasia or hyperplasia at similar formaldehyde concentrations, these data may be consistent with the evolution of hyperplasia and metaplasia from other lesions with increasing exposure duration.

Concentration dependency of nasal lesions

The development of nasal lesions in rodents and monkeys has routinely been shown to exhibit a strong concentration dependency in terms of incidence, frequency, severity, and location of the observed lesions. This is particularly true for both squamous metaplasia and hyperplasia in the respiratory epithelium. Importantly, several studies have reported the occurrence of

metaplasia in the absence of hyperplasia at a given exposure level (see Tables 1-26 and 1-27 for study details).

Squamous metaplasia

Although there is a demonstrated exposure duration dependency for the development of squamous metaplasia, formaldehyde concentration appears to be at least as important, if not more so. With increasing formaldehyde concentration, squamous metaplasia is observed in more posterior regions of the nasal tissue, and there is a marked increase in both lesion incidence and severity.

In a chronic study reporting metaplasia throughout the rat nasal passage (Kerns et al., 1983; Battelle, 1982), metaplasia was observed in the anterior nose (i.e., Level I) after exposure to 2.5 mg/m^3 and progressed in incidence toward the posterior nose, reaching Level V only after exposure to 17.6 mg/m^3. Consistent observations of the anterior-to-posterior progression of metaplasia with increasing exposure concentration were reported by another *high* confidence chronic study (Woutersen et al., 1989). These findings are supported by results from a *low* confidence chronic study with limited endpoint reporting (Monticello et al., 1996), as well as by *medium* confidence subchronic (Andersen et al., 2010) and short-term (Speit et al., 2011) studies.

With a constant duration of exposure, concentration-dependent increases for metaplasia in rat noses (Level II) after 24 months were reported in a chronic study where 1.1, 62.2, and 100% of rats were observed to have squamous metaplasia after exposure to 2.5, 6.9, or 17.6 mg/m^3, respectively (Kerns et al., 1983; Battelle, 1982). Additional studies provide support for a concentration-dependent increase in squamous metaplasia incidence following chronic and subchronic exposures in rats and mice (Andersen et al., 2010; Kamata et al., 1997; Woutersen et al., 1989; Feron et al., 1988; Maronpot et al., 1986). The incidence of squamous metaplasia and hyperplasia (lesions were reported together) also increased with concentration in rats and cynomolgus monkeys (Rusch et al., 1983).

The severity of metaplasia (e.g., from very slight to severe) also increased with concentration, as reported by subchronic studies (Andersen et al., 2010; Feron et al., 1988; Woutersen et al., 1987) and a short-term study with a relatively small sample size (Speit et al., 2011). In general, while concentration-dependent increases in more mild instances of metaplasia are typically observed at concentrations of 2.5 mg/m^3 and above (see previous section), moderate or severe lesions were only observed at the highest formaldehyde concentrations (approximately 12 mg/m^3 or more). The available studies demonstrate that formaldehyde exposure concentration occupies a central role in the development of squamous metaplasia.

Hyperplasia

Concentration-dependent increases in the incidence and severity of hyperplasia have also been observed in rats with chronic, subchronic, or short-term exposure durations (Andersen et al., 2008; Kamata et al., 1997; Woutersen et al., 1989; Appelman et al., 1988) and with subchronic

exposure in F344 rats and cynomolgus monkeys (Rusch et al., 1983). Overall, the concentration dependence of these lesions, in terms of location, incidence, and severity, closely paralleled the pattern of changes observed for squamous metaplasia, identifying a strong influence of exposure concentration on the development of hyperplasia.

Necrosis, nasal damage, and cytotoxicity

Results for concentration-dependent cytotoxicity are varied, as reported by less-than-chronic studies. A subchronic study observed no concentration-dependent increase in necrosis in the noses of Wistar rats exposed to 1.2 or 2.5 mg/m^3 for 13 weeks (Wilmer et al., 1989). Following ≤13 weeks of exposure to 0.8–18.5 mg/m^3, however, the incidence of necrosis/erosions in F344 noses generally increased with concentrations of 7.4 mg/m^3 and greater (Andersen et al., 2010). Following 4 weeks of formalin exposure from 0.63 to 18.4 mg/m^3, degeneration was observed only after exposure to the highest concentration in F344 rats (Speit et al., 2011), while focal thinning and epithelial disarrangement of the respiratory epithelium was observed in Wistar rats exposed to ≥12 mg/m^3 (Wilmer et al., 1987).

Studies comparing potential differential contributions of duration and concentration

Several animal respiratory pathology studies employed designs that compared intermittent and continuous exposure scenarios to examine the extent to which Haber's rule ($C \times t = K$; where C is concentration, t is time, and K is a constant) applies to formaldehyde-induced nasal pathology. If, for example, Haber's rule can be strictly applied, similar pathological lesions should result whether rats are exposed to 12 mg/m^3 for 3 hours (12 × 3 = 36) or to 6 mg/m^3 for 6 hours (6 × 6 = 36).

Wilmer et al. (1987) and Wilmer et al. (1989) used continuous and intermittent exposure scenarios to assess whether lesion formation appears to be influenced more by concentration or duration of exposure. In Wilmer et al. (1987), male rats were exposed to formaldehyde 5 days/week for 4 weeks. Groups of rats were either continuously exposed for 8 hours/day to target concentrations of 0, 6, or 12 mg/m^3 formaldehyde, or intermittently exposed (30 minutes of exposure followed by 30 minutes of nonexposure) to 0, 12, or 25 mg/m^3 formaldehyde (the analytical concentrations were not reported). Thus, the weekly inhaled concentrations (concentration × hours × days) were the same for the continuous and intermittent exposure groups: 0, 240, or 480 mg/m^3-h/week. The main difference was that the intermittently exposed rats were exposed to higher concentrations than the continuously exposed rats. The rats exposed intermittently to the higher concentrations (12 or 25 mg/m^3) had greater nasal cell proliferation and histopathologic lesions, including squamous metaplasia and basal cell hyperplasia, than did the rats exposed continuously to the lower concentrations (6 or 12 mg/m^3).

Similar results were seen in a 13-week study (Wilmer et al., 1989) in which groups of male rats were either continuously exposed for 8 hours/day to target concentrations of 0, 1, or 2 mg/m^3 formaldehyde, or intermittently exposed (30 minutes of exposure followed by 30 minutes of nonexposure) to 0, 2, or 5 mg/m^3 formaldehyde (again, the analytical concentrations were not

reported). The rats exposed continuously had greater incidences of diffuse disarrangement, diffuse necrosis, focal and diffuse basal cell hyperplasia, focal squamous metaplasia, keratinization, and diffuse goblet cell hyperplasia than the rats exposed intermittently. For some of these lesions, the incidences were greater in the rats exposed continuously to 2 mg/m^3 than to 5 mg/m^3, the interpretation of which is unclear. Overall, the Wilmer et al. studies suggest that in rats exposed for 4 or 13 weeks the extent of nasal lesions and cell proliferation appears to be driven more by concentration than by duration of exposure or cumulative dose. These findings are consistent with changes in cell proliferation reported in an acute and a short-term study using similar approaches (Wilmer et al., 1987; Swenberg et al., 1983); (see Appendix A.5.6).

While the authors of another subchronic rat study reached similar conclusions, the data did not fully support a clear concentration over duration driver for the observed effects. Rusch et al. (1983) compared the findings in their 6-month rat study against the 6-month exposure phase in the 2-year rat study by Kerns et al., as reported in the supporting report by Battelle for CIIT (Kerns et al., 1983; Battelle, 1982). Rusch et al. (1983) exposed animals 22 hours/day, 7 days/week for a total of 154 hours/week, compared to 6 hours/day, 5 days/week in the Kerns et al. (1983; 1982) study, for a total of 30 hours/week; that is, the rats in the Rusch et al. (1983) study were exposed five times longer than in the Kerns et al. (1983; 1982) study. At 6 months, squamous metaplasia was observed at 2.5 mg/m^3 by Kerns et al. (1983; 1982) versus at 3.6 mg/m^3 in the Rusch et al. (1983) study. However, the incidence was ~60% at 3.6 mg/m^3 in Rusch et al. (1983), as compared to only 20% at 2.5 mg/m^3 in the Kerns et al. (1983; 1982) study. In addition, while Kerns et al. (1983; 1982) did not test lower formaldehyde levels, metaplasia incidence went from 2/38 in controls to 3/36 at 1.2 mg/m^3 in Rusch et al. (1983), introducing the possibility that the study may have been inadequately powered to detect an effect at lower levels. Regardless, these data do support the possibility of an increased dependence on concentration, as compared to duration, as the rats in Rusch et al. (1983) did not appear to be five-fold more sensitive.

In summary, several rat studies suggest that formaldehyde, perhaps similar to mortality responses following acute exposure to some other local irritants, may not adhere strictly to Haber's rule for the induction of nasal pathology. Although duration of exposure has a clear and substantial role for the development of these nasal lesions (see discussion above), the experiments by Wilmer et al. (1987) and Wilmer et al. (1989) suggest that a power-law function ($C^n \times t = K$) where n is >1 may better represent formaldehyde exposure-induced nasal lesions than the linear $C \times t = K$, at least when interpreting short-term or subchronic exposure (the exposure scenarios examined by Wilmer et al.). Although a value for n was not identified for formaldehyde, or for exposure-induced nasal pathology, in particular, studies of acute exposure to other local irritants and the concentration-duration dependence for mortality suggest that the value for n, on average, is approximately

1.8–1.9 (ranging from 0.5 to 4.0).[15] It is difficult to speculate where within this range a value for *n* might be most applicable to formaldehyde, particularly within the context of respiratory pathology and long-term exposures (i.e., since these *n* values are for mortality after acute exposure); however, based on the data discussed in previous sections, it might be reasonable to expect that an *n* defined for associations with hyperplasia should be higher than one defined for metaplasia.

Species and sex differences in respiratory pathology

While most respiratory pathology studies have been conducted in rats, studies conducted with mice, hamsters, and monkeys have reported interspecies differences in susceptibility (i.e., lesion incidence and severity), and in the location of lesions. Additionally, differences between sexes of the same species have also been observed.

Rats have consistently been shown to be more susceptible than mice to the formation of various nasal lesions after chronic, subchronic, and short-term exposures. A well-conducted bioassay exposing F344 rats and B6C3F1 mice to 2.5, 6.9, or 17.6 mg/m^3 formaldehyde for 24 months reported that squamous metaplasia was observed in rat noses at all exposure levels, whereas in mice metaplasia was only observed after exposure to the intermediate and high concentrations. Additionally, lesions observed in mice were less severe than in rats at the same concentration level. In fact, similar incidences of squamous cell carcinoma were observed in rats exposed at 6.9 mg/m^3 and in mice exposed at 17.6 mg/m^3 (Kerns et al., 1983). Likewise, Kuper et al. (2011) observed hyperplasia of the NALT lymphoepithelium in rats, but not in mice. A possible explanation for these species disparities is that mice have a greater reflex bradypnea response than rats and thus inhaled lower doses of formaldehyde than rats. Unfortunately, minute volume and body temperature were not measured in the 2-year Battelle study or in Kuper et al. (2011), so there is no way of knowing whether reflex bradypnea played a significant role (see Appendix A.3 for a discussion on reflex bradypnea).

Rats also show differences with other species. Rats, and, to a lesser extent, mice, appear to be more sensitive than Syrian hamsters (Appelman et al., 1988; Rusch et al., 1983; Dalbey, 1982). The comparisons to nonrodent experimental models are less clear. Squamous metaplasia and hyperplasia were specifically found in the anterior, middle, and posterior nasal turbinates of F344 rats, but lesions were predominantly in the middle nasal turbinates of cynomolgus monkeys (Rusch et al., 1983) and rhesus monkeys (Monticello et al., 1989). Monticello et al. (1989) observed lesions that extended to proximal regions of the URT (outside of the nasal cavity) at lower concentrations than in the rat studies (7.4 mg/m^3, as compared to >15 mg/m^3), likely because the monkey nose is less efficient than the rodent nose at scrubbing formaldehyde from inhaled air.

[15]Values of *n* for 11 local irritants as estimated by ten Berge et al. (1986) averaged 1.9 (range 1.0–3.5), while 21 local irritants relying on data in rats or mice, as summarized in Appendix G by California EPA (OEHHA, 2008), averaged 1.8 (range 0.5–4.0). Of potential interest to this assessment, the chemicals included ammonia (*n* = 2.0) and acrolein (*n* = 1.2).

In addition to differences between species, the formation of histopathological lesions was sometimes observed to differ between sexes, although most studies only examined male animals. A subchronic study in Wistar rats reported that males generally had more severe damage, including metaplasia, to the nasal respiratory, olfactory epithelium, and larynx (Woutersen et al., 1987). Supportive findings of increased incidence or severity of lesions in males as compared to females was also reported in a second subchronic study of Wistar rats (Zwart et al., 1988), as well as in mouse studies of subchronic (Maronpot et al., 1986) and chronic (Kerns et al., 1983; Battelle, 1982) duration. Male rats have a higher metabolic rate and oxygen demand than female rats, and therefore greater minute volumes; thus, these findings might also reflect a greater inhaled dose of formaldehyde in males as compared to females at the concentrations tested.

Table 1-26. Chronic respiratory pathology studies in animals

Reference and study design	Results			
Rats				
High confidence				
Kerns et al. (1983) Fischer 344 rats; males and females; 119 to 121/sex/group. *Exposure*: Rats were exposed to FA in dynamic whole-body chambers 6 hours/day, 5 days/week for up to 24 months. Animals sacrificed at 27 and 30 months had 3- and 6-month periods of nonexposure, respectively, after 24-months of exposure. *Test article*: Paraformaldehyde. Actual concentrations were 0, 2.5 (±0.01), 6.9 (±0.02), or 17.6 (±0.05) mg/m^3.[a] *Histopathology:* 5 midsagittal sections of nasal turbinates (Levels I–V; see Figure 1-14) for all animals that died or were sacrificed at scheduled intervals (i.e., at month 6, 12, 18, 24, 27, and 30). *Related studies/earlier reports*: Battelle (1982, 1981); Swenberg et al. (1980a). See Battelle, 1982 for a more detailed study report. *Note*: transient viral infection at 52 weeks was noted, but considered unlikely to influence these findings.		***Pathological changes***[a,b]		
	Exposure duration	*2.5 mg/m^3*	*6.9 mg/m^3*	*17.6 mg/m^3*
	6 months	NR[c]	Levels I, II, and III: purulent rhinitis, epithelial dysplasia, and squamous metaplasia observed	Lesions first noted in anterior sections (Levels I, II, and III) of nose; changes in epithelium restricted to ventral portion of nasal septum and distal tips of nasoturbinates and maxilloturbinates
	12 months	Level I[d]: purulent rhinitis, epithelial dysplasia, and squamous metaplasia observed		NR
	18 months	NR		NR
	24 months	Frequency of metaplasia exceeded that of prior sacrifices; dysplasia and metaplasia only observed in Level I		NR
	27 months[e]	Significant decrease ($p < 0.05$) in frequency of metaplasia	Levels I, II, and III: regression ($p < 0.05$) of squamous metaplasia	Levels IV and V: regression ($p < 0.05$) of squamous metaplasia

Reference and study design	Results

[a]Severity of lesions most intense in Level I for all exposure groups. Exposure-related effects observed in Levels II, III, IV, and V for 6.9- and 17.6-mg/m^3 groups. Lesion frequency in exposed groups greater than the <15% lesion frequency observed for 0 mg/m^3 group, where lesions (e.g., dysplasia and metaplasia) only present in Level I.
[b]Authors defined squamous metaplasia as zones of altered epithelium characterized by a well-differentiated germinal cell layer (stratum germinativum) and superficial epithelial layers (stratum spinosum and stratum corneum). Authors further noted that keratin was only produced in areas of squamous metaplasia, and that in all exposure groups epithelial dysplasia was detected earlier than squamous metaplasia.
[c]Chart nine of Kerns et al. (1983) provides graphical representation of the frequency of squamous metaplasia observed for Levels I–V for all exposure groups during 24-month exposure and 3-month nonexposure period.
[d]At this location, authors observed a transition in the mucosa from normal nonciliated simple cuboidal epithelium to an epithelial lining several cells thick and squamoid in appearance. The organization and polarity of the individual epithelial cells changed from vertical to horizontal with respect to the basement membrane. The authors termed such alterations as zones of epithelial dysplasia and noted that similar histomorphological alterations have been called basal cell hyperplasia and epidermoid metaplasia.
[e]24 months of exposure and 3 months of nonexposure.

General observations (respiratory epithelium):

17.6 mg/m^3—squamous metaplasia with zones of squamous epithelial hyperplasia and increased keratin production appeared to precede area of squamous papillary hyperplasia with foci of cellular atypia; dyspnea and death caused by excessive accumulation of keratin and inflammatory exudate in lumen of nasal cavity of rats (with and without carcinomas).

General observations (tracheal pathology):

17.6 mg/m^3—rats (frequency NR) sacrificed at 18 months exhibited multifocal areas of mild epithelial hyperplasia, epithelial dysplasia, or squamous metaplasia of proximal tracheal mucosa; similar lesions at a greater frequency ($p < 0.05$) observed in rats from 24-month sacrifice and unscheduled death groups; tracheal lesions not observed in postexposure group.

0, 2.5, or 6.9 mg/m^3—no significant tracheal lesions observed

Incidence of squamous metaplasia in nasal cavity of rats

Level I[a]				
Duration	*0 mg/m^3*	*2.5 mg/m^3*	*6.9 mg/m^3*	*17.6 mg/m^3*
6 months	NA[b]	4/20	10/20	NA
12 months	NA	7/20	11/20	NA
18 months	0/40	24/40	35/40	38/39
24 months	1/101	91/94	81/82	27/27
27 months[d]	3/19	4/20[c]	8/19[c]	5/5
30 months	1/10	2/5	1/8	NR
Level II				
6 months	NA	0/20	10/20	NA
12 months	NA	0/20	8/20	NA
18 months	0/40	0/40	24/40	38/39
24 months	0/101	1/94	51/82	27/27
27 months	0/19	0/20	5/19[c]	5/5

Reference and study design	Results

30 months	0/10	0/5	5/8	NR
Level III				
6 months	0/20	0/20	0/20	6/20
12 months	0/20	0/20	0/20	10/20
18 months	0/40	0/40	0/40	38/39
24 months	0/101	0/94	9/82	26/27
27 months	0/19	0/20	0/19	4/5
30 months	0/10	0/5	0/8	NR
Level IV				
6 months	NA	0/20	0/20	NA
12 months	NA	0/20	0/20	NA
18 months	0/40	0/40	0/40	14/39
24 months	0/101	0/94	1/82	21/27
27 months	0/19	0/20	0/19	1/5[c]
30 months	0/10	0/5	0/8	NR
Level V				
6 months	NA	0/20	0/20	NA
12 months	NA	0/20	0/20	NA
18 months	0/40	0/40	0/40	11/39
24 months	0/101	0/94	0/82	19/27
27 months	0/19	0/20	0/19	0/5[c]
30 months	0/10	0/5	0/8	NR

[a]Data reported in part in Kerns et al. (1983) and further adapted from Battelle (1982)[b] tissue section not available for histopathology; [c]$p < 0.05$, regression of squamous metaplasia 3 months postexposure; [d]data for 27 and 30 months represent incidence after 3 and 6 months of nonexposure, respectively, following 24 months of exposure.

Woutersen et al. (1989)

Wistar rats; male; 30/group.

Exposure: Rats were exposed to FA in dynamic whole-body chambers 6 hours/day, 5 days/week for 3 or 28 months. All survivors sacrificed at 28 months.

Test article: Paraformaldehyde. Actual concentrations were 0, 0.1 (±0.07), 1.2 (±0.22), or 11.3 (±2.0) mg/m^3 for 3-month exposures and 0, 0.1 (±0.05), 1.2 (±0.14), or 12.1 (±1.60) mg/m^3 for 28-month exposures.[1]

Histopathology: 6 standard cross sections of the nose.

Note: This study also evaluated the effects of FA in a parallel group of rats that had undergone bilateral electrocoagulation (i.e., damaged nose group) prior to the initiation of FA exposure. Data presented here in the **Results** column are for FA-only (i.e., undamaged nose group) exposed rats.

3 months of exposure followed by a 25-month observation period with no exposure:

FA-related histological changes generally not observed for Levels IV–VI.

Histopathological nasal changes after 3 months of exposure and 25-month recovery period

	Incidence of lesions in Levels I–II			
	0 mg/m^3	0.1 mg/m^3	1.2 mg/m^3	11.3 mg/m^3
Type of lesions (Severity NR)				
Respiratory epithelium				
Disarrangement	0/26[a]	0/30	0/29	1/26
Squamous metaplasia	3/26	6/30	4/29	17/26
Keratinization	0/26	0/30	1/29	2/26
Basal cell/pseudoepithelial hyperplasia	1/26	0/30	0/29	4/26
Nest-like infolds/goblet cell hyperplasia	11/26	3/30	15/29	9/26
Invaginations	3/26	0/30	0/29	0/26
Rhinitis	5/26	4/30	3/29	13/26
Olfactory epithelium				
Thinning/disarrangement	0/26	0/30	0/29	0/26
Basal cell hyperplasia	0/26	0/30	0/29	0/26
Vacuolation/proteinaceous material/numeric atrophy	0/26	0/30	0/29	0/26

Reference and study design	Results

Replaced by respiratory epithelium	0/26	0/30	0/29	0/26

[a]Denominator represented by the effective number of animals and not the initial number of animals.

Large variation observed for nest-like infolds/goblet cell hyperplasia; due to lack of exposure-response, this change was not considered to be exposure-related.

28 months of exposure:
12.1 mg/m^3—Incidence of rhinitis elevated in Level I–VI; other FA-related histological changes in respiratory epithelium generally found in Level II and III; lesions observed in olfactory epithelium in Levels III and IV.

Histopathological nasal changes after 28 months of exposure period

	Incidence of lesions **in Levels I–II**			
	0 mg/m^3	0.1 mg/m^3	1.2 mg/m^3	12.1 mg/m^3
Type of lesions (Severity NR)				
Respiratory epithelium				
Disarrangement	0/26[a]	0/26	1/28	1/26
Squamous metaplasia	3/26	1/26	6/28	25/26
Keratinization	0/26	1/26	0/28	2/26
Basal cell/pseudoepithelial hyperplasia	0/26	1/26	2/28	14/26
Nest-like infolds/goblet cell hyperplasia	5/26	6/26	14/28	4/26
Invaginations	0/26	0/26	1/28	3/26
Rhinitis	2/26	1/26	2/28	18/26
Olfactory epithelium				
Thinning/disarrangement	0/26	0/26	0/28	0/26
Squamous metaplasia	0/26	0/26	0/28	0/26
Basal cell hyperplasia	0/26	0/26	0/28	0/26
Vacuolation/proteinaceous material/numeric atrophy	0/26	0/26	0/28	0/26
Replaced by respiratory epithelium	0/26	0/26	0/28	0/26

[a]Denominator represented by the effective number of animals and not the initial number of animals.

Highest incidence for nest-like infolds/goblet cell hyperplasia observed for Level II at 1.2 mg/m^3; due to lack of exposure-response, this change was not considered to be exposure-related.

28 months of exposure (continued):

Histopathological nasal changes after 28 months of exposure period

	Incidence of lesions **in Level III**			
	0 mg/m^3	0.1 mg/m^3	1.2 mg/m^3	12.1 mg/m^3
Type of lesions (Severity NR)				
Respiratory epithelium				
Disarrangement	4/26[a]	0/26	2/28	1/26
Squamous metaplasia	0/26	0/26	0/28	13/26
Keratinization	0/26	0/26	0/28	1/26
Basal cell/pseudoepithelial hyperplasia	1/26	0/26	2/28	7/26

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr><td></td><td>
<table>
<tr><td>Nest-like infolds/goblet cell hyperplasia</td><td>1/26</td><td>2/26</td><td>2/28</td><td>1/26</td></tr>
<tr><td>Invaginations</td><td>0/26</td><td>0/26</td><td>0/28</td><td>0/26</td></tr>
<tr><td>Rhinitis</td><td>1/26</td><td>0/26</td><td>2/28</td><td>6/26</td></tr>
<tr><td>Olfactory epithelium</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Thinning/disarrangement</td><td>1/26</td><td>1/26</td><td>1/28</td><td>7/26</td></tr>
<tr><td>Squamous metaplasia</td><td>0/26</td><td>0/26</td><td>0/28</td><td>2/26</td></tr>
<tr><td>Basal cell hyperplasia</td><td>3/26</td><td>3/26</td><td>4/28</td><td>3/26</td></tr>
<tr><td>Vacuolation/proteinaceous material/numeric atrophy</td><td>1/26</td><td>1/26</td><td>3/28</td><td>0/26</td></tr>
<tr><td>Replaced by respiratory epithelium</td><td>0/26</td><td>0/26</td><td>1/28</td><td>2/26</td></tr>
</table>
[a]Denominator represented by the effective number of animals and not the initial number of animals.
</td></tr>
<tr><td colspan="2">Medium confidence</td></tr>
<tr><td>Appelman et al. (1988)
SPF Wistar rat; male; 20/group.
Exposure: Rats were exposed to FA in dynamic whole-body chambers 6 hours/day, 5 days/week for 52 weeks. Half of the rats in each group were sacrificed at 13 weeks.
Test article: Paraformaldehyde. Actual concentrations were 0, 0.1 (±0.05), 1.2 (±0.18), or 11.6 (±1.60) mg/m^3.[a]
Histopathology: nose (6 standard cross levels), larynx, trachea, and lungs.

Main limitations: small N; limited reporting of lesion severity (note: this 12-month study was shorter than the other available chronic studies).

Note: This study also evaluated the effects of FA in a parallel group of rats that had undergone bilateral electrocoagulation 20 to 26 hours prior to the initiation of FA exposure (not shown).</td><td>
Histopathological nasal changes after 13 weeks of exposure (data included for comparison with 52 weeks of exposure)
<table>
<tr><th>Type of lesion</th><th>0 mg/m^3</th><th>0.1 mg/m^3</th><th>1.2 mg/m^3</th><th>11.6 mg/m^3</th></tr>
<tr><td>Respiratory epithelium</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Focal squamous metaplasia:</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Slight</td><td>0/10</td><td>0/10</td><td>1/10</td><td>9/10[a]</td></tr>
<tr><td>Moderate/severe</td><td>0/10</td><td>0/10</td><td>0/10</td><td>1/10</td></tr>
<tr><td>Focal basal cell hyperplasia:</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Slight</td><td>0/10</td><td>0/10</td><td>0/10</td><td>7/10[a]</td></tr>
<tr><td>Moderate/severe</td><td>0/10</td><td>0/10</td><td>0/10</td><td>0/10</td></tr>
<tr><td>Focal rhinitis</td><td>0/10</td><td>0/10</td><td>0/10</td><td>6/10[b]</td></tr>
<tr><td>Nest-like infolds</td><td>0/10</td><td>0/10</td><td>0/10</td><td>0/10</td></tr>
<tr><td>Olfactory epithelium</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Focal thinning/disarrangement</td><td>0/10</td><td>0/10</td><td>0/10</td><td>0/10</td></tr>
<tr><td>Focal basal cell hyperplasia</td><td>0/10</td><td>0/10</td><td>0/10</td><td>0/10</td></tr>
<tr><td>Focal rhinitis</td><td>0/10</td><td>0/10</td><td>0/10</td><td>0/10</td></tr>
</table>
[a]$p < 0.01$; [b]$p < 0.05$

Histopathological nasal changes after 52 weeks of exposure
<table>
<tr><th>Type of lesion</th><th>0 mg/m^3</th><th>0.1 mg/m^3</th><th>1.2 mg/m^3</th><th>11.6 mg/m^3</th></tr>
<tr><td>Respiratory epithelium</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Squamous metaplasia</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Focal</td><td>0/10</td><td>0/10</td><td>0/10</td><td>6/10[a]</td></tr>
<tr><td>Diffuse</td><td>0/10</td><td>0/10</td><td>0/10</td><td>0/10</td></tr>
<tr><td>Keratinization</td><td>0/10</td><td>0/10</td><td>0/10</td><td>5/10[a]</td></tr>
<tr><td>Basal cell hyperplasia</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Focal</td><td>0/10</td><td>0/10</td><td>0/10</td><td>5/10[a]</td></tr>
<tr><td>Diffuse</td><td>0/10</td><td>0/10</td><td>0/10</td><td>5/10[a]</td></tr>
<tr><td>Focal rhinitis</td><td>2/10</td><td>0/10</td><td>0/10</td><td>10/10[a]</td></tr>
<tr><td>Nest-like infolds</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Focal</td><td>6/10</td><td>2/10</td><td>3/10</td><td>4/10</td></tr>
<tr><td>Diffuse</td><td>2/10</td><td>4/10</td><td>3/10</td><td>0/10</td></tr>
<tr><td>Olfactory epithelium</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Thinning/disarrangement</td><td>1/10</td><td>0/10</td><td>0/10</td><td>3/10</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr><td></td><td>
<table>
<tr><td>Focal basal cell hyperplasia</td><td>0/10</td><td>0/10</td><td>0/10</td><td>2/10</td></tr>
<tr><td>Focal squamous metaplasia</td><td>0/10</td><td>0/10</td><td>0/10</td><td>0/10</td></tr>
<tr><td>Loosely arranged submucosal connective tissue</td><td>0/10</td><td>0/10</td><td>0/10</td><td>0/10</td></tr>
<tr><td>Focal rhinitis</td><td>0/10</td><td>0/10</td><td>0/10</td><td>0/10</td></tr>
</table>
[a]$p < 0.05$

Histopathological changes in larynx, trachea, and lungs were those commonly found in this strain of rat and were about equally distributed among controls and exposed groups or were only found in one rat; these changes ultimately characterized as unrelated to FA exposure.</td></tr>
<tr><td>Kamata et al. (1997)
Fischer 344 rats; male; 32/group.
Exposure: Rats were exposed to FA in dynamic nose-only chambers 6 hours/day, 5 days/week for 28 months with interim sacrifices at the end of months 12, 18, and 24.
Test article: Formalin (37% FA aqueous solution containing 10% methanol). Actual concentrations were 0, 0.40 (±0.09), 2.67 (±0.40), or 18.27 (±2.73) mg/m^3.[a] The concentration of methanol in the 0 and 18.27 groups was estimated to be 5.5 mg/m^3.[b] A room control served as a no exposure group.
Histopathology: nasal region (sections from five anatomical levels, A-E; see Figure 1-14) and trachea.

Main limitations: formalin; small N for interim sacrifices; lesion severities NR</td><td>
<table>
<tr><th>Group</th><th>Squamous cell metaplasia no epithelial cell hyperplasia</th><th>Epithelial cell hyperplasia with squamous cell metaplasia</th><th>Epithelial cell hyper-keratosis</th><th>Papillary hyperplasia</th></tr>
<tr><td>Room control</td><td>No nasal lesions observed</td><td>No nasal lesions observed</td><td>No nasal lesions observed</td><td>No nasal lesions observed</td></tr>
<tr><td>0 mg/m^3 (5.5 mg/m^3 MeOH)</td><td>No nasal lesions observed</td><td>No nasal lesions observed</td><td>No nasal lesions observed</td><td>No nasal lesions observed</td></tr>
<tr><td>0.40 mg/m^3</td><td>1/32[a] (1/5 at 18-month)</td><td>4/32 (1/5 at 24-month, 3/11 at 28-month)</td><td>No nasal lesions observed</td><td>No nasal lesions observed</td></tr>
<tr><td>2.67 mg/m^3</td><td>5/32[b] (2/5 at 18-month, 1/5 at 24-month, 2/7 at 28-month)</td><td>7/32[c] (2/5 at 18-month, 1/7 at 28-month, 4/10 of dead)</td><td>1/32 (1/10 of dead)</td><td>No nasal lesions observed</td></tr>
<tr><td>18.27 mg/m^3 (5.5 mg/m^3 MeOH)</td><td>NR</td><td>29/32[c] (3/5 at 12-month, 4/5 at 18-month, 2/2 at 24-month, 20/20 of dead)</td><td>26/32[c] (4/5 at 12-month, 1/5 at 18-month, 1/2 at 24-month, 20/20 of dead)</td><td>2/32 (2/5 at 12-month)</td></tr>
</table>
[a]data reported as group total (i.e., dead animals plus scheduled sacrifices at 12, 18, 24, and 28 months); number in parenthesis represent incidence at sacrifice; [b]$p < 0.05$, compared to 0 mg/m^3 group; [c]$p < 0.01$, compared to 0 mg/m^3 group</td></tr>
<tr><td>Sellakumar et al. (1985)
Sprague Dawley rats; male; 100/group.
Exposure: Rats were exposed to FA in dynamic whole-body chambers 6 hours/day, 5 days/week for life.</td><td>
<table>
<tr><th>Observation</th><th>0 mg/m^3</th><th>18.2 mg/m^3</th></tr>
<tr><td>Larynx</td><td></td><td></td></tr>
<tr><td>Hyperplasia</td><td>2/99</td><td>21/100</td></tr>
<tr><td>Squamous metaplasia</td><td>0/99</td><td>4/100</td></tr>
</table>
</td></tr>
</table>

Reference and study design	Results		
Test article: Paraformaldehyde. Actual concentrations were 0 and 18.2 (±2.6) mg/m^3.[a] *Histopathology:* multiple sections of the head (from just behind the nostril to the eye orbits) as well as sections of lung (each lobe), trachea, and larynx. *Preliminary study*: Albert et al. (1982) **Main limitations:** likely coexposure to paraffin oil (kerosene); lesion severities NR	**Trachea**		
	Hyperplasia	6/99	21/100
	Squamous metaplasia	0/99	7/100
	Nasal Mucosa		
	Rhinitis (mild to severe)	72/99	74/100
	Epithelial or squamous hyperplasia	51/99	57/100
	Squamous metaplasia	5/99	60/100
	Additional observations (frequencies NR) from FA exposures included: exudation in the nasal cavity lumen; necrosis; desquamation of respiratory epithelial cells of respiratory epithelial covering of naso-maxillary turbinates and nasal septum; and inflammation of olfactory epithelium lining the ethmoidal turbinates, with seropurulent exudate in lumen.		
Mice			
Medium confidence			
Kerns et al. (1983) B6C3F1 mice; males and females; 119 to 121/sex/group. *Exposure*: Mice were exposed to FA in dynamic whole-body chambers 6 hours/day, 5 days/week for up to 24 months. Animals sacrificed at 27 and 30 months had 3- and 6-month periods of nonexposure, respectively, after 24-months of exposure. *Test article*: Paraformaldehyde. Actual concentrations were 0, 2.5 (±0.01), 6.9 (±0.02), or 17.6 (±0.05) mg/m^3.[a] *Histopathology*: 5 midsagittal sections of nasal turbinates corresponding to the regions evaluated in rats in this study (levels I–V; see Figure 1-14) for all animals that died or were sacrificed at scheduled intervals (i.e., at month 6, 12, 18, 24, 27, and 30). *Earlier reports*: Battelle (1981); Battelle (1982) **Main limitations:** high mortality in all groups; limited sampling (i.e., sections); lesion incidence and severity NR		*Pathological changes*[a]		
	Exposure duration	2.5 mg/m^3	6.9 mg/m^3	17.6 mg/m^3
	12 mos	ND	ND	Serous rhinitis in Levels III and V
	18 mos	ND	Few mice[c] had dysplastic changes associated with serous rhinitis in Level II	~90% of mice had dysplastic and metaplastic alterations of nasal mucosa in Level II with a serous to purulent change in nasal exudate
	24 mos	Few animals had serous rhinitis in Level II, but no significant nasal lesions; hyperplasia (minimal to moderate) of squamous epithelium lining nasolacrimal duct	Few mice had dysplasia, metaplasia, or serous rhinitis in Level II; hyperplasia (minimal to moderate) of squamous epithelium lining nasolacrimal duct; focal atrophy of olfactory epithelium lining the ethmoturbinates	>90% of mice had dysplastic and metaplastic changes associated with seropurulent rhinitis; hyperplasia (minimal to moderate) of squamous epithelium lining nasolacrimal duct, greatest frequency and distribution found in this FA level; focal atrophy of olfactory epithelium lining the ethmoturbinates, greatest frequency at this FA level
	27 mos[b]	FA-related lesions ND	FA-related lesions ND; regression observed for squamous	Dysplastic epithelial lesions with serous exudate observed; squamous metaplasia

Reference and study design	Results
	metaplasia and rhinitis for all affected Levels | in Level II in (~20% of mice), but not in Levels III and IV; regression observed for squamous metaplasia and rhinitis for all affected Levels [a]Unless noted, severities NR; [b]24 months of exposure and 3 months of nonexposure; [c]Unless noted, exact frequency of lesion NR. No tracheal lesions were observed.
Hamsters	
Medium confidence	
Dalbey (1982) Syrian golden hamsters; male; 132 untreated controls and 88 exposed. *Exposure*: Hamsters were exposed to FA in dynamic whole-body chambers 5 hours/day, 5 days/week for a lifetime. *Test article*: Paraformaldehyde. Actual FA concentrations were 0 and 12.3 (±5%) mg/m^3.[a] *Histopathology*: 2 transverse sections of the nasal turbinates, longitudinal sections of larynx and trachea, and all lung lobes cut along the bronchus. **Main limitations:** lesion severities NR *Note:* this study also evaluated the effects of FA on tumorigenicity of diethylnitrosamine (DEN), either from concurrent exposures or from DEN then FA exposures (not shown).	Hamsters exposed at 12.3 mg/m^3 had slightly reduced survival ($p < 0.05$) relative to controls. Nasal epithelium: **Hyperplastic lesions** 12.3 mg/m^3–4/88 (5%) 0 mg/m^3–0/132 **Metaplastic lesions** 12.3 mg/m^3–4/88 (5%) 0 mg/m^3–0/132 **Rhinitis** 12.3 mg/m^3–21/88 (24%) 0 mg/m^3–41/132 (31%)

Abbreviations: FA = formaldehyde, NA = not available, ND = not detected, NR = not reported, SD = standard deviation.

[a]Study authors originally reported FA concentrations in ppm. These values were converted based on 1 ppm = 1.23 mg/m^3, assuming 25°C and 760 mm Hg.

[b]Study authors did not report methods for specific methanol measurements, but appeared to estimate the concentration based on the proportion of methanol in the formalin solutions to determine their control group methanol concentrations (see *Preface on assessment methods and organization* for relevant discussion of the uncertainties related to this assumption). Study authors originally reported methanol concentrations in ppm. These methanol values were converted based on 1 ppm = 1.31 mg/m^3.

Table 1-27. Subchronic respiratory pathology studies in animals

Reference and study design	Results
Rats	
High confidence	
Feron et al. (1988) Wistar rats; male; 45/group.	**4 weeks of exposure followed by observation period of 126 weeks** | Incidence of lesions

Reference and study design	Results

Exposure: Rats were exposed to FA in dynamic whole-body chambers 6 hours/day, 5 days/week for either 4, 8, or 13 weeks followed by nonexposure periods of 126, 122, or 117 weeks, respectively.
Test article: Paraformaldehyde.
Actual concentrations were 0, 11.3 (±0.25), or 24.2 (±0.12) mg/m^3 for the 4-week exposed groups; 0, 11.6 (±0.21), or 24.2 (±0.11) mg/m^3 for the 8-week exposed groups; and 0, 11.9 (±0.15), or 24.4 (±0.09) mg/m^3 for the 13-week exposed groups.[a]
Histopathology: 6 standard cross levels of the nose.

Note: only tested high formaldehyde levels

	0 mg/m^3	11.3 mg/m^3	24.2 mg/m^3
Focal hyperplasia of respiratory epithelium			
Very slight	0/44	0/44	0/45
Slight	0/44	3/44	8/45[c]
Moderate	0/44	0/44	1/45
Focal stratified squamous metaplasia of respiratory epithelium			
Very slight	3/44	6/44	14/45[c]
Slight	4/44	2/44	19/45[c]
Moderate	0/44	2/44	3/45
Severe	0/44	0/44	0/45
Rhinitis	7/44	7/44	18/45[b]
Simple or stratified cuboidal or squamous metaplasia of epithelium in the dorsomedial area where respiratory and olfactory epithelium join[a]	0/44	0/44	4/45
Focal replacement of olfactory epithelium by respiratory, respiratory-like or regenerating olfactory epithelium			
Very slight	0/44	0/44	0/45
Slight	1/44	0/44	6/45
Moderate	0/44	0/44	1/45
Severe	0/44	0/44	0/45

[a]The changes in this area were scored separately because their origin from either respiratory or olfactory epithelium was not clear; [b]$p < 0.05$; [c]$p < 0.01$

8 weeks of exposure followed by observation period of 122 weeks

	Incidence of lesions		
	0 mg/m^3	11.6 mg/m^3	24.2 mg/m^3
Focal hyperplasia of respiratory epithelium			
Very slight	0/45	1/44	3/43
Slight	2/45	2/44	12/43[c]
Moderate	0/45	1/44	0/43
Focal stratified squamous metaplasia of respiratory epithelium			
Very slight	8/45	16/44	17/43[b]
Slight	2/45	1/44	20/43[c]
Moderate	0/45	0/44	2/43
Severe	0/45	0/44	0/43
Rhinitis	4/45	6/44	22/43[b]
Simple or stratified cuboidal or squamous metaplasia of epithelium in the dorsomedial area where respiratory and olfactory epithelium join	0/45	0/44	17/43[c]
Focal replacement of olfactory epithelium by respiratory, respiratory-like or regenerating olfactory epithelium			
Very slight	0/45	0/44	2/43
Slight	0/45	0/44	14/43[b]
Moderate	0/45	0/44	3/43
Severe	0/45	0/44	1/43

[a]See above for explanation; [b]$p < 0.05$; [c]$p < 0.01$

13 weeks of exposure followed by observation period of 117 weeks

	Incidence of lesions

Reference and study design	Results

	0 mg/m^3	11.9 mg/m^3	24.4 mg/m^3
Focal hyperplasia of respiratory epithelium			
Very slight	0/45	5/44[b]	2/44
Slight	1/45	6/44	14/44[c]
Moderate	0/45	0/44	4/44
Focal stratified squamous metaplasia of respiratory epithelium			
Very slight	2/45	10/44[b]	2/44
Slight	3/45	18/44[c]	26/44[c]
Moderate	1/45	5/44	14/44[c]
Severe	0/45	0/44	1/44
Rhinitis	8/45	11/44	23/44[c]
Simple or stratified cuboidal or squamous metaplasia of epithelium in the dorsomedial area where respiratory and olfactory epithelium join[a]	0/45	2/44	23/44[c]
Focal replacement of olfactory epithelium by respiratory, respiratory-like or regenerating olfactory epithelium			
Very slight	0/45	0/44	1/44
Slight	0/45	0/44	12/44[c]
Moderate	0/45	0/44	12/44[c]
Severe	0/45	0/44	1/44

[a]See above for explanation; [b]$p < 0.05$; [c]$p < 0.01$

Woutersen et al. (1987)

Wistar rats; male and female; 10/sex/group.
Exposure: Rats were exposed to FA in dynamic whole-body chambers for 6 hours/day, 5 days/week for 13 weeks.
Test article: Paraformaldehyde.
Actual concentrations were 0, 1.2 (±0.00), 11.9 (±0.15), or 24.4 (±0.09) mg/m^3.[a]
Histopathology: sections of the lungs, trachea, larynx (3 longitudinal) and nose (6 standard cross sections).

[Males] Histological changes in the nose at 13 weeks

	Incidence of lesions			
	0 mg/m^3	1.2 mg/m^3	11.9 mg/m^3	24.4 mg/m^3
Respiratory epithelial squamous metaplasia				
Diffuse				
Slight	0/10	0/10	0/10	0/10
Moderate	0/10	0/10	0/10	5/10[a]
Severe	0/10	0/10	0/10	5/10[a]
Focal				
Very slight	0/10	1/10	0/10	0/10
Slight	0/10	1/10	6/10[a]	0/10
Moderate	0/10	0/10	4/10	0/10
Focal respiratory epithelial hyperplasia				
Very slight	0/10	0/10	1/10	1/10
Slight	0/10	0/10	6/10[a]	7/10[b]
Moderate	0/10	0/10	1/10	0/10
Focal respiratory epithelial disarrangement				
Very slight	0/10	0/10	1/10	0/10
Slight	0/10	0/10	3/10	0/10
Moderate	0/10	0/10	1/10	0/10
Focal respiratory epithelial keratinization				
Very slight	0/10	2/10	6/10[a]	1/10
Slight	0/10	0/10	3/10	6/10[a]
Moderate	0/10	0/10	0/10	1/10
Focal olfactory epithelial thinning				
Slight	0/10	0/10	0/10	2/10
Moderate	0/10	0/10	0/10	1/10
Severe	0/10	0/10	0/10	5/10[a]
Focal olfactory epithelial squamous metaplasia				

Reference and study design	Results				
	Slight	0/10	0/10	0/10	4/10
	Moderate	0/10	0/10	0/10	4/10
	Olfactory epithelial keratinization				
	Very slight	0/10	0/10	0/10	1/10
	Slight	0/10	0/10	0/10	2/10
	Rhinitis	0/10	2/10	5/10[a]	10/10[b]
	Slight submucosal loosely arranged connective tissue	0/10	0/10	0/10	2/10
	Pharyngeal duct mononuclear cell infiltrate	9/10	10/10	10/10	8/10
	Nasolachrymal duct sinusitis	3/10	6/10	7/10	2/10
	Maxillary sinus sinusitis	7/10	3/10	4/10	2/10
	[a]$p < 0.05$; [b]$p < 0.01$				
	[Females] Histological changes in the nose at 13 weeks				
		Incidence of lesions			
		0 mg/m^3	1.2 mg/m^3	11.9 mg/m^3	24.4 mg/m^3
	Respiratory epithelial squamous metaplasia				
	Diffuse				
	Slight	0/10	0/10	0/10	3/10
	Moderate	0/10	0/10	0/10	4/10
	Severe	0/10	0/10	0/10	3/10
	Focal				
	Very slight	0/10	0/10	1/10	0/10
	Slight	0/10	1/10	7/10[b]	0/10
	Moderate	0/10	0/10	2/10	0/10
	Focal respiratory epithelial hyperplasia				
	Very slight	0/10	0/10	2/10	1/10
	Slight	0/10	1/10	6/10[a]	6/10[a]
	Moderate	0/10	0/10	0/10	0/10
	Focal respiratory epithelial disarrangement				
	Very slight	0/10	0/10	2/10	1/10
	Slight	0/10	1/10	6/10[a]	6/10[a]
	Moderate	0/10	0/10	0/10	0/10
	Focal respiratory epithelial keratinization				
	Very slight	0/10	0/10	6/10[a]	6/10[a]
	Slight	0/10	0/10	2/10	4/10
	Moderate	0/10	0/10	0/10	0/10
	Focal olfactory epithelial thinning				
	Slight	0/10	0/10	0/10	2/10
	Moderate	0/10	0/10	0/10	2/10
	Severe	0/10	0/10	0/10	2/10
	Focal olfactory epithelial squamous metaplasia				
	Slight	0/10	0/10	0/10	3/10
	Moderate	0/10	0/10	0/10	1/10
	Olfactory epithelial keratinization				
	Very slight	0/10	0/10	0/10	0/10
	Slight	0/10	0/10	0/10	0/10
	Rhinitis	0/10	0/10	3/10	2/10
	Slight submucosal loosely arranged connective tissue	0/10	0/10	0/10	4/10

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr><td></td><td>
<table>
<tr><td>Pharyngeal duct mononuclear cell infiltrate</td><td>10/10</td><td>10/10</td><td>10/10</td><td>10/10</td></tr>
<tr><td>Nasolachrymal duct sinusitis</td><td>3/10</td><td>5/10</td><td>2/10</td><td>4/10</td></tr>
<tr><td>Maxillary sinus sinusitis</td><td>1/10</td><td>1/10</td><td>5/10</td><td>0/10</td></tr>
</table>
[a]$p < 0.05$; [b]$p < 0.01$
Lung:
Histological changes (e.g., focal accumulation of alveolar macrophages) in the lung were considered not to be exposure related but as common findings in this strain and rat age.

Larynx:
Squamous metaplasia (males)
24.4 mg/m^3—3/10, very slight; 1/10, slight; 1/10, moderate
11.9 mg/m^3—no lesions observed
1.2 mg/m^3—no lesions observed
0 mg/m^3—no lesions observed
Very slight keratinization (males)
24.4 mg/m^3—2/10
11.9 mg/m^3—no lesions observed
1.2 mg/m^3—no lesions observed
0 mg/m^3—no lesions observed
Squamous metaplasia (females)
24.4 mg/m^3—no lesions observed
11.9 mg/m^3—not examined
1.2 mg/m^3—not examined
0 mg/m^3—no lesions observed
Very slight keratinization (females)
24.4 mg/m^3—no lesions observed
11.9 mg/m^3—not examined
1.2 mg/m^3—not examined
0 mg/m^3—no lesions observed
</td></tr>
<tr><td colspan="2">Medium Confidence</td></tr>
<tr><td>Andersen et al. (2010)
Fischer 344; male; 8/group.
Exposure: Rats were exposed to FA in dynamic whole-body chambers 6 hours/day, 5 days/week for 1, 4, or 13 weeks. Rats sacrificed immediately after last exposure.
Test article: Paraformaldehyde.
Actual concentrations reported in the Results column. Target concentrations were 0, 0.8, 2.5, 7.4, 12.3, or 18.5 mg/m^3.[a]
Histopathology: nasal sections at the nose tip and standard cross-section levels (I–V).

Main limitations: small N; data for levels III–V were not reported.</td><td>
Target and Actual FA Concentrations
<table>
<tr><td></td><td colspan="3">Actual concentration (mg/m^3) for each exposure time</td></tr>
<tr><td>Target</td><td>1 week</td><td>4 weeks</td><td>13 weeks</td></tr>
<tr><td>0</td><td>0 ± 0</td><td>0 ± 0</td><td>0 ± 0</td></tr>
<tr><td>0.8</td><td>0.77 ± 0.06</td><td>0.8 ± 0.09</td><td>0.83 ± 0.07</td></tr>
<tr><td>2.5</td><td>2.5 ± 0.0</td><td>2.5 ± 0.0</td><td>2.5 ± 0.1</td></tr>
<tr><td>7.4</td><td>7.3 ± 0.2</td><td>7.4 ± 0.2</td><td>7.4 ± 0.2</td></tr>
<tr><td>12.3</td><td>12.2 ± 0.6</td><td>12.3 ± 0.7</td><td>12.3 ± 0.7</td></tr>
<tr><td>18.5</td><td>18.9 ± 0.1</td><td>18.5 ± 0.6</td><td>18.3 ± 0.5</td></tr>
</table>
Incidence and severity of nasal squamous metaplasia[a]
<table>
<tr><td></td><td colspan="6">FA (target concentrations)</td></tr>
<tr><td>Region</td><td>0 mg/m^3</td><td>0.8 mg/m^3</td><td>2.5 mg/m^3</td><td>7.4 mg/m^3</td><td>12.3 mg/m^3</td><td>18.5 mg/m^3</td></tr>
<tr><td>Level I</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>1 week</td><td>4[b] (1)[c]</td><td>5 (1)</td><td>8 (1.9)</td><td>8 (1.6)</td><td>8 (1.5)</td><td>6 (1.2)</td></tr>
<tr><td>4 weeks</td><td>1 (1)</td><td>6 (1)</td><td>7 (1)</td><td>8 (1.5)</td><td>8 (1.7)</td><td>8 (2.2)</td></tr>
<tr><td>13 weeks</td><td>1 (1)</td><td>2 (1)</td><td>8 (1.1)</td><td>8 (1.8)</td><td>8 (1.9)</td><td>8 (2.4)</td></tr>
<tr><td>Level II</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>1 week</td><td>0 (NA)</td><td>0 (NA)</td><td>0 (NA)</td><td>6 (1.1)</td><td>8 (1.5)</td><td>8 (1.5)</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr><td></td><td>
<table>
<tr><td>4 weeks</td><td>0 (NA)</td><td>0 (NA)</td><td>0 (NA)</td><td>5 (1)</td><td>8 (1.2)</td><td>8 (1.7)</td></tr>
<tr><td>13 weeks</td><td>0 (NA)</td><td>0 (NA)</td><td>0 (NA)</td><td>0 (NA)</td><td>8 (2.9)</td><td>8 (3.4)</td></tr>
</table>
Data NR for levels III, IV, and V.
[a]Squamous metaplasia diagnosed in areas with change in transitional or respiratory epithelium to squamous epithelium, with or without keratinization; [b]8 animals examined at each time point and dose; [c]Average severity score (1 = minimal, 2 = slight/mild, 3 = moderate, 4 = moderately severe).

Incidence of nasal necrosis/erosion
<table>
<tr><td></td><td colspan="4">FA (target concentrations)</td></tr>
<tr><td>Region</td><td>0 mg/m^3</td><td>7.4 mg/m^3</td><td>12.3 mg/m^3</td><td>18.5 mg/m^3</td></tr>
<tr><td>Level I</td><td></td><td></td><td></td><td></td></tr>
<tr><td>1 week</td><td>0[a]</td><td>6</td><td>8</td><td>8</td></tr>
<tr><td>4 weeks</td><td>0</td><td>3</td><td>3</td><td>6</td></tr>
<tr><td>13 weeks</td><td>0</td><td>0</td><td>7</td><td>4</td></tr>
<tr><td>Level II</td><td></td><td></td><td></td><td></td></tr>
<tr><td>1 week</td><td>0</td><td>0</td><td>7</td><td>7</td></tr>
<tr><td>4 weeks</td><td>0</td><td>0</td><td>5</td><td>8</td></tr>
<tr><td>13 weeks</td><td>0</td><td>0</td><td>0</td><td>6</td></tr>
</table>
Lesions ND at 0.8 and 2.5 mg/m^3.
[a]8 animals examined at each time point and dose.
</td></tr>
<tr><td>Rusch et al. (1983)
Fischer 344 rats; male and female; 20/group.
Exposure: Rats were exposed to FA in dynamic whole-body chambers for 22 hours/day, 7 days/week for 26 weeks.
Test article: Unstabilized 5% solution of formaldehyde (0.03% methanol).
Actual concentrations were 0.23 (±0.02), 1.2 (±0.1), or 3.6 (±0.22) mg/m^3.[a] Controls exposed to 0.011 (±0.009) mg/m^3.
Histopathology: Four sections of lung, one section of trachea, and three transverse sections of nasal turbinates (anterior, middle, and posterior regions) and one transverse section of ethmoturbinate.

Main limitations: lesion severities were NR; data only reported for one section; metaplasia and hyperplasia reported together.</td><td>
Microscopic evaluation of lungs and trachea for Groups I, III, V, and VI showed lesions frequently observed in laboratory animals but not considered exposure-related. Electron microscopic evaluation for Group I and II animals (5/sex) did not reveal turbinate, tracheal, or pulmonary ultrastructure changes associated with treatment.

Observations in middle region of nasal turbinate
<table>
<tr><th>Group</th><th>Exposure</th><th>Squamous metaplasia and hyperplasia</th><th>Basal cell hyperplasia</th></tr>
<tr><td>I (control for II and III)</td><td>0 mg/m^3</td><td>2/38</td><td>0/38</td></tr>
<tr><td>II</td><td>0.23 mg/m^3</td><td>1/38</td><td>0/38</td></tr>
<tr><td>III</td><td>1.2 mg/m^3</td><td>3/36</td><td>0/36</td></tr>
<tr><td>V (control for VI)</td><td>0 mg/m^3</td><td>3/39</td><td>4/39</td></tr>
<tr><td>VI</td><td>3.6 mg/m^3</td><td>23/37</td><td>25/37</td></tr>
</table>
For anterior nasal turbinates, no evidence of exposure-related effects with the possible exception for Group VI. When comparing to Group V, fourfold increase for the incidences of squamous metaplasia/hyperplasia and basal cell hyperplasia in Group VI; for posterior nasal turbinates, only Group VI showed evidence of squamous metaplasia (3/37); no evidence of exposure-related effects in ethmoturbinates; level of rhinitis comparable in Groups I, II, and III, but most frequent in Group VI.
</td></tr>
<tr><td>Wilmer et al. (1989)
Wistar rats; male; 25/group.
Exposure: Rats were exposed to FA in dynamic whole-body chambers either continuously for 8 hours/day, 5 days/week for 13 weeks or intermittently 8 hours/day (successive periods of 0.5 hour of exposure</td><td>
Histopathological changes in respiratory epithelium (cross section II) observed after 13 weeks of exposure
<table>
<tr><td></td><td colspan="5">Incidence of lesions</td></tr>
<tr><td></td><td>A</td><td>B</td><td>C</td><td>D</td><td>E</td></tr>
<tr><td></td><td>Control</td><td>1.23 mg/m^3 Contin.</td><td>2.46 mg/m^3 Contin.</td><td>2.46 mg/m^3 Inter.</td><td>4.92 mg/m^3 Inter.</td></tr>
<tr><td>Disarrangement</td><td></td><td></td><td></td><td></td><td></td></tr>
</table>
</td></tr>
</table>

Reference and study design	Results
and 0.5 hour of nonexposure), 5 days/week for 13 weeks. *Test article*: Paraformaldehyde. Actual concentrations were not determined. Target concentrations were 0, 1.23, or 2.46 mg/m^3 for continuous exposures and 0, 2.46, or 4.92 mg/m^3 for intermittent exposures.[a] *Histopathology:* 6 standard cross sections of the nose [note: same as Woutersen et al. (1989)] **Main limitations:** analytical concentrations and lesion severities were not reported.	Focal 12/25 4/22 8/24 3/23[a] 8/25 Diffuse 1/25 1/22 0/24 15/23[c] 11/25[b] **Necrosis** Focal 4/25 3/22 0/24 2/23 3/25 Diffuse 0/25 0/22 0/24 2/23 2/25 **Basal cell hyperplasia** Focal 9/25 4/22 6/24 11/23 10/25 Diffuse 4/25 0/22 0/24 4/23 11/25 **Squamous metaplasia** Focal 5/25 0/22 1/24 7/23 16/25[b] **Keratinization** 0/25 0/22 1/24 0/23 3/25 **Nest-like infolds** Focal 5/25 4/22 11/24 14/23[b] 7/25 Diffuse 0/25 3/22 1/24 0/23 1/25 **Goblet cell hyperplasia** Focal 0/25 1/22 1/24 2/23 1/25 Diffuse 5/25 2/22 8/24 13/23[a] 10/25 **Rhinitis** 3/25 2/22 3/24 16/23[c] 8/25 A = 0 mg/m^3; B = 1.23 mg/m^3 continuous (9.8 mg/m^3 h/d); C = 2.46 mg/m^3 continuous (19.7 mg/m^3 h/d); D = 2.46 mg/m^3 intermittent (9.8 mg/m^3 h/d); E = 4.92 mg/m^3 intermittent (19.7 mg/m^3 h/d). [a]$p < 0.05$; [b]$p < 0.01$; [c]$p < 0.001$.
Zwart et al. (1988) Wistar rats; male and female; 50/group/sex. *Exposure*: Rats were exposed to FA in dynamic whole-body chambers 6 hours/day, 5 days/week for 13 weeks. *Test article*: Paraformaldehyde. Actual concentrations were 0, 0.37 (±0.02), 1.2 (±0.10), or 3.7 (±0.27) mg/m^3.[a] *Histopathology:* 6 standard cross sections of the nose [note: same as Woutersen et al. (1989)] **Main limitations:** failed to completely report lesion incidence and lesion severities were not reported.	*[Data only reported for cross sections II and III]* **3 days:** Nose: 3.7 mg/m^3—Focal basal cell hyperplasia concomitant with loss of cilia observed at section III, number of rats and sex NR. Histological changes NR for other groups. **13 weeks:** Nose: 3.7 mg/m^3—Histological changes including epithelial disarrangement to epithelial hyperplasia and squamous metaplasia (with or without keratinization) found in 37/50 males and 21/50 females. Changes localized to the anterior part of section II that is normally covered by respiratory epithelium. Histological changes NR for other exposure groups at section II. No histological changes in respiratory epithelium observed in section III for any rat exposed to FA. Statistically significant differences in the incidences of inflammatory lesions (e.g., rhinitis, sinusitis, and aggregates of mononuclear cell infiltrates) in the pharyngeal ducts observed between control and treatment groups, although quantitative data NR and exposure-related response was absent. 3.7 mg/m^3—Electron microscopic evaluation revealed: changes in nasal septa epithelium including loss of cilia, but not slender microvilli; strongly indented and disarranged epithelial cell nuclei; the presence of small blood vessels; interdigitations between epithelial cells and the presence of cilia in intracellular spaces; foci of keratinized squamous epithelium; and glandularization of goblet cells, which were arranged in gland-like structures. 0.37 and 1.2 mg/m^3—Electron microscopic evaluation of section II showed no differences except for irregularly shaped and strongly indented nuclei when compared to controls.
Mice	

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr><td colspan="2">Medium confidence</td></tr>
<tr><td>Maronpot et al. (1986)
B6C3F1 mice; male and female; 10/sex/group.
Exposure: Mice were exposed to FA in dynamic whole-body chambers for 6 hours/day, 5 days/week for 13 weeks.
Test article: Formalin (9.2% w/v), assumed to contain methanol.
Actual concentrations were 2.41 (±0.25), 5.02 (±0.62), 12.4 (±0.80), 25.1 (±1.1), or 49.6 (±3.2) mg/m^3.
Histopathology: sections of the nasal turbinates (3 sections), larynx, trachea, and lung.

Main limitations: formalin; small N</td><td>Lesions after 13 weeks of exposure:
<table>
<tr><th>mg/m^3:</th><th colspan="2">0</th><th colspan="2">5.02</th><th colspan="2">12.4</th><th colspan="2">25.1</th><th colspan="2">49.6</th></tr>
<tr><th>Nasal cavity</th><th>M</th><th>F</th><th>M</th><th>F</th><th>M</th><th>F</th><th>M</th><th>F</th><th>M</th><th>F</th></tr>
<tr><td>Metaplasia, squamous</td><td>0/10</td><td>0/10</td><td>1/10</td><td>0/10</td><td>10/10</td><td>10/10</td><td>10/10</td><td>10/10</td><td>10/10</td><td>10/10</td></tr>
<tr><td>Inflammation, seropurulent</td><td>0/10</td><td>0/10</td><td>0/10</td><td>0/10</td><td>4/10</td><td>0/10</td><td>10/10</td><td>8/10</td><td>10/10</td><td>10/10</td></tr>
</table>
No lesions observed after exposure to 2.41 mg/m^3.
<table>
<tr><th>mg/m^3:</th><th colspan="2">0</th><th colspan="2">25.1</th><th colspan="2">49.6</th></tr>
<tr><th></th><th>M</th><th>F</th><th>M</th><th>F</th><th>M</th><th>F</th></tr>
<tr><td>Larynx</td></tr>
<tr><td>Metaplasia, squamous</td><td>0/8</td><td>0/8</td><td>6/9</td><td>3/9</td><td>10/10</td><td>7/8</td></tr>
<tr><td>Trachea</td></tr>
<tr><td>Metaplasia, squamous</td><td>0/10</td><td>0/9</td><td>3/10</td><td>5/10</td><td>10/10</td><td>10/10</td></tr>
<tr><td>Hyperplasia, epithelial</td><td>0/10</td><td>0/9</td><td>4/10</td><td>2/10</td><td>2/10</td><td>0/10</td></tr>
<tr><td>Inflammation, purulent</td><td>0/10</td><td>0/9</td><td>0/10</td><td>0/10</td><td>8/10</td><td>5/10</td></tr>
<tr><td>Fibrosis, submucosal</td><td>0/10</td><td>0/9</td><td>0/10</td><td>0/10</td><td>9/10</td><td>5/10</td></tr>
<tr><td>Lung</td></tr>
<tr><td>Bronchus, metaplasia squamous</td><td>0/10</td><td>0/10</td><td>0/10</td><td>0/10</td><td>4/10</td><td>3/10</td></tr>
<tr><td>Bronchus, inflammation</td><td>0/10</td><td>0/10</td><td>0/10</td><td>0/10</td><td>3/10</td><td>2/10</td></tr>
<tr><td>Bronchus, fibrosis, submucosal</td><td>0/10</td><td>0/10</td><td>0/10</td><td>0/10</td><td>2/10</td><td>0/10</td></tr>
</table>
No laryngeal lesions observed after 2.41, 5.02, or 12.4 mg/m^3; no tracheal lesions observed after 2.41, 5.02, or 12.4 mg/m^3, except 1/10 females (squamous metaplasia) after 12.4 mg/m^3; no lung lesions after 12.4 mg/m^3; data were NR for 2.41 and 5.02 mg/m^3.</td></tr>
<tr><td colspan="2">Hamsters</td></tr>
<tr><td colspan="2">Medium confidence</td></tr>
<tr><td>Rusch et al. (1983)
Syrian golden hamsters; male and female; 10/sex/group.
Exposure: Hamsters were exposed to FA in dynamic whole-body chambers for 22 hours/day, 7 days/week for 26 weeks.
Test article: Unstabilized 5% solution of formaldehyde (0.03% methanol).
Actual concentrations were 0.23 (±0.02), 1.2 (±0.1), or 3.6 (±0.22) mg/m^3.[a] Controls were exposed to 0.011 (±0.009) mg/m^3.
Histopathology: 4 sections of lung, 1 section of trachea, and the hamster equivalent of the rat turbinate sections (i.e., 3 transverse sections of nasal</td><td>Microscopic evaluation of lungs and trachea for Groups I (controls for Groups II and III), III (1.2 mg/m^3), V (controls for Group VI), and VI (3.6 mg/m^3) showed lesions frequently observed in laboratory animals but not considered exposure related. Histopathological data for Group II (0.23 mg/m^3) not reported.

No evidence of exposure-related effects for the incidence of squamous metaplasia even at 3.6 mg/m^3 exposure level.</td></tr>
</table>

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr><td>turbinates [anterior, middle, and posterior regions] and one transverse section of ethmoturbinate).

Main limitations: lesion incidences NR (note: only metaplasia was investigated).</td><td></td></tr>
<tr><td colspan="2">Monkeys</td></tr>
<tr><td colspan="2">Medium confidence</td></tr>
<tr><td>Rusch et al. (1983)
Cynomolgus monkeys; male; 6/group.
Exposure: Monkeys were exposed to FA in dynamic whole-body chambers for 22 hours/day, 7 days/week for 26 weeks.
Test article: Unstabilized 5% solution of formaldehyde (0.03% methanol).
Actual concentrations were 0.23 (±0.02), 1.2 (±0.1), or 3.6 (±0.22) mg/m^3. Controls exposed to 0.011 (±0.009) mg/m^3.[a]
Histopathology: 4 sections of lung, 1 section of trachea, and the monkey equivalent of the rat turbinate sections (i.e., 3 transverse sections of nasal turbinates [anterior, middle, and posterior regions] and one transverse section of ethmoturbinate).

Main limitations: lesion severities NR; incidence of squamous metaplasia and hyperplasia reported together; data reported for only one nasal section.</td><td>Microscopic evaluation of lungs and trachea for Groups I (controls for Groups II and III), III (1.2 mg/m^3), V (controls for Group VI), and VI (3.6 mg/m^3) showed lesions frequently observed in laboratory animals but not considered exposure related. Histopathological data for Group II (0.23 mg/m^3) not reported.

Observations in middle region of nasal turbinate
<table><tr><th>Group</th><th>Exposure</th><th>Squamous metaplasia and hyperplasia</th></tr><tr><td>I (control for II and III)</td><td>0 mg/m^3</td><td>0/6</td></tr><tr><td>II</td><td>0.23 mg/m^3</td><td>0/6</td></tr><tr><td>III</td><td>1.2 mg/m^3</td><td>1/6</td></tr><tr><td>V (control for VI)</td><td>0 mg/m^3</td><td>0/6</td></tr><tr><td>VI</td><td>3.6 mg/m^3</td><td>6/6</td></tr></table>For anterior and posterior nasal turbinates, no exposure-related effects reported.
Rhinitis observed in numerous animals from all Groups but with no apparent exposure-response.
For Group VI, observations of hoarseness, congestion, and nasal discharge were reported.</td></tr>
</table>

Abbreviations: FA = formaldehyde; NR = not reported, SD = standard deviation.
[a]Study authors originally reported FA concentrations in ppm. These values were converted based on 1 ppm = 1.23 mg/m^3, assuming 25°C and 760 mm Hg.

Table 1-28. Selected short-term respiratory pathology studies in animals (see Appendix A.5.5 for others)

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr><td colspan="2">Rats</td></tr>
<tr><td colspan="2">High confidence</td></tr>
<tr><td>Kuper et al. (2011)
Fischer rats; males; 8/group.
Exposure: Mice were exposed to FA in dynamic whole-body chambers 6 hours/day, 5 day/week for 4 weeks.
Test article: Formalin (10.21% FA; although NR, the description supports the assumption that it was freshly prepared).Actual concentrations were 0, 0.63 (±0.06), 1.23 (±0.14), 2.48 (±0.18), 7.53 (±0.42), 12.3 (±0.48), and 18.4 (±0.06) mg/m^3.[a]
Histopathology: 2 sections of nasopharynx-associated lymphoid tissues (NALT) and one section of an upper respiratory tract-draining lymph node (i.e., posterior and superficial cervical lymph nodes).

Note: small N</td><td>Incidence of lesions/changes after 4 weeks
<table>
<tr><td></td><td colspan="7">FA (mg/m^3)</td></tr>
<tr><td>NALT</td><td>0</td><td>0.63</td><td>1.23</td><td>2.48</td><td>7.53</td><td>12.3</td><td>18.4</td></tr>
<tr><td>Size</td></tr>
<tr><td>Very small</td><td>1</td><td>0</td><td>0</td><td>1</td><td>0</td><td>2</td><td>1</td></tr>
<tr><td>Small</td><td>2</td><td>1</td><td>2</td><td>2</td><td>3</td><td>3</td><td>6</td></tr>
<tr><td>Medium</td><td>2</td><td>7</td><td>5</td><td>5</td><td>5</td><td>3</td><td>1</td></tr>
<tr><td>Large</td><td>3</td><td>0</td><td>1</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Decreased cellularity</td></tr>
<tr><td>Slight</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>1</td></tr>
<tr><td>Moderate</td><td>0</td><td>0</td><td>0</td><td>1</td><td>0</td><td>0</td><td>2</td></tr>
<tr><td>Germinal center development</td></tr>
<tr><td>Very slight</td><td>1</td><td>5</td><td>3</td><td>3</td><td>3</td><td>3</td><td>0</td></tr>
<tr><td>Moderate</td><td>3</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Score expanded total</td><td>4</td><td>5</td><td>3</td><td>3</td><td>3</td><td>3</td><td>0</td></tr>
<tr><td>Epithelial hyperplasia</td></tr>
<tr><td>Slight</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>2</td></tr>
<tr><td>Moderate</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>5</td></tr>
<tr><td>Score expanded total</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>7[a]</td></tr>
</table>
[a]$p < 0.01$.

Incidence of lesions/changes after 4 weeks
<table>
<tr><td></td><td colspan="7">FA (mg/m^3)</td></tr>
<tr><td></td><td>0</td><td>0.63</td><td>1.23</td><td>2.48</td><td>7.53</td><td>12.3</td><td>18.4</td></tr>
<tr><td>Posterior cervical lymph nodes</td></tr>
<tr><td>Germinal center development</td></tr>
<tr><td>Very slight</td><td>3</td><td>3</td><td>2</td><td>4</td><td>4</td><td>5</td><td>5</td></tr>
<tr><td>Slight</td><td>0</td><td>1</td><td>2</td><td>1</td><td>2</td><td>0</td><td>0</td></tr>
<tr><td>Moderate</td><td>1</td><td>0</td><td>1</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Marked</td><td>1</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Very marked</td><td>0</td><td>1</td><td>0</td><td>0</td><td>0</td><td>1</td><td>1</td></tr>
<tr><td>Score expanded totals</td><td>5</td><td>5</td><td>5</td><td>5</td><td>6</td><td>6</td><td>6</td></tr>
<tr><td>Superficial cervical lymph nodes</td></tr>
<tr><td>Germinal center development</td></tr>
<tr><td>Very slight</td><td>5</td><td>3</td><td>2</td><td>0</td><td>3</td><td>1</td><td>0</td></tr>
<tr><td>Very marked</td><td>0</td><td>0</td><td>1</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Score expanded totals</td><td>5</td><td>3</td><td>3</td><td>0[a]</td><td>3</td><td>1</td><td>0[a]</td></tr>
</table>
[a]$p < 0.05$.</td></tr>
</table>

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr><td colspan="2">Medium confidence</td></tr>
<tr><td>Wilmer et al. (1987)
Wistar rats; male; 10/group.
Exposure: Rats were exposed to FA in a dynamic whole-body chamber either continuously for 8 hours/day, 5 days/week for 4 weeks or intermittently 8 hours/day (successive periods of 0.5 hour of exposure and 0.5 hour of nonexposure), 5 days/week for 4 weeks.
Test article: Paraformaldehyde.
Actual concentrations were not determined. Target concentrations were 0, 6.2, or 12.3 mg/m^3 for continuous exposures and 0, 12.3, or 24.6 mg/m^3 for intermittent exposures.[1]
Histopathology: 6 standard nasal cross sections.

Main limitations: analytical concentrations NR; lesion incidence and severities NR</td><td>Respiratory epithelium:
Focal thinning and disarrangement of mainly the lateral wall observed in all animals exposed to 24.6 mg/m^3.
Squamous metaplasia and basal cell hyperplasia observed mainly in 12.3 and 24.6 mg/m^3.
Rhinitis (minimal to moderate) observed in all groups.

Severity of nasal lesions
<table><tr><td>intermittent exposure to 24.6 mg/m^3 (98.4 mg/m^3-h/day)</td><td>></td><td>continuous exposure to 12.3 mg/m^3 (98.4 mg/m^3-h/day)</td></tr><tr><td>intermittent exposure to 12.3 mg/m^3 (49.2 mg/m^3-h/day)</td><td>></td><td>continuous exposure to 6.2 mg/m^3 (49.6 mg/m^3-h/day)</td></tr><tr><td>intermittent exposure to 12.3 mg/m^3 (49.2 mg/m^3-h/day)</td><td>=</td><td>continuous exposure to 12.3 mg/m^3 (98.4 mg/m^3-h/day)</td></tr></table></td></tr>
<tr><td colspan="2">Mice</td></tr>
<tr><td colspan="2">High confidence</td></tr>
<tr><td>Kuper et al. (2011)
B6C3F1 mice; females; 6/group.
Exposure: Mice were exposed to FA in dynamic whole-body chambers 6 hours/day, 5 day/week for 4 weeks.
Test article: Formalin (10.21% FA; although NR, the description supports the assumption that it was freshly prepared).
Actual concentrations were 0, 0.63 (±0.06), 1.23 (±0.14), 2.48 (±0.18), 7.53 (±0.42), 12.3 (±0.48), and 18.4 (±0.06) mg/m^3.[a]
Histopathology: 2 sections of nasopharynx-associated lymphoid tissues (NALT) and one section of an upper respiratory tract-draining lymph node (i.e., posterior and superficial cervical lymph nodes).

Note: small N</td><td><table><tr><td>Group</td><td>Observation</td></tr><tr><td>Controls</td><td>NALT: varied in size from small to large; scarce germinal centers</td></tr><tr><td>Exposed</td><td>Posterior and cervical lymph nodes: no FA-related changes

NALT: no FA-related changes; no significant change in size compared to controls; scarce germinal centers</td></tr></table></td></tr>
<tr><td colspan="2">Medium confidence</td></tr>
<tr><td>Morgan et al. (2017)
C3B6.129F1-Trp53^{tm1Brd} (C3B6 TP53±) and B6.129-Trp53^{tm1Brd} (B6 TP53±) mice; males; 24-35/group
Exposure: Mice were exposed to FA in dynamic whole-body chambers 6 hours/day, 5 day/week for 8 weeks.
Test article: Paraformaldehyde</td><td>Incidence (and severity) of noncancer nasal lesions at 32 weeks post-exposure
<table><tr><td></td><td>FA (mg/m^3)</td><td></td><td></td></tr><tr><td></td><td>0</td><td>9.23</td><td>18.45</td></tr><tr><td colspan="4">C3B6 TP53± mice</td></tr><tr><td>Squamous Metaplasia (respiratory epithelium)</td><td>0/21</td><td>14/21 (1.2)</td><td>22/23 (1.5)</td></tr><tr><td>Hyperplasia (respiratory epithelium)</td><td>0/21</td><td>0/21</td><td>1/23 (1.0)</td></tr></table></td></tr>
</table>

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr><td>Nominal concentrations were 0, 9.23, or 18.45 mg/m^3.[a]
Histopathology: 3 sections of the nasal cavity and one section of the larynx

Main limitations: somewhat limited sampling and minor reporting limitations; potentially short duration (however, lesions are observed)</td><td>
<table>
<tr><td>Osteogenesis (turbinate)</td><td>0/21</td><td>0/21</td><td>3/23 (3.0)</td></tr>
<tr><td colspan="4">B6 TP53± mice</td></tr>
<tr><td>Squamous Metaplasia (respiratory epithelium)</td><td>0/22</td><td>13/27 (1.0)</td><td>17/26 (1.5)</td></tr>
<tr><td>Osteogenesis (turbinate)</td><td>0/22</td><td>1/27 (1.0)</td><td>1/26 (1.0)</td></tr>
</table>
Average severity score based on 1= minimal; 2= mild; 3= moderate; 4= marked
No laryngeal lesions were reported</td></tr>
<tr><td colspan="2">Monkeys</td></tr>
<tr><td colspan="2">Medium confidence</td></tr>
<tr><td>Monticello et al. (1989)
Rhesus monkeys; males; 3/group.
Exposure: Monkeys were exposed to FA in dynamic whole-body chambers 6 hours/day, 5 days/week for 1 or 6 weeks.
Test article: Paraformaldehyde.
Actual concentrations were not determined. Target concentration was 0 or 7.4 mg/m^3.[a]
Histopathology: 5 transverse sections of the nasal passages (A-E) extending from the nares to the soft palate. The evaluation also included cross sections of larynx and mid-trachea, a frontal section of the carina, and sections of all lung lobes, which were trimmed mid-sagitally to include airway bifurcations.

Main limitations: analytical concentrations NR; lesion incidence and severities NR</td><td>
<table>
<tr><th>Exposure</th><th>Observations (truncated from original article)</th></tr>
<tr><td>Control</td><td>Nasal passages
Four types of epithelium lining rhesus nasal passages were identified:
(1) stratified squamous in the vestibule (Level A); (2) transitional (Level A), present in narrow zone just posterior to vestibule; (3) olfactory in mid-dorsal region (Levels B–D); and (4) respiratory, the most extensive (Levels B–E) and present throughout remaining areas.

Extranasal respiratory tract
Typical pseudostratified columnar respiratory epithelium observed for the larynx, trachea, and major bronchi; mild inflammatory changes from pulmonary acariasis in one monkey</td></tr>
<tr><td>7.4 mg/m^3
1-week</td><td>Nasal passages
Characteristic changes in respiratory epithelium described as generally being bilaterally symmetrical and consistent in nature and severity for all three monkeys in group

Changes included loss of goblet cells and cilia, minimal-to-mild epithelial hyperplasia with or without early stages of squamous metaplasia, and an accompanying neutrophilic inflammatory response

Squamous metaplasia present in various stages; metaplastic epithelium eroded (mild) in some areas; neutrophils occasionally found in metaplastic epithelium; maxillary sinuses exhibited no treatment-related lesions

Extranasal respiratory tract
Lesions of larynx, trachea, and carina were considered mild and included multifocal loss of cilia; extent of lesions covering surface area of larynx/trachea of 1-week group (3.0 ± 1.3%) was minimal compare to 6-week group (26.0 ± 10.0%); no treatment-related lesions in lungs</td></tr>
<tr><td>7.4 mg/m^3
6-week</td><td>Erosions absent; mild squamous metaplasia (more developed than in 1-week group); maxillary sinuses exhibited no treatment-related lesions; in two monkeys, olfactory epithelium exhibited small discrete areas of mild squamous metaplasia close to olfactory/respiratory epithelial interface</td></tr>
</table>
</td></tr>
</table>

Reference and study design	Results	
		Extranasal respiratory tract Lesions included multifocal areas of respiratory mucosa with loss of cilia and goblet cells, mild epithelial hyperplasia, and early squamous metaplasia with occasional squamous cell formation on the surface; no treatment-related lesions in lungs
	Exposure	Morphometric analysis of monkey nasal passages
	7.4 mg/m^3 1-week	Anterio-posterior severity gradient for percentage of surface area with treatment-related lesions
	7.4 mg/m^3 6-week	Of all nasal passage regions, middle turbinate had greatest percentage of surface area affected Greater respiratory epithelium surface area with treatment-related lesions compared with 1-week group ($p \leq 0.05$) More extensive lesions in the posterior nasal passages (Levels D–E) and larynx/trachea compared with same locations in 1-week group ($p \leq 0.05$)
	7.4 mg/m^3 1- and 6-week	Anterior regions (Levels B–C) had highest percentage of nasal mucosal surface area with treatment-related lesions

Abbreviations: FA = formaldehyde, NA = not applicable, ND = not detected, NR = not reported, SD = standard deviation, SE = standard error of the mean.
[a]Study authors originally reported FA concentrations in ppm. These values were converted based on 1 ppm = 1.23 mg/m^3, assuming 25°C and 760 mm Hg.

Evidence on Mode of Action for Respiratory Tract Pathology

Based primarily on studies in experimental animals or acutely exposed human volunteers (most of these endpoints are difficult to examine in long-term observational epidemiology studies), induction of histopathological lesions in the respiratory tract following formaldehyde exposure appears to result, at least in part, from a series of increasingly severe effects, including altered mucociliary function, damage to the nasal epithelium (e.g., sustained cytotoxicity), and sustained reparative cell proliferation culminating in a hyperplastic epithelium, or transitioning to an adaptive, metaplastic tissue (see Figure 1-18; see Appendix A.5.6 for additional details). Consistent with observations of metaplasia without hyperplasia in many of the rodent health effect studies, this pathway illustrates that metaplasia may develop following damage to the epithelium in the absence of hyperplasia (i.e., hyperplasia may not be an essential precursor). All the mechanistic events and relationships between events in the proposed pathway are based on robust or moderate evidence, indicating that this is likely a mechanism by which formaldehyde exposure causes squamous metaplasia. However, because modification of epithelial cell health and function in the URT can occur via multiple direct and indirect mechanisms following formaldehyde inhalation, which are expected to vary due to differences in both exposure duration and intensity, there are likely to be other plausible mechanisms by which formaldehyde exposure could cause this health

effect. The current understanding provides strong biological support for an association between formaldehyde exposure and respiratory tract pathology. Additionally, as many of the mechanistic events in this pathway have been observed in both humans (sometimes indirectly) and experimental animals, including effects on mucociliary function and cell proliferation, as well as evidence of elevated oxidative stress, findings from experimental animals are considered relevant to humans.

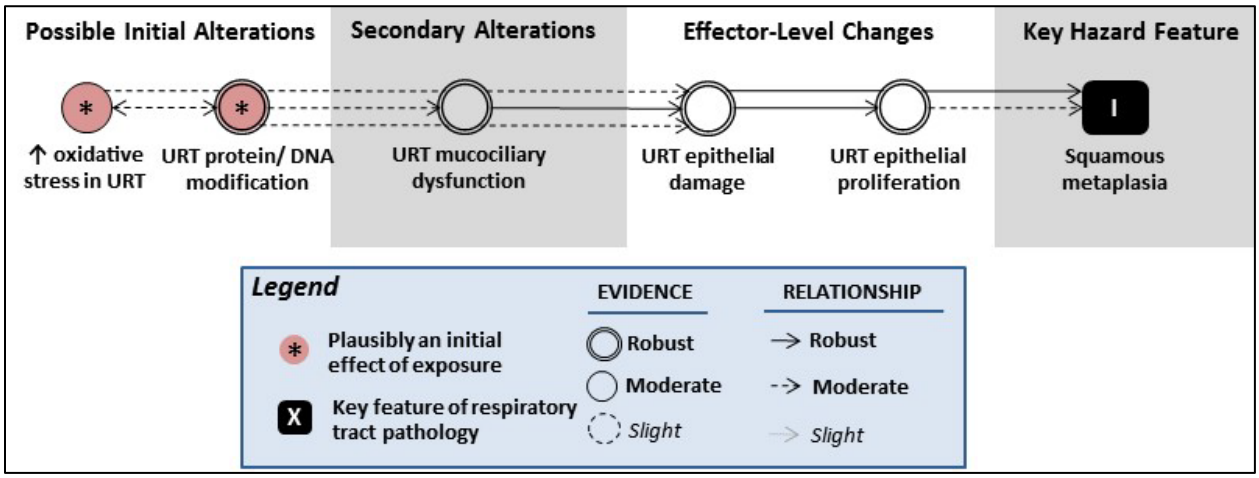


Figure 1-18. Possible mechanistic associations between formaldehyde exposure and respiratory tract pathology.

An evaluation of the formaldehyde exposure-specific mechanistic evidence informing the potential for formaldehyde exposure to cause respiratory health effects (see Table 1-29 and Appendix A.5.6) identified this sequence of mechanistic events as likely to be a mechanism by which formaldehyde inhalation could cause respiratory tract pathology, specifically squamous metaplasia, although it is assumed that other plausible pathways explaining this association have yet to be defined.

Some uncertainties remain regarding this pathway. Effects on the mucociliary system are likely secondary to the production of reactive byproducts in the URT or covalent modification to mucosal structural components following physical interactions of formaldehyde with proteins in the mucus, the latter of which at least would be expected to be driven largely by concentration. The nasal mucociliary apparatus cleans the airways by moving contaminant-laden mucus out of the URT. When damage to the cilia slows or disrupts the movement of the mucus, formaldehyde or other reactive molecules dissolved into the mucus may accumulate to a concentration that may be overtly toxic to the cells beneath the mucus. Thus, alterations to this normally protective apparatus could allow for greater access of inhaled formaldehyde (and other inhaled chemical and nonchemical substances) to epithelium lining the nasal passages (Harkema et al., 2006). Conversely, gradual tissue changes following exposure might also lead to resilience (e.g., increases in epithelial cell barrier function). Unfortunately, animal studies of mucociliary function and other detailed mechanistic studies characterizing the initial molecular interactions of formaldehyde in the URT following long-term exposure are unavailable. However, given the formaldehyde removal and

metabolism processes in the nasal respiratory epithelium (see Appendix A.2), it would generally be expected that low levels of formaldehyde would be rapidly detoxified in healthy tissues, noting that changes in mucus flow patterns have been observed at lower formaldehyde levels than those eliciting URT epithelial lesions (i.e., at ≤0.3 mg/m^3 in exposed humans and >0.6mg/m^3 in animals).

Relatedly, while both hyperplasia and metaplasia, which generally represent attempts to protect the nasal epithelium from further insult, are often correlated with areas of cell proliferation (see Appendix A.5.6), similar evaluations were not identified for lesions such as necrosis. Although cell proliferation can occur in response to tissue damage, the concentrations at which cytotoxicity and tissue damage begin to occur are poorly defined compared to other respiratory tract lesions (i.e., hyperplasia; metaplasia), partly due to differences in methodology and reporting across studies. This complicates the interpretation of the potential progression (at least in terms of concentration) of these URT changes. Regardless, since increases in cell proliferation are largely adaptive responses to replace damaged and dying cells within the epithelial tissue layer, and proliferation is typically not observed below 1.23 mg/m^3 (note: while proliferation is clearly increased above ~3.7 mg/m^3, results across studies are mixed between 1.23 and 3.7 mg/m^3; see Appendix A.5.6), cellular damage-induced proliferation at similar levels is assumed to represent an important mechanistic component for the development of URT pathology.

Interestingly, cellular proliferation "rates" (i.e., the available studies labeled dividing cells only during the last few days of exposures that varied in duration) did not appear to be strongly influenced by exposure duration (see Appendix A.5.6). Although differences exist, the general pattern of proliferation was similar across sets of studies exposing rats for either ≤1 week, 1–6 weeks, or ≥12 weeks. This similarity adds further support that cellular damage or pathology resulting in cell proliferation (i.e., hyperplasia) may not be highly dependent on exposure duration; it remains unclear whether the cumulative proliferative potential (i.e., proliferative events across the entire duration of exposure) might vary more strongly as a function of exposure duration, or to what extent this association might hold for lesions that may not be as dependent on proliferation (e.g., metaplasia). The broader implications of this relationship are discussed elsewhere (see Sections 1.2.5 (Evidence on MOA for URT cancers) and 2.2.1 and Appendix B.2.2).

In addition, there are potential modifying factors that are not illustrated in Figure 1-18. One significant uncertainty relates to the potential for inflammatory and immunological changes in the upper airways (see Sections 1.2.2 and 1.2.3), which generally have been observed only after longer formaldehyde exposures, to modify the pattern or progression of mechanistic changes leading to the development of respiratory tract pathology. This understanding is further complicated because the available data are limited both in terms of understanding the specific initiating events leading to upper airway inflammatory changes, as well as their ability to clearly define the concentration and duration requirements for effects on URT immunological processes. As with the other examined health effects, uncertainties also exist regarding interindividual sensitivity to these effects, with respiratory health status and sensitivity to allergens expected to be strong modifiers of these

effects. Nasal lesions are far more severe in rodents with prior nasal damage (e.g., Woutersen et al., 1989; Appelman et al., 1988), and similar observations have been made in exposed humans (e.g., Falk et al., 1994), while changes in mucus flow and related nasal features in allergic individuals would be expected to modify the more direct effects of formaldehyde on the mucociliary apparatus. Genetics may also play a role. For example, possibly complementing the hypothesized role of p53 in nasal genotoxicity (see Appendix A.4), two strains of p53 deficient mice (*Trp53* heterozygotes) exhibited pronounced metaplasia after short-term (8-week) exposure (Morgan et al., 2017); however, this study did not include metaplasia rates in wild-type mice for comparison[16] and there are no corresponding rat models, which would be presumed to be even more sensitive.

Overall, although uncertainties remain, the mechanistic evidence supports the conclusion that metaplasia and hyperplasia are likely to result, at least in part, from direct or indirect (e.g., through disruption of normal mucociliary function) effects on epithelial cell health, which often appears to involve sustained cellular proliferation, particularly for hyperplasia.

Table 1-29. Mechanistic evidence most informative to the development of respiratory tract pathology after formaldehyde inhalation

Endpoint		Study-specific findings and confidence	Summary of evidence	Conclusion
The majority of these mechanistic changes have been discussed in previous sections. *See Table 1-3 for presentation of the evidence for:* ↑ **URT oxidative stress** (moderate) *See Table 1-10 for presentation of the evidence for:* **URT protein/DNA modification** (robust); **URT mucociliary dysfunction** (robust); and **URT epithelial damage** (robust)				
↑ **URT Cellular (epithelial) Prolifera-tion** (see Appendix A.5.6 for additional detail and discussion)	*High or Medium*	*Human*: None (note: indirect data from human studies indicating an increase in histopathological scores that included hyperplasia were not specific enough to independently evaluate proliferation).	Increased cell proliferation in rats at all tested durations. Proliferation increases were typically observed in the anterior nasal cavity at tested levels ≥~3.5–4 mg/m^3, and were generally not observed at ≤1.23 mg/m^3. Sites of proliferation correlated with the development of hyperplasia and metaplasia, although the temporal and exposure levels specifics of this association are unclear. Indirect data from observations of	Robust
		Animal: Acute dose-dependent increases in cell proliferation in rats, measured primarily by DNA labeling during the final days of exposure, were consistently observed following acute, short-term, and subchronic exposure, and generally with a similar magnitude of responses across durations. Proliferation was typically highest in anterior regions (e.g., "level 2"), with little evidence of proliferation at ≤1.23 mg/m^3, mixed findings between 1.24 and 3.5 mg/m^3, and studies generally reporting increases with exposure at higher levels, particularly with longer exposure duration. These data are supported by consistent observations of formaldehyde exposure-induced increases in hyperplasia in pathology studies, some of which provided information showing a correlation between acute proliferation and hyperplasia and metaplasia. The only rat study that measured exposure longer than 13 weeks suggests that increases in acute proliferation may begin to decrease in magnitude with chronic exposure at ≥6 mg/m^3 (Monticello et al., 1996). A		

[16]Lesion frequency or severity in the study by NTP (2017) was not noticably different from the other available studies of wild-type mice similarly exposed to >9 mg/m^3 (i.e., 12.4 and 17.6 mg/m^3) for subchronic [e.g., (Maronpot et al., 1986)] or chronic [e.g., (Kerns et al., 1983)] duration.

Endpoint	Study-specific findings and confidence		Summary of evidence	Conclusion
		few studies suggest that mice may exhibit less robust responses than rats, while monkeys may exhibit proliferation in more posterior nasal regions at >7 mg/m^3.	hyperplasia in exposed animals and humans are consistent with these data.	
	Low	N/A: Sufficient information for 'robust' from *high or medium* confidence studies.		

Integrated Summary of Evidence on Respiratory Tract Pathology

The literature on formaldehyde effects on respiratory tract pathology in animals provides *robust* evidence that inhaled formaldehyde exposure can induce histopathologic lesions in the URT of animals, primarily in the nasal cavity, in a manner dependent on both the concentration and, to a lesser extent (particularly for hyperplasia), duration of exposure. Based on numerous *high* and *medium* confidence studies of chronic and subchronic exposure duration, formaldehyde exposure resulted in lesions in the respiratory epithelium, including goblet and basal epithelial cell hyperplasia, necrosis, and squamous metaplasia (see Tables 1-26 and 1-27). These lesions have been observed across experimental animal species, including monkeys, mice, and hamsters, but primarily in rats. In general, rats appear to be more sensitive than mice or hamsters, while the limited data in monkeys suggest a similar sensitivity to rats with possible differences in lesion location. While these lesions consistently develop in rodents of both sexes, several studies suggest an increased susceptibility of males as compared to females, potentially due to differences in breathing patterns. Presumably due to the high reactivity and water solubility of formaldehyde, these pathological lesions have been primarily assessed (and subsequently observed) in the epithelium lining the anterior regions of the rodent nasal passages following formaldehyde inhalation exposure, mostly in regions containing respiratory epithelium. Generally, at higher concentrations or longer durations, similar effects are seen in more posterior sections of the nasal cavity (and sometimes beyond), as well as in the olfactory epithelium. Additionally, lesions progress in severity (e.g., slight to moderate) at specific anatomical locations (e.g., cross-section level) with increasing concentration or duration of exposure, indicating cumulative effects. While several studies support that an increased incidence of nasal lesions such as hyperplasia and metaplasia persists after cessation of exposure, partial regression (e.g., a reduced severity or smaller increase in incidence) of these lesions appears to occur, at least in mice and rats.

Although the evidence is more equivocal in one study (Boysen et al., 1990), the four human epidemiology studies examining histopathology found that participants exposed to average formaldehyde levels between 0.05 and 0.6 mg/m^3 had a higher average histopathology score than their respective comparison group (Ballarin et al., 1992; Holmstrom et al., 1989c; Edling et al., 1988). Although the studies were limited by probable survival bias, and in some cases other limitations that resulted in a bias toward the null, a consistent association with histopathological endpoints, including squamous metaplasia, was observed. Therefore, the observational human

data provide *moderate* evidence that inhaled formaldehyde induces histopathological lesions in the URT.

Mechanistic insights based on a large amount of animal data (some similar effects were observed in humans, although the data were sparse) indicate a likely role for altered mucociliary function or cellular proliferation in the occurrence of these exposure-induced lesions (see Appendix A.5.6). Overall, the strength of the evidence for hyperplasia and squamous metaplasia includes *robust* evidence from animal studies and *moderate* human evidence from observational epidemiology studies, and strong support for a plausible MOA based largely on mechanistic evidence in animals (supported by more limited, coherent findings in human mechanistic studies), Therefore, the **evidence demonstrates** that inhalation of formaldehyde causes respiratory tract pathology in humans given the appropriate exposure circumstances. The primary basis for this conclusion is rat bioassays of chronic exposure that consistently observed squamous metaplasia at formaldehyde exposure levels ≥2.5 mg/m^3.

Table 1-30. Evidence integration summary for effects of formaldehyde inhalation on respiratory pathology

Evidence	Evidence judgment	Hazard determination
Human	*Moderate* based on: *Human health effect studies:* Of the four occupational studies interpreted with *medium* confidence (less sensitive due to healthy survival bias), 3 observed a higher prevalence of abnormal nasal histopathology, including loss of ciliated cells, hyperplasia, and squamous metaplasia at concentrations ranging from 0.1–2 mg/m^3, while the remaining (1) study had more equivocal findings. *Biological plausibility:* Mechanistic changes in two studies (one interpreted with *medium* confidence) in humans provides evidence of changes in mucociliary clearance and mucus flow beginning at formaldehyde concentrations of 0.25–0.3 mg/m^3.	The **evidence demonstrates** that inhalation of formaldehyde causes respiratory tract pathology in humans given appropriate exposure circumstances[a] Primarily based on rat bioassays of chronic exposure which consistently observed squamous metaplasia at formaldehyde exposure levels ≥2.5 mg/m^3. *Potential Susceptibilities:* Variation in sensitivity may depend on differences in URT immunity, allergen sensitivity, and nasal structure or past injury (e.g., studies support increased sensitivity of rodents with intentionally damaged nasal cavities), and males may be more sensitive than females.
Animal	*Robust,* based on: *Animal health effect studies:* • Consistent evidence of squamous metaplasia and hyperplasia in the nasal respiratory epithelium across numerous independent studies interpreted with *high or medium* confidence*,* with generally the most sensitive effects being metaplasia observed after chronic exposure to ≥2.5 mg/m^3 formaldehyde. • Evidence of both metaplasia and hyperplasia in monkeys, rats, mice, and hamsters; the data were more limited for monkeys; mice and hamsters exhibited less sensitivity. • Multiple studies provided clear evidence of a concentration dependence for lesion development, as demonstrated by increases in the incidence, severity, and anatomical location of the observed lesions with increasing exposure. *Biological plausibility:* Robust or moderate evidence for mechanistic events based predominantly on experimental animal studies supports a biological progression of changes that appears to include mucociliary dysfunction, epithelial damage, and	

	often cellular proliferation, leading to the eventual development of nasal lesions, including squamous metaplasia.	
Other inferences	• *Relevance to humans:* Similarities in the function and properties of the nasal epithelium across species, as well as similar mechanistic and apical effects observed in both humans and animals, provide strong support for the relevance of the findings in experimental animals to humans. • *MOA*: Although it may be incomplete, a MOA involving effects on mucociliary function and epithelial cell health is well supported and considered to be a major contributor to these effects. • *Other:* Data from animal studies suggest that lesion development may be driven more by concentration than duration, particularly for hyperplasia. While estimates for formaldehyde were not identified, estimates for other irritants indicate that concentration is ~1.8- to 1.9-fold (on average) more influential than duration regarding exposure-induced mortality after acute exposure.	

[a]The "appropriate exposure circumstances" are more fully evaluated and defined through dose-response analysis in Section 2.

1.2.5. Respiratory Tract Cancers

This section examines the evidence pertaining to the carcinogenic effect of formaldehyde exposure on the upper respiratory tract (URT) of humans and animals. The specific endpoints considered in this section include diagnoses of nasopharyngeal cancer, sinonasal cancer, cancers of the oropharynx and hypopharynx, and laryngeal cancer in exposed humans; experimental animal studies examining the potential for cancers of the nasal cavity and proximal regions of the URT (note: the results of several studies that also included examinations of more distal regions of the respiratory tract are discussed); and mechanistic studies relevant to interpreting potential carcinogenic effects on the URT. In humans, URT cancers were reviewed independently of one another based on primary data from case-control and cohort studies (the approximate structural delineations referred to in the section on human evidence are shown below in Figure 1-19).

Epidemiological findings provide *robust* evidence for nasopharyngeal cancers (NPCs), and sinonasal cancer, based on groups with occupational exposure. Epidemiological evidence is *slight* for oropharyngeal/hypopharyngeal cancers, and *inadequate* for laryngeal cancers, respectively. Evidence for a carcinogenic effect in the URT of humans is further supported by experimental animal studies. Precancerous lesions (e.g., dysplasia) and tumors (primarily squamous cell carcinomas) were observed in the nasal cavities of multiple species/strains of rodents. Such observations in animals were concentration and duration dependent. Mechanistic data suggest that URT cancers are likely the result of genotoxicity and mutagenicity, cytotoxicity, and cell proliferation. Together, genotoxicity, cellular proliferation, and cytotoxicity-induced regenerative proliferation exhibit multiple layers of coherence as a function of species, anatomy, temporality, concentration, and duration of exposure, and when these factors are integrated, they form a biologically relevant MOA for formaldehyde-induced URT carcinogenesis.

The **evidence demonstrates** that formaldehyde inhalation causes nasopharyngeal cancer (NPC) in humans, given appropriate exposure circumstances, based on *robust* epidemiological

evidence of an increased risk of the occurrence of NPCs from studies of occupational formaldehyde exposure in several geographic locations among different occupational populations representing diverse exposure settings; *robust* evidence from long-term bioassays in two animal species providing consistent and reliable evidence of nasal cancers following exposure; and reliable and consistent mechanistic evidence in both animals and humans supporting causality. The nasopharynx, although not typically specified in animal studies, is the region adjacent to the nasal cavity, where the animal evidence was predominantly observed, providing plausible coherence between the animal and human data (and thus, the animal evidence is reflected as *robust* for the purpose of interpreting human NPC). The evidence is sufficient to conclude that a mutagenic mode of action of formaldehyde is operative in formaldehyde-induced nasopharyngeal carcinogenicity.

The **evidence demonstrates** that formaldehyde inhalation causes sinonasal cancer (SNC) in humans, given appropriate exposure circumstances, based on *robust* epidemiological evidence of an increased risk of the occurrence of sinonasal cancer from studies of occupational formaldehyde exposure in several geographic locations among different occupational populations representing diverse exposure settings. This evidence is supported by the apical and mechanistic evidence for nasal cancers across multiple animal species, although some uncertainty remains in the interpretation of the animal nasal data as wholly applicable to interpreting sinonasal cancer (and thus, the animal evidence is reflected as *moderate* for the purpose of interpreting human SNC). Although uncertainties remain, the nasal cancer MOA, including mutagenicity, is interpreted as relevant to this cancer type.

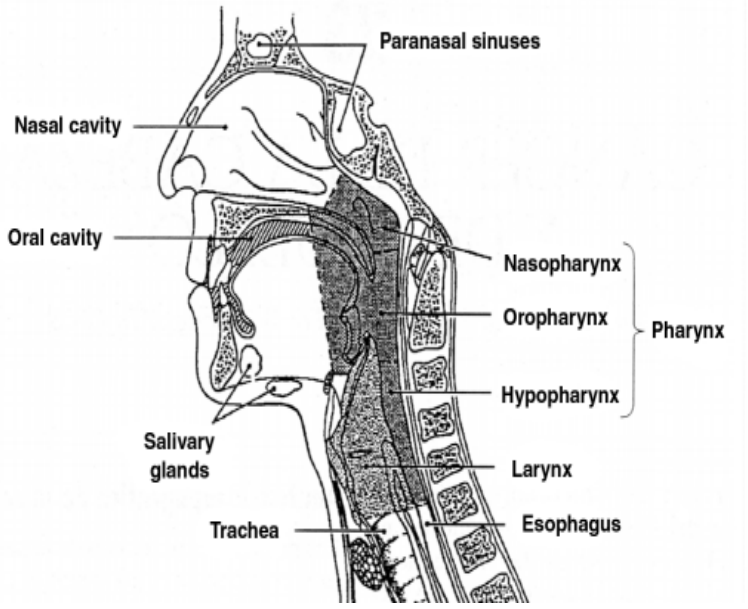


Figure 1-19. Schematic diagram of the human upper respiratory tract (i.e., nose, nasal cavity, paranasal sinuses, pharynx, larynx), as well as neighboring structures (from Vokes et al. (1993)).

Literature Search and Screening Strategy

The primary databases used for the literature searches were PubMed, Web of Science, and Toxline, with the last update of the search completed in September 2016 (see Appendix A.4.7, A.5.9 and A.5.6), and a systematic evidence map updating the literature through 2021 (see Appendix F). The occurrences of upper respiratory tract (URT) cancers in humans have been described and grouped according to the International Classification of Disease (ICD) coding rubrics. This review focused on the specific cancer diagnoses available in the epidemiological literature. The specific cancers of the URT that are most commonly reported are sinonasal cancers (cancers of the nose and nasal sinuses), cancers of the pharynx (comprising the nasopharynx, oropharynx and hypopharynx), and laryngeal cancer. Rarely, cancers of the buccal cavity as a whole are reported, but as this grouping includes lip, tongue, salivary glands, gums, and the floor of the mouth, which combine cancers of potentially different etiology and cell origin, the collection of cancers of the buccal cavity are not reviewed here. Only primary epidemiological studies of specific cancer endpoints with identified or inferred formaldehyde exposure were included. Additional studies were identified from review articles and government documents.

Evidence from animal experiments included precancerous lesions (i.e., dysplasia) and neoplasms (tumors) of the respiratory tract. Animal studies investigating formaldehyde-induced respiratory carcinogenesis were carried out primarily in rats and to a lesser extent in mice, hamsters, and nonhuman primates. The most consistent evidence of formaldehyde-induced respiratory cancers in animals is restricted to the nasal cavity and consists primarily of squamous cell carcinomas (SCCs). Other neoplasms that have been observed include carcinomas other than SCCs, sarcomas, papillomas, and adenomas (Kamata et al., 1997; Monticello et al., 1996; Morgan et al., 1986b; Sellakumar et al., 1985; Kerns et al., 1983).

The bibliographic databases, search terms, and specific strategies used to search them are provided in Appendix A.4.7, A.5.5, and A.5.9 for the cancer outcomes and relevant mechanistic endpoints. The specific PECO criteria for the human and animal health effects studies are provided in Appendix A.5.9. Literature flow diagrams summarize the results of the sorting process using these criteria and indicate the number of studies that were selected for consideration in the assessment through 2016 (see Appendix F for the identification of newer studies through 2021).

Upper Respiratory Tract Cancers in Human Studies

Each specific type of upper respiratory tract (URT) cancer (nasopharyngeal cancer, sinonasal cancer, cancers of the oropharynx and hypopharynx, and laryngeal cancer) is reviewed and evaluated independently in the sections below. For each type of URT cancer, the evidence is organized by considerations that inform the strength of evidence (e.g., consistency, exposure-response) and evaluation of the potential for bias and insensitivity in individual studies to affect the estimates of relative risk. Evidence tables for each type of URT cancer (Tables 1-32 through 1-35)

are included and are organized first by the study evaluation conclusions (i.e., *high, medium, low*) and then by publication year.

Methodological issues and approaches for evaluation

The epidemiology studies generally examined occupational exposure to formaldehyde either in specific work settings (e.g., cohort studies) or in case-control studies. The considerations with respect to design, exposure assessment, outcome assessment, potential bias and confounding, and analysis differ for these different types of studies, and are discussed in more detail in Appendix A.5.9. Developing an outcome-specific study evaluation for each cancer outcome encompasses two concepts: minimization or control of bias (internal validity) and sensitivity (the ability of the study to detect a true effect). Because a single epidemiology study may report on several different cancer endpoints, the confidence classifications are for the specific cancer results and are not judgments on the study as a whole except when a study has only a single cancer endpoint. The distinction here is important in that a study of adequate quality overall may still report an effect estimate judged to be of *low* confidence due to the rarity of the cancer outcome, the rarity of the exposure, or noncritical biases, which are expected to yield effect estimates that underestimate any true effect.

The diagnosis of cancers in epidemiological studies has historically been ascertained from death certificates according to the version of the International Classification of Diseases (ICD) in effect at the time of study subjects' deaths [i.e., ICD-8 and ICD-9: (WHO, 1987a, b)]. The most specific classification of diagnoses commonly reported across the epidemiological literature was based on the first three digits of the ICD code without further differentiation. For some cancers, the reliance of cohort studies on death certificates to detect cancers with relatively high survival may have underestimated the actual incidence of those cancers, especially when the follow-up time may have been insufficient to capture all cancers that may have been related to exposure. The potential for bias may depend on the specific survival rates for each cancer. Five-year survival rates vary among the selected cancers, from 59.6% for nasopharyngeal cancer (NPC) to less than 50% for oropharyngeal/hypopharyngeal cancer.

The overwhelming majority of information bias in epidemiological studies of formaldehyde stems from the use of occupational records to gauge exposures with some degree of exposure misclassification or exposure measurement error considered to be commonplace. A primary consideration in the evaluation of these studies is the ability of the exposure assessment to reliably distinguish among levels of exposure within the study population or between the study population and the referent population. A large variety of occupations were included within the studies; some represented work settings with a high likelihood of exposure to high levels of formaldehyde, and some represented work settings with variable exposures and in which the proportion of people exposed was quite small. In the latter case, the potential effect of formaldehyde would be "diluted" within the larger study population, limiting the sensitivity of the study. The exposure-assessment methods of the identified studies were classified into four groups (A through D), reflecting greater

or lesser degree of reliability and sensitivity of the measures (see Appendix A.5.9). Outcome-specific associations based on Group A exposures were considered to be without appreciable information bias due to exposure measurement error while those based on Groups B–D were considered to be more biased towards the null.

Additional exposure measurement error may arise in circumstances when the period of exposure assessment is not well aligned with the period when formaldehyde exposure could induce carcinogenesis that develops to a detectable stage (incident cancer) or could result in death from a specific cancer. The cohort studies were evaluated to ensure that they analyzed the analytic impact of different lengths of "latency periods" (i.e., excluded from the analyses the formaldehyde exposure most proximal to each individual's cancer incidence or cancer mortality). Analyses that did not evaluate latency were considered to be more biased towards the null because irrelevant exposure periods were included (Coggon et al., 2014).

Studies with small case counts may have little statistical power to detect divergences from the null but are not necessarily expected to be biased and no study was excluded solely on the basis of case counts as this methodology would have excluded any study that saw no effect of exposure. Therefore, cohort studies with extensive follow-up that reported outcome-specific results on a number of different cancers, including very rare cancers, were evaluated even when few or even no cases were observed, if information on the expected number of cases in the study population was provided so that confidence intervals could be presented to show the statistical uncertainty in the associated effect estimated. For example, Coggon et al. (2014) followed the mortality of 14,008 workers and yet expected only 1.7 deaths from nasopharyngeal cancer in the exposed workers and observed just one resulting in an unstable estimated RR = 0.38 (95% CI 0.02, 1.90). Meyers et al. (2013) followed the mortality of 11,043 workers and expected only 1.33 deaths from nasopharyngeal cancer and did not observe any deaths, resulting in an SMR = 0 (95% CI 0, 2.77).

In addition to potential bias, study sensitivity was specifically evaluated; study results with low sensitivity could result in effect estimates that underestimated a "true" association if it existed. For example, an outcome-specific effect estimate based on fewer than five observed cases of a particular cancer would be classified as *low* based on a lack of sensitivity—even if there were no appreciable biases. Another example would be a study that might have relied on exposure-assessment methodologies that were unbiased, but nonspecific in nature so as to yield effect estimates that were likely biased towards the null and thus underestimates of any true effect. Finally, cohort studies should have a sufficiently long follow-up period for any exposure-related cancer cases to develop and be detected and, ideally, allow for analyses of potential cancer latency. Outcome-specific effect estimates from cohort studies with short follow-up could be considered uninformative depending on the size of the study population and the baseline frequency of the cancer.

Nasopharyngeal cancer

Epidemiological evidence

The most specific classification of nasopharyngeal cancer diagnosis that is commonly reported on death certificates across the epidemiological literature has been based on the first three digits of the Seventh (i.e., nasopharyngeal cancer ICD-7: 146), Eighth, or Ninth Revision of the ICD code (i.e., nasopharyngeal cancer ICD-8/9: 147) although some studies did report the histological type of cancer (i.e., squamous cell carcinoma and nonkeratinizing or undifferentiated cancer), the histological type is infrequently reported on death certificates.

Evidence describing the association between formaldehyde exposure and the risk of developing or dying from nasopharyngeal cancer is available from 20 epidemiological studies—12 case-control studies (Li et al., 2006; Yang et al., 2005; Yu et al., 2004; Hildesheim et al., 2001; Armstrong et al., 2000; Vaughan et al., 2000; West et al., 1993; Vaughan, 1989; Roush et al., 1987b; Vaughan et al., 1986a, b; Olsen et al., 1984) and eight cohort studies (Coggon et al., 2014; Beane Freeman et al., 2013; Meyers et al., 2013; Siew et al., 2012; Hauptmann et al., 2009; Dell and Teta, 1995; Hansen and Olsen, 1995; West et al., 1993; Malker et al., 1990; Vaughan, 1989; Roush et al., 1987a; Vaughan et al., 1986a, b; Olsen et al., 1984). These are the only primary studies that provide evidence of the effect of formaldehyde exposure on the risk of dying from nasopharyngeal cancer. The outcome-specific evaluations of confidence in the precise effect estimate of an association from each study are provided in Appendix A.5.9. Note that the confidence judgments are for the confidence in the precise effect estimate of an association from each study—and not a confidence judgment in the overall study. The distinction here is important in that a study of adequate quality overall may still report an effect estimate judged to be of *low* confidence due to the rarity of the cancer outcome, the rarity of the exposure, or noncritical biases that are expected to yield effect estimates that underestimate any true effect. The results from Li et al. (2006) were classified as *not informative* due to the rarity of exposure in both the case and control groups; for details see Appendix A.5.9. The reported result from a case-control study by Armstrong et al. (2000) was classified as *not informative* due, primarily, to the rarity of relevant exposure data as only 8/564 subjects (1.4%) had more than 10 years of potential exposure beyond a 10-year latency period, and thus the study lacked sensitivity to detect any true effect (see Appendix A.5.9). The results from Dell et al. (1995) were classified as *not informative* due to the rarity of exposure in the cohort with 111 men exposed to formaldehyde out of 5932 (1.9%) and there were no observed cases of nasopharyngeal cancer; for details see Appendix A.5.9. Details of the reported results of *high*, *medium*, and *low* confidence are provided in the evidence table for nasopharyngeal cancer (see Table 1-32) following the causal evaluation.

Consistency of the observed association

Seventeen informative studies reported risks of nasopharyngeal cancer among subjects with formaldehyde exposure based on occupational or residential history. These studies examined

different populations, in different geographical locations, under different exposure settings and employing different study designs. Importantly, for nasopharyngeal cancer, these studies were conducted in low background risk populations (e.g., Europe and the United States) and high background risk populations (e.g., China and Taiwan). Table 1-31 provides the incidence rates of nasopharyngeal cancer per year by country/region based on the IARC publication *Cancer Incidence in Five Continents* (Curado et al., 2007) for each of the 17 studies.

Table 1-31. Age-standardized (world) incidence rates of nasopharyngeal cancer per 100,000 per year

Study	Country	Region	Incidence rate/year (per 100,000)
Siew et al. (2012)	Finland		0.3
Coggon et al. (2014)	England and Wales	South and Western	0.4
Hansen and Olsen (1995)	Denmark		0.4
Malker et al. (1990)	Sweden		0.4
Olsen et al. (1984)	Denmark		0.4
Vaughan et al. (2000)	United States	CT, Detroit, IA, Seattle, UT	0.4–0.7
Meyers et al. (2013)	United States	Georgia and Pennsylvania	0.5–0.6
Beane Freeman et al. (2013)	United States	National Cancer Registries	0.6
Hauptmann et al. (2009)	United States	National Cancer Registries	0.6
Vaughan (1989)	United States	Washington	0.6
Roush et al. (1987a)	United States	Connecticut	0.6
Vaughan et al. (1986a)	United States	Washington	0.6
Vaughan et al. (1986b)	United States	Washington	0.6
Yang et al. (2005)	Taiwan[a]		3.5–8.3
Hildesheim et al. (2001)	Taiwan[a]		3.5–8.3
West et al. (1993)	Philippines		5.8
Yu et al. (2004)	China	Hong Kong	17.8

[a]Taiwan is not included in the IARC publication of cancer incidence rate so data were obtained from Chen et al. (2002).

Also important for nasopharyngeal cancer is the consideration of histological subtype, which may be of a keratinizing or nonkeratinizing cell type as the proportion of each cell type varies in low and high-risk populations. The study results presented in Table 1-32 (by confidence level and publication date) detail all of the reported associations. Results are plotted in Figure 1-20; results are grouped by population background risk and arrayed from lowest to highest by the percentage of cases in each study's results, which were considered likely to be squamous cell carcinomas.

Fourteen out of 17 studies reported increased risks of nasopharyngeal cancer with at least one metric of formaldehyde exposure—often with both clear statistical significance and exposure-response relationships. These included the results of large cohort study of 25,619 U.S. workers (Beane Freeman et al., 2013) classified with *high* confidence, and all four sets of results classified with *medium* confidence (see Table 1-32). Nine studies in eight independent populations reported relative effect estimates greater than three-fold. Yang et al. (2005) reported an OR of 4.29 (95% CI 2.45, 7.51) among cases with the highest cumulative formaldehyde exposure; Yu et al. (2004) reported a mortality odds ratio (MOR) of 3.75 (95% CI 1.12, 12.54) for restaurant workers in Hong Kong; West et al. (1993) reported an OR = 4.0 (95% CI 1.3,12.3) among Philippine cases with greater than 25 years of time since first exposure (TSFE); Roush et al. (1987a) reported an OR = 4.0 (95% CI 1.3, 12.0) among Connecticut cases aged 68+ years with the highest duration of exposure and 20+ years TSFE; Beane Freeman et al. (2013) reported an RR = 11.54 (95% CI 1.38, 96.81) for workers with the highest average intensity of exposure; Malker et al. (1990) reported a standardized incidence ratio (SIR) of 3.9 (95% CI 1.24, 9.40); Vaughan et al. (1986b) reported an OR = 6.7 (95% CI 1.2, 38.9) for cases living and working in a mobile home; Vaughan (1989) reported an OR = 31.8 (no CI provided) for the highest duration of working as a carpenter; and Vaughan et al. (2000), after excluding undifferentiated and nonkeratinizing histological types, reported an OR = 13.3 (95% CI 2.5, 70) for cases with the highest likelihood of formaldehyde exposure.

Results showing increased risks were consistently reported in populations from high-risk areas with endemic Epstein-Barr infection such as Hong Kong (Yu et al., 2004), Taiwan (Yang et al., 2005; Hildesheim et al., 2001), the Philippines (West et al., 1993) as well as in populations from low/medium-risk areas such as the United States (Beane Freeman et al., 2013; Vaughan et al., 2000; Vaughan, 1989; Roush et al., 1987a; Vaughan et al., 1986a, b). Results showing increased risks were also consistently reported across study populations with different proportions of squamous cell carcinomas (SCC) (i.e., Hildesheim et al. (2001) and Yang et al. (2005) reported only 9% of their cases were keratinizing SCC), more heterogeneous mixes of keratinizing and nonkeratinizing carcinomas [i.e., Malker et al. (1990), (48% keratinizing SCC); Vaughan et al. (2000), (60%); Vaughan et al. (1986a, b), (78%)], and study populations restricted to only squamous cell carcinomas (Vaughan et al., 2000; Vaughan, 1989) (100% keratinizing SCC)].

Of these 17 studies, all but three reported increased risks of nasopharyngeal cancer that appeared to be associated with exposure to formaldehyde; the three exceptions were the results from the large occupational cohort studies by Siew et al. (2012), Coggon et al. (2014), and Meyers et al. (2013)—all of which were classified with *low* confidence. One additional study (Andjelkovich et al., 1995) reported zero cases of NPC among 3,929 U.S. workers exposed to formaldehyde over 83,064 person-years but reported no data on the number of expected cases and thus was not included here.[17] An additional study (Edling et al., 1987b) reported one case of NPC among 521 Swedish workers exposed to formaldehyde over 7,011 person-years but reported no data on the number of expected cases and was not included here.[18] One possible explanation for the inconsistency is the rarity of NPC in the populations studied by Siew and by Coggon. Table 1-32 shows that the Finnish population studies by Siew et al. (2012) had a background incidence rate of 0.3 cases per year for each 100,000 people—the lowest of all the available populations reviewed here. The English and Welch population studied by Coggon et al. (2014) had the second lowest incidence rate at 0.4 cases per year for each 100,000 people.[19] The very low national incidence rates of NPC can make studies of these populations lack the statistical sensitivity to detect any true association—even when the number of people being followed appears to be large.

It is important to understand that the statistical power of these cohort studies depends directly on the number of observed and expected cases. While there are exact methods to compute the variance of the standardized mortality ratio, the general formula illustrates the dependence on the case counts. The variance of the standardized mortality ratio is generally a function of the inverse of the observed and expected case count, specifically, *var*(SMR) = [# observed cases/(# of expected cases)^2]. Smaller case counts produce larger statistical variances and wider confidence intervals. Because the SMR is a measure of relative effect bounded between zero and infinity, it may be more straightforward to consider the width of confidence intervals on the scale of the natural logarithm, which bounds the estimates symmetrically between negative infinity and positive infinity. Coggon et al. (2014) expected only 1.7 deaths from nasopharyngeal cancer in the exposed workers and observed just one resulting in an unstable estimated RR = 0.38 (95% CI 0.02, 1.90); on the natural log scale the ln(RR) = −0.97 (95% CI −3.91, to 0.64). Meyers et al. (2013) expected only 1.33 deaths and did not observe any deaths, resulting in an SMR = 0 (95% CI 0, 2.77); on the natural log scale, the ln(RR) = negative infinity (95% CI negative infinity to +1.99). These effect estimates result in wide confidence intervals. For comparison, the other large cohort study (Beane Freeman et al., 2013) expected 4.89 deaths and observed nine deaths from NPC, resulting in

[17]For Andjelkovich et al. (1995), assuming a rate of NPC for U.S. workers of 0.6 per 100,000 person-years (Curado et al., 2007), the expected number of cases would have been 0.33 and the ~SMR = 0 (95% CI 0, 5.99).
[18]For Edling et al. (1987b), assuming a rate of NPC for Swedish workers of 0.4 per 100,000 person-years (Curado et al., 2007), the expected number of cases would have been 0.028 and the ~SMR = 35.71 (95% CI 1.79, 176.1).
[19]For comparison, the background incidence rate in the United States is 0.6 cases per year for each 100,000 people and ranges from 3.5 to 17.8 cases per year for each 100,000 people in the Philippines, Taiwan, and Hong Kong (see Table 1-31).

a SMR = 1.84 (95% CI 0.84, 3.49); on the natural log scale, the ln(RR) = negative infinity (95% CI −0.17, 1.25). The NPC results from the Coggon et al. (2014), Meyers et al. (2013) and Siew et al. (2012) studies were all considered to lack sensitivity to detect any true effect, which contributed to their classifications of *low* confidence.

In summary, the majority of studies from different populations, in different locations, exposure settings, and using different study designs reported increased risks of nasopharyngeal cancer associated with formaldehyde exposure. There are reasonable alternative explanations for the three studies that did not observe an increased risk.

Strength of the observed association

While reported relative effect estimates were consistently elevated above the null value of one across 14 of the 17 studies, the magnitude of the relative risk estimates varied with the quality of the exposure assessment. Studies with higher quality exposure data that were capable of stratifying subjects by exposure level, exposure probability, and timing of exposure (including lagged exposures) generally reported higher relative effect estimates. Nine studies reported greater than three-fold increased risks of nasopharyngeal cancer that appeared to be associated with exposure to formaldehyde (Beane Freeman et al., 2013; Yang et al., 2005; Yu et al., 2004; Vaughan et al., 2000; West et al., 1993; Malker et al., 1990; Vaughan, 1989; Roush et al., 1987a; Vaughan et al., 1986b). Three studies reported greater than 10-fold increased risks of nasopharyngeal cancer in the highest exposure categories. These increased risks appeared to be associated with duration of exposure to formaldehyde after accounting for a latency period (Beane Freeman et al., 2013; Vaughan et al., 2000; Vaughan, 1989). Results from the studies with higher quality exposure data were judged with greater confidence.

Temporal relationship of the observed association

Two related aspects of time are encompassed in the consideration of temporality. One aspect is the necessity for the exposure to precede the onset of the disease. In each of the studies, the formaldehyde exposures among the study participants started before their diagnoses of NPC, and in the studies that ascertained individual-level exposures, the estimation of formaldehyde exposures was based on job titles and done in a blinded fashion with respect to outcome status.

The second aspect involves the time course of formaldehyde exposures in relation to the incidence of NPC and death from NPC. From the epidemiological literature, it is known that there can be an induction/latency period for some environmental agents and that the induction period may exceed 10 years. Three studies provided analyses of this temporal relationship showing some evidence of the effect of time since first exposure on the risk of dying from nasopharyngeal cancer (Hildesheim et al., 2001; West et al., 1993; Roush et al., 1987b); however, none of them did so by histological subtype. Hildesheim et al. (2001) reported conflicting evidence of lower risks among all NPC cases for first exposure to formaldehyde more than 20 years earlier, but higher risks with greater time since first exposure (TSFE) when analyses were limited to only those who were

positive for Epstein-Barr virus. Roush et al. (1987b) reported somewhat greater risks among those first exposed more than 20 years and a stronger such pattern among those considered to be highly exposed more than 20 years prior to dying of nasopharyngeal cancer. Even higher risks were found among those with high early exposures and who were 68 years or older at death (OR = 4.0; 95% CI 1.3, 12.0), which may imply that TSFE much greater than 20 years carries greater risk. The results from West et al. (1993) support this assertion; in multivariate analyses, they reported a low odds ratio for TSFE less than 25 years but higher risks for greater than 25 years (OR = 4.0; 95% CI 1.3, 12.3). In separate analyses controlling only for TSFE to formaldehyde, dust, and exhaust fumes, West et al. (1993) reported even higher risk among those first exposed to formaldehyde more than 35 years earlier (OR = 5.6; 95% CI 0.58, 52.9).

The histological subtype and background rate of nasopharyngeal cancer is important in considering latency as the population studied by Hildesheim et al. (2001) resided in Taiwan (a high background risk population), and cases were more than 90% nonkeratinizing. In contrast, the population Roush et al. (1987b) studied was from Connecticut (a low background risk population), which may have only ~28% nonkeratinizing cases, if consistent with a U.S. study of nasopharyngeal cancer that included cases from Connecticut (Vaughan, 1989). West et al. (1993) studied subjects from the Philippines where the background rate is intermediate to the high rates of some East Asians and the low rates in populations of European descent (Hildesheim et al., 1993).

The association between exposure to formaldehyde and risk of nasopharyngeal cancer may be weaker for nonkeratinizing cases (Vaughan et al., 2000). This may explain the apparent lack of a clear latency effect in the Hildesheim et al. (2001) study, which has more than 90% of cases diagnosed with nonkeratinizing cases. The remaining limited evidence on the time course of death following initial formaldehyde exposure is consistent with expectation of a lengthy latency period for cancer development and subsequent deaths.

Exposure-response relationship

In their large population-based case-control study including 196 cases of nasopharyngeal cancer, Vaughan et al. (2000) clearly demonstrated two important points: (1) that there was an exposure-response relationship between increased formaldehyde exposure and increased risk of nasopharyngeal cancer, and (2) that the exposure-response differed by nasopharyngeal cancer subtype in the U.S. population. Vaughan et al. (2000) reported statistically significant trends for differentiated squamous cell carcinomas ($p = 0.033$) and for cases of epithelial carcinoma without specification of histological type ($p = 0.036$). However, there was no trend with duration of exposure to formaldehyde among cases with undifferentiated/nonkeratinizing histology ($p = 0.82$). Grouping of all histological subtypes appeared to mask the underlying relationship seen in squamous cell carcinoma in this study. Excluding nasopharyngeal cancer cases with undifferentiated or nonkeratinizing histology, Vaughan et al. (2000) reported a clear exposure-response with increased probability of exposure to formaldehyde with the highest risks seen in subjects with the highest probability of occupational exposure to formaldehyde (OR = 13.3;

95% CI 2.5, 70; $p = 0.0007$). Among those subjects considered to be "definitely exposed," there were increasing risks of nasopharyngeal cancer with increasing duration of formaldehyde exposure ($p < 0.001$) and with increased cumulative formaldehyde exposure ($p < 0.001$).

Further evidence of exposure-response relationships was reported by Beane Freeman et al. (2013) for peak formaldehyde exposures ($p = 0.005$), and, to a lesser degree, for cumulative exposures ($p = 0.06$) and with average intensity of formaldehyde exposure ($p = 0.09$)[20]. Other supporting evidence of an exposure-response relationship between increased exposure to formaldehyde and increased risk of NPC come from three reports on the same study population in Washington state (Vaughan, 1989; Vaughan et al., 1986a, b). These studies reported higher risks with increasing occupational exposures but did not report tests of trend (Vaughan et al., 1986a); for example, with a 15-year lag, compared to the lowest exposure score, those in the second level had an OR = 1.7 (95% CI 0.5, 5.7), while those in the third level had an OR = 2.1 (95% CI 0.4, 10.0). These researchers also reported increased risks with length of residence in mobile homes with the risk peaking among those with more than 10 years of occupancy (OR = 5.5; 95% CI 1.6, 19.4) (Vaughan et al., 1986b). The majority (84%) of mobile homes in the United States at this time were reported to have mean formaldehyde exposures in excess of 100 ppb, with 22% having mean exposures in excess of 500 ppb (Breysse, 1984) as cited in WHO (1989). A qualitative exposure-response relationship was shown for overall mobile home exposures with the risk of nasopharyngeal cancer for working in a mobile home but not living in a mobile home (OR = 1.7; 95% CI 0.5, 5.7) being exceeded by the risk of living in a mobile home (OR = 2.8; 95% CI 1.0, 7.9). However, the greatest risk was reported for living and working in a mobile home (OR = 6.7; 95% CI 1.2, 38.9). Vaughan (1989) also reported increasing risk with duration of employment as a carpenter after lagging exposures by 15 years to account for cancer latency (χ^2 trend = 8.65; $p = 0.01$ with 2 df)—especially as a carpenter in the construction industry (χ^2 trend = 14.86; $p = 0.0006$ with 2 df). Carpentry is considered to be a formaldehyde-related job since many products used in construction and building trades involve exposure to formaldehyde (Hildesheim et al., 2001; Vaughan et al., 1986a). Carpentry also involves coexposure to wood dust, which is likely to be a potential confounder for NPC, as it a potent risk factor. The potential for confounding by wood dust is evaluated in the following section. Other evidence generally consistent with an exposure-response relationship was reported by Yu et al. (2004), Hildesheim et al. (2001), and West et al. (1993). Yu et al. (2004) reported mortality ORs (MORs) for three levels of increasing cumulative exposure based on years of union membership compared to none and report MORs of 2.5, 3.41, and 3.75 (95% CI 1.12, 12.54). Hildesheim et al. (2001) reported an OR = 1.3 for less than 25 years of cumulative exposure and OR = 1.5 for more than 25 years of cumulative exposure

[20]Möhner et al. (2019) argued that there might have been a diagnostic bias in coding the specific and non-specific pharyngeal cancer in the NCI cohort study which could have affected the pharyngeal cancer SMRs; however, potential administrative miscoding of cancer mortality on death certificates would be independent of the quantitative estimates of workers' exposures, and any misclassification of diagnostic codes would not be expected to yield evidence of exposure-response relationships.

(95% CI 0.88, 2.7, *p*-trend = 0.10); West et al. (1993) reported that daily use of antimosquito coils [which have been shown in experiments to emit formaldehyde concentrations of between 0.87 and 25 μg/m^3; see (Liu et al., 2003)] had an OR = 5.9 (95% CI 1.7, 20.1), while less than daily use had an OR = 1.4.

Potential impact of selection bias, information bias, confounding bias, and chance

Selection bias may alter epidemiological findings when participation or follow-up rates are related to the probability of exposure or the outcome. However, this is an unlikely bias in the epidemiological studies of nasopharyngeal cancer, as the case-control studies evaluated exposure status without regard to outcome status and had participation levels of 85–100%. Each of the cohort studies included at least 72% of eligible participants and lost relatively few participants over the course of mortality follow-up.

The issue of potential selection bias was relevant to the results from two study populations —all classified with *low* confidence (Yang et al., 2005) and the three Vaughan papers (1989; 1986a, b). Both Yang et al. (2005) and Vaughan (1989) with Vaughan et al. (1986a, b) used more than 40% of case interviews completed by next of kin due to cancer mortality among cases and no proxy respondent was included for the controls. When next-of-kin is used to provide proxy information on cases, measurement error is likely to be present to some degree. If the quality of those data differs between cases and controls, this can result in selection bias if any differences are related to exposure. Hence, EPA considers that there is some risk of selection bias in the results of these studies (e.g., (Yang et al., 2005; Vaughan, 1989; Vaughan et al., 1986a, b).

Information bias may distort findings when subjects' true personal exposures are inaccurately assigned. Differential misclassification, in which exposure status influences disease classification (or disease status influences exposure classification), can lead to bias toward or away from the null (i.e., spurious or "false positive" associations). This scenario is considered unlikely among these studies of nasopharyngeal cancer mortality because the likelihood of differential misclassification based on these study designs is low. The assignment of exposure status or calculation of exposure measures in the case-control and cohort studies was done independently of knowledge of the cause of death. Therefore, an exposure-related bias in subjects' recall or reconstruction of their occupational histories seems unlikely.

Another aspect of information bias stems from random measurement error or nondifferential misclassification. This type of error typically will bias the risk estimate toward the null, thereby obscuring real effects by underestimating their magnitude. Given the difficulty in accurately estimating personal exposure over time or in the use of proxies to represent exposure to formaldehyde, the likelihood of random measurement error is almost certain in many studies. The implication of such information bias is that the consistently reported increases in risks of formaldehyde-related mortality may be underestimates and the true risk could be larger than was demonstrated in these epidemiological studies.

A third possible scenario for information bias could arise from systematic measurement error that is nondifferential with respect to disease. Such a scenario would be unusual in a study with exposure assessment based in industrial settings with extensive industrial hygiene data used to determine levels of exposure (e.g., Beane Freeman et al., 2013). However, a claim was made by Marsh et al. (2007b; 2002) that the exposure assessment used for the NCI formaldehyde cohort reported on by Beane Freeman et al. (2013) was 10-fold higher than those estimated by Marsh et al. (2007b; 2002). If this were true, then the same amount of observed risk in Beane Freeman et al. (2013) would be apportioned to one-tenth the same exposure, which would yield an exposure-response 10-fold greater in magnitude. The claim by Marsh et al. (2007b; 2002) suggests a one-sided uncertainty in the exposure-response reported by Beane Freeman et al. (2013), which may be 10 times more potent than reported.

Confounding is a potential bias that could arise if another cause of nasopharyngeal cancer was also associated with formaldehyde exposure. There does not appear to be any evidence of a common confounder that would provide an alternative explanation for the consistently observed association of formaldehyde exposure with increased risk of nasopharyngeal cancer seen across these studies. Chemicals and other coexposures that have not been independently associated with nasopharyngeal cancer are not expected to confound results. Other known risk factors for nasopharyngeal cancer include childhood consumption of Chinese salted fish (Yu et al., 1986), wood dust (Hildesheim et al., 2001), smoking, and alcohol consumption (Vaughan, 1996). While these other exposures may be independent risk factors for nasopharyngeal cancer, consumption of Chinese salted fish (or other dietary exposures to nitrosamines) and alcohol are unlikely to be generally related to formaldehyde exposures, and therefore, these other exposures are not expected to be consistent confounders across all of the studies. Additionally, Epstein-Barr virus is thought to be a cause of nasopharyngeal cancer due to its ubiquitous presence in nasopharyngeal cancer cases, but Hildesheim (2001) described Epstein-Barr virus as an effect modifier of the association between formaldehyde and nasopharyngeal cancer, and not as a confounder.

Wood dust may be an independent risk factor for nasopharyngeal cancer, but three studies specifically controlled for the potential confounding of the effects of wood dust on the risk of nasopharyngeal cancer and did not find wood dust to be a confounder (Hildesheim et al., 2001; Vaughan et al., 2000; West et al., 1993). Similarly, smoking was specifically controlled for in a number of studies (Vaughan et al., 2000; West et al., 1993; Vaughan, 1989; Vaughan et al., 1986a, b) and was not likely to have been a major confounder of the formaldehyde-associated results. Marsh et al. (2005) re-evaluated the association between formaldehyde exposure and NPC in the NCI cohort and reported that the majority of the cases of NPC arose in one of the 10 plants included in the cohort and that this findings suggested that there might be something specific to the experience in Plant 1 (in Wallingford , CT) that may have given rise to the excess of NPC cases there – perhaps a confounder. Marsh et al. (2007b) suggests that silversmithing may be a cause of NPC in Plant 1 and that the reported association between formaldehyde and NPC may be due to confounding; however,

Beane Freeman et al. (2013) noted that the reported association for formaldehyde on the risks of NPC did not decrease when analyses adjusted for silversmithing (see Table 5 of Marsh et al., 2007b). The details of Table 1 in (Marsh and Youk, 2005) show the SMRs for NPC for each of the 10 plants. The two plants with the highest average intensity of formaldehyde exposure had the two highest SMR estimates for NPC. It is plausible that the observation that the majority of the cases of NPC in the NCI cohort come from Plant 1 reflects generally higher formaldehyde exposures and a larger number of people at that plant than at other plants. This overall evidence does not indicate confounding of the formaldehyde association with increased risk of NPC.

Consistency across multiple studies is demonstrated by a pattern of increased risk in different populations, exposure scenarios, and time periods. Such consistency makes unmeasured confounding an unlikely alternative explanation for the observed associations. This consistency also reduces the likelihood of chance as an alternative explanation by increasing the statistical strength of the findings through the accumulation of a larger body of similar evidence. The observations of multiple instances of very strong associations, as well as exposure-response trends with increased formaldehyde exposure using multiple metrics of exposure similarly, reduce the likelihood that chance, confounding, or other biases can explain the observed association.

Causal evaluation

The causal evaluation for formaldehyde exposure and the risk of developing or dying from nasopharyngeal cancer placed the greatest weight on five particular considerations: (1) the consistency of the observed increases in risk across several studies—including results classified with *high*, *medium*, and *low* confidence with higher risks among Asian populations that have higher background rates of nasopharyngeal cancer and reasonable explanations for the lack of findings in a few studies with very low background rates of nasopharyngeal cancer; (2) the strength of the association with eight studies reporting at least a three-fold increase in risk; (3) the reported exposure-response relationships showing that multiple measures of increased exposure to formaldehyde were repeatedly associated with increased risk of dying from nasopharyngeal cancer—especially among studies primarily focused on squamous cell carcinomas; (4) a biologically coherent temporal relationship consistent with a pattern of exposure to formaldehyde and subsequent death from nasopharyngeal cancer, allowing time for cancer induction, latency, and mortality; and (5) reasonable confidence that alternative explanations are ruled out, including chance, bias, and confounding within individual studies or across studies. Consistent observations of genotoxicity in exfoliated buccal cells or nasal mucosal cells across several occupational studies involving diverse exposure settings further supports the evidence in humans.

Conclusion

The available epidemiological studies provide robust evidence of an association consistent with causation between formaldehyde exposure and increased risk of nasopharyngeal cancer.

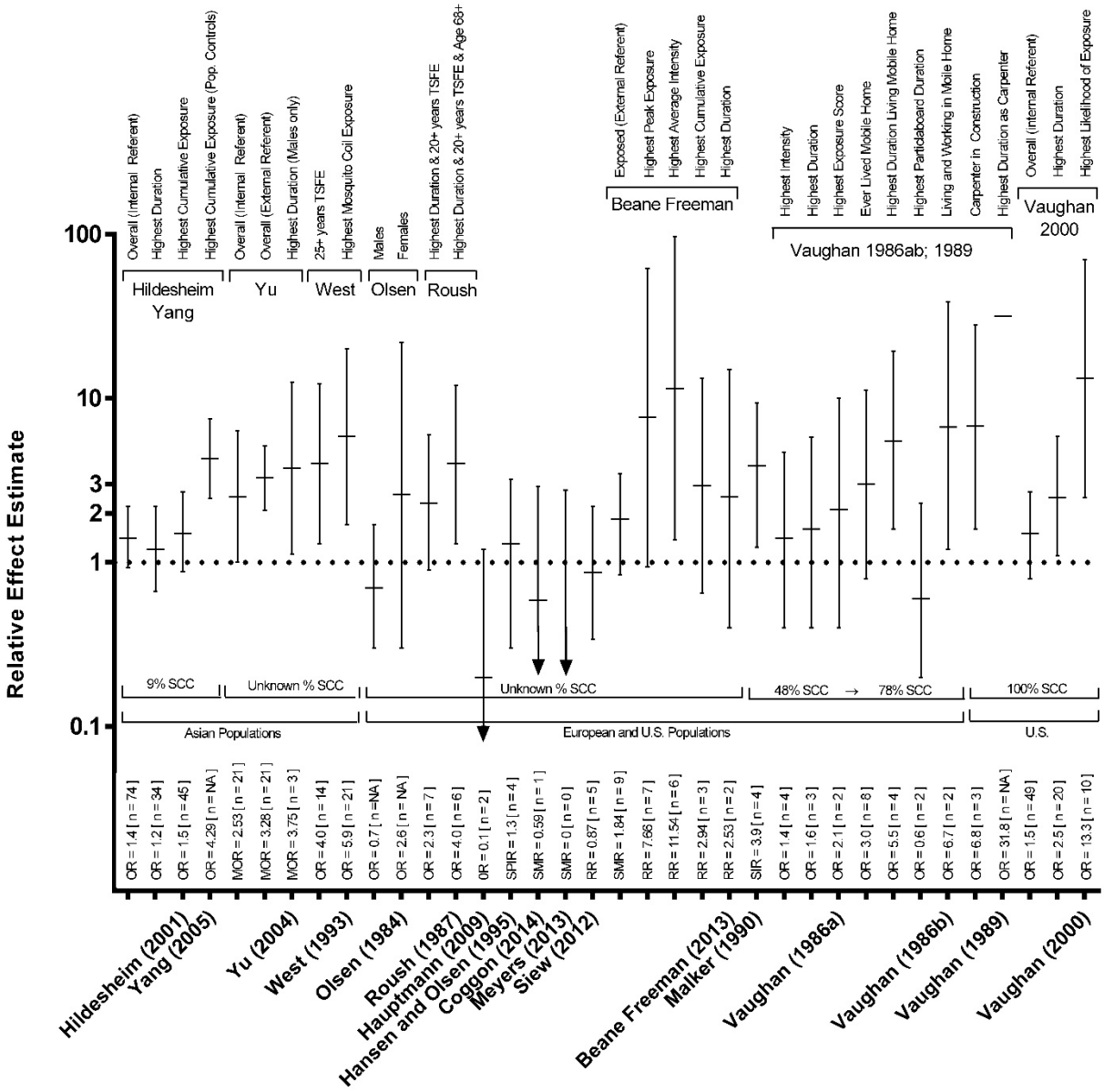


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Figure 1-20. Epidemiological studies reporting nasopharyngeal cancer risk estimates.

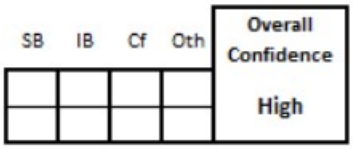
Results are grouped by population background risk and arrayed from lowest to highest by the percentage of cases in each study's results that were considered likely to be squamous cell carcinomas (SCC). SMR: standardized mortality ratio. PMR: proportionate mortality ratio. SPIR: Standardized Proportional Incidence Ratio. RR: relative risk. OR: odds ratio. MOR: mortality odds ratio. TSFE: time since first exposure. For each measure of association, the number of exposed cases is provided in brackets

(e.g., [*n* = 74]). For studies reporting results on multiple metrics of exposure, only the highest category of each exposure metric is presented in the figure.

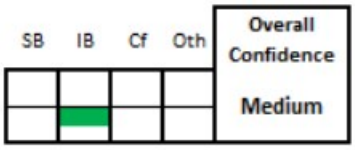
Table 1-32. Epidemiological studies of formaldehyde exposure and risk of nasopharyngeal cancers

Study	Exposures	Results: effect estimate (95% CI) [# of Cases]

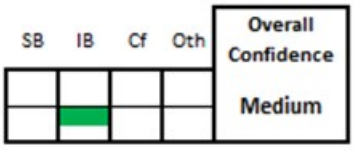
Reference: Beane Freeman et al. (2013)
Population: 25,619 workers employed at 10 formaldehyde-using or formaldehyde-producing plants in the United States followed from either the plant start-up or first employment through 2004. Deaths were identified from the National Death Index with remainder assumed to be living. 676 workers (3%) were lost to follow-up. Vital status was 97.4% complete and only 2.6% lost to follow-up.
 	
Outcome definition: Death certificates used to determine underlying cause of death from nasopharyngeal cancer (ICD-8: 147). Histological typing not reported.
 	
Design: Prospective cohort mortality study with external and internal comparison groups.
 	
Analysis: RRs estimated using Poisson regression stratified by calendar year, age, sex, and race; adjusted for pay category compared to workers in lowest exposed category. Lagged exposures were evaluated to account for cancer latency. Results were presented for 15-year lag.
 	
SMRs calculated using sex, age, race, and calendar-year-specific U.S. mortality rates.
 	
Related studies:
Blair et al. (1986)
Hauptmann et al. (2004)
Beane Freeman et al. (2009)
 	
Confidence in effect estimates:[a]
	Exposure assessment: Individual-level exposure estimates based on job titles, tasks, visits to plants by study industrial hygienists who took 2,000 air samples from representative job, and monitoring data from 1960 through 1980.
	Median TWA (over 8 hours) = 0.3 ppm (range 0.01−4.3). Median cumulative exposure = 0.6 ppm-years (range 0−107.4).
	
	Multiple exposure metrics including peak, average, and cumulative exposures were evaluated using categorical and continuous data.
	
	Duration and timing: Exposure period from <1946 to 1980. Median length of follow-up: 42 years. Median length of employment was 2.6 years (range 1 day−47.7 years). Duration and timing since first exposure were not evaluated.
	Variation in exposure:
	Peak exposure:
	Level 1 (>0 to <2.0 ppm)
	Level 2 (2.0 to <4.0 ppm)
	Level 3 (≥4.0 ppm)
	Average intensity:
	Level 1 (>0 to <0.5 ppm)
	Level 2 (0.5 to <1.0 ppm)
	Level 3 (≥1.0 ppm)
	Cumulative exposure:
	Level 1 (>0 to <1.5 ppm-yrs)
	Level 2 (1.5 to <5.5 ppm-yrs)
	Level 3 (≥5.5 ppm-yrs)
	Duration of exposure:
	Level 1 (0 years)
	Level 2 (>0 to <5 years)
	Level 3 (5 to <15 years)
	Level 4 (≥15 years)
	
	Coexposures: Exposures to 11 other compounds were identified and evaluated as potential confounders and found not be confounders.
		Internal comparisons:
		Peak exposure
		Unexposed RR = 4.39 (0.36−54.05) [2]
		Level 1 RR = 1.00 (Ref. value) [1]
		Level 2 RR = NA [0]
		Level 3 RR = 7.66 (0.94−62.34) [7]
		p-trend (exposed) = 0.005;
		p-trend (all) = 0.10
		
		Average intensity
		Unexposed
		RR = 6.79 (0.55−83.64) [2]
		Level 1 RR = 1.00 (Ref. value) [1]
		Level 2 RR = 2.44 (0.15−39.07) [1]
		Level 3 RR = 11.54 (1.38−96.81) [6]
		p-trend (exposed) = 0.09;
		p-trend (all) = 0.16
		
		Cumulative exposure
		Unexposed RR = 1.87 (0.30−11.67) [2]
		Level 1 RR = 1.00 (Ref. value) [4]
		Level 2 RR = 0.86 (0.10−7.70) [1]
		Level 3 RR = 2.94 (0.65−13.28) [3]
		p-trend (exposed) = 0.06;
		p-trend (all) = 0.07
		Duration of exposure
		Level 1 RR = 1.00 (Ref. value) [4]
		Level 2 RR = 0.86 (0.10−7.70) [1]
		Level 3 RR = 2.94 (0.65−13.28) [3]
		Level 4 RR = 2.53 (0.4−15.0) [not given]
		p-trend (all) = 0.4
		
		External comparisons:
		$SMR_{Unexposed}$ = 1.45 (0.17−5.25) [2]
		$SMR_{Exposed}$ = 1.84 (0.84−3.49) [9]

Study	Exposures	Results: effect estimate (95% CI) [# of Cases]
 **HIGH** ● (No appreciable bias) **IB**: Exposure Group A	[As noted in Appendix A.5.9: There was no information on smoking, however, according to Blair et al. (1986), "The lack of a consistent elevation for tobacco-related causes of death, however, suggests that the smoking habits among this cohort did not differ substantially from those of the general population." Beane Freeman et al. (2013) report that among a sample of 379 cohort members, they "found no differences in prevalence of smoking by level of formaldehyde exposure."]	
Reference: Hauptmann et al. (2009) **Population:** 6,808 embalmers and funeral directors who died during 1960–1986. Identified from registries of the National Funeral Directors' Association, licensing boards and state funeral directors' associations, NY State Bureau of Funeral Directors, and CA Funeral Directors and Embalmers. Deaths were identified from the National Death Index. Next of kin interviews conducted for 96% of cases and 94% of controls. **Outcome definition:** Death certificates used to determine UCOD from nasopharyngeal cancer (ICD-8: 147). **Design:** Nested case-control study within a prospective cohort mortality study using two internal comparison groups; the first composed of those who had never embalmed (1 case and 55 controls) and the second composed of those who had fewer than 500 embalmings (five cases and 83 controls). **Analysis:** ORs calculated using unconditional logistic regression adjusted for date of birth, age at death, sex, data source, and smoking. Lagged exposures were evaluated to account for cancer latency. These	**Exposure assessment:** Occupational history obtained by interviews with next of kin and coworkers using detailed questionnaires. Exposure was assessed by linking questionnaire responses to an exposure assessment experiment providing measured exposure data. Exposure levels (peak, intensity, and cumulative) were assigned to each individual using a predictive model based on the exposure data. The model explained 74% of the observed variability in exposure measurements. Multiple exposure metrics including duration (mean = 31.3 yrs in cases), # of embalming, peak, average, and cumulative exposures were evaluated using categorical and continuous data. **Duration and timing:** Exposure period from <1932 through 1986. Duration of exposure was evaluated. Duration is also a surrogate for time because first exposure since dates of death was closely related to cessation of workplace exposures. **Variation in exposure:** Level 1 Never embalmed Level 2 Ever embalmed **Coexposures:** None evaluated as potential confounders. [As noted in Appendix A.5.9: Coexposures may have included:	**Internal comparisons:** Never embalming: OR = 1.00 (Ref. value) [2] Ever embalming: OR = 0.1 (0.01–1.2) [2]

Study	Exposures	Results: effect estimate (95% CI) [# of Cases]
results are shown in table 3 of Hauptmann et al. (2009). Results from the second internal comparison group with <500 embalmings were selected to increase statistical stability. These results are shown in table 4 of Hauptmann et al. (2009) **Related studies:** Hayes et al. (1990) Walrath and Fraumeni (1983) Walrath and Fraumeni (1984) **Note:** The original cohorts from these three original studies were combined in Hauptmann et al. (2009) and follow-up was extended so the case-series overlap and are not independent. However, the three original cohorts used external reference groups for comparison while Hauptmann et al. (2009) selected internal controls, which were independent of the reference groups used in the original studies. **Confidence in effect estimates:**[a]  **Medium** ↓ (low sensitivity) **IB**: Exposure Group A **Oth**: Low power due to rarity of cases.	phenol, methyl alcohol, glutaraldehyde, mercury, arsenic, zinc, and ionizing radiation. Chemical coexposures are not known risk factors for this outcome. Radiation exposure likely to be poorly correlated with formaldehyde so confounding is unlikely.]	
Reference: Hildesheim et al. (2001) **Population:** Male and female Taiwanese aged <75 years newly diagnosed with nasopharyngeal cancer identified between July 1991 and January 1995 from two hospitals. Participation of eligible cases was 99 and 87% for controls. **Outcome definition:** Diagnosis of nasopharyngeal was confirmed by histological review with >90% diagnosed with nonkeratinizing and undifferentiated carcinomas and 9% with squamous cell carcinoma.	**Exposure assessment:** Occupational history obtained from interviews of cases and controls for jobs held for ≥1 year since age 16 and identified job title, typical activities/duties, type of industry, and tools and/or materials used. Industrial hygienist assigned Standard Industry Classification/Standard Occupational Classification codes to jobs, assigning each a probability and intensity of exposure on a 0 (not exposed) to 9 (strong) scale. Cumulative exposure defined as the product of average intensity and duration.	**Internal comparisons:** All cases and controls Exposure to formaldehyde: Level 1 OR = 1.0 (Ref. value) [301] Level 2 OR = 1.4 (0.93–2.2) [74] Duration (overall): Level 1 OR = 1.0 (Ref. value) [301] Level 2 OR = 1.3 (0.69–2.3) [31] Level 3 OR = 1.6 (0.91–2.9) [43] *p*-trend (exposed) = 0.08 Duration (excluding 10 yrs before diagnosis): Level 1 OR = 1.0 (Ref. value) [307]

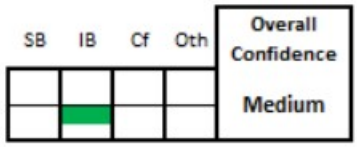
Study	Exposures	Results: effect estimate (95% CI) [# of Cases]
Design: Population-based case-control study of 375 cases of nasopharyngeal cancer. 325 controls identified from a random sample of households from a national household registration system and matched by age, sex, and area of residence. **Analysis: RRs estimated by** ORs calculated by logistic regression and adjusted for age, sex, education, and ethnicity. An induction period of 10 years was also utilized to account for latency in evaluating duration of exposure. All subjects were tested for the EBV; subset analysis based on EBV positivity (360 cases and 94 controls). EBV seropositives defined as positive for one of the following anti-EBV antibodies known to be associated with nasopharyngeal cancer: viral capsid antigen IgA, EBV nuclear antigen one IgA, early antigen IgA, DNA binding protein IgG, and anti-DNase IgG. **Related studies:** Yang et al. (2005); Cheng et al. (1999); Hildesheim et al. (1997) **Confidence in effect estimates:**[a]  **LOW** ↓ (Potential bias toward the null) **IB**: Exposure Group B **Oth**: Low sensitivity due to incomplete control of matching factors.	Multiple exposure metrics including average intensity, average probability, cumulative, years since first exposure, and age at first exposure were evaluated. **Duration and timing:** Duration and timing of exposure were evaluated. **Variation in exposure:** Exposure to formaldehyde: Level 1 (no) Level 2 (yes) Duration (overall): Level 1 (none) Level 2 (≤10 years) Level 3 (>10 years) Duration (excluding 10 yrs before diagnosis): Level 1 (none) Level 2 (≤10 years) Level 3 (>10 years) Cumulative exposure: Level 1 (none) Level 2 (<25 years) Level 3 (≥25 years) Time since first exposure: Level 1 (none) Level 2 (<20 years) Level 3 (≥20 years) Age at first exposure: Level 1 (none) Level 2 (<25 years) Level 3 (≥25 years) **Other exposures:** wood dust, solvents, and smoking. [As noted in Appendix A.5.9: The observed associations were not materially affected when controlling for wood dust, solvent exposure, or smoking.]	Level 2 OR = 1.6 (0.89–3.0) [34] Level 3 OR = 1.2 (0.67–2.2) [34] Cumulative exposure: Level 1 OR = 1.0 (Ref. value) [301] Level 2 OR = 1.3 (0.70–2.4) [29] Level 3 OR = 1.5 (0.88–2.7) [45] *p*-trend (exposed) = 0.10 Time since first exposure: Level 1 OR = 1.0 (Ref. value) [301] Level 2 OR = 2.3 (0.95–5.8) [19] Level 3 OR = 1.2 (0.76–2.0) [55] Age at first exposure: Level 1 OR = 1.0 (Ref. value) [301] Level 2 OR = 1.3 (0.80–2.0) [62] Level 3 OR = 3.4 (0.94–12) [12] No notable findings were reported between formaldehyde exposure and the risk of nasopharyngeal cancer when considering an induction period of 10 years. Authors reported that the observed associations were not materially affected when analyses additionally controlled for wood dust and solvent exposure.
Reference: Hildesheim et al. (2001)	**Exposure assessment:** Occupational history obtained from interviews of cases and controls for jobs held for ≥1 year since age 16 and identified job title, typical activities/duties, type of	**Internal comparisons:** EBV positive subjects (based on 360 cases and 94 controls) Exposure to formaldehyde: Level 1 OR = 1.0 (Ref. value) [# not given]

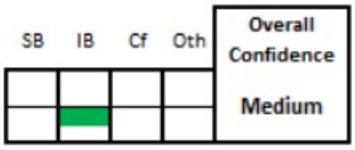
Study	Exposures	Results: effect estimate (95% CI) [# of Cases]
	industry, and tools and/or materials used. Industrial hygienist assigned Standard Industry Classification/Standard Occupational Classification codes to jobs, assigning each a probability and intensity of exposure on a 0 (not exposed) to 9 (strong) scale. Cumulative exposure defined as the product of average intensity and duration. Multiple exposure metrics including average intensity, average probability, cumulative, years since first exposure, and age at first exposure were evaluated. **Duration and timing:** Duration and timing of exposure were evaluated. **Variation in exposure:** Exposure to formaldehyde: Level 1 (no) Level 2 (yes) Duration (overall): Level 1 (none) Level 2 (≤10 years) Level 3 (>10 years) Duration (excluding 10 yrs before diagnosis): Level 1 (none) Level 2 (≤10 years) Level 3 (>10 years) Cumulative exposure: Level 1 (none) Level 2 (<25 years) Level 3 (≥25 years) Time since first exposure: Level 1 (none) Level 2 (<20 years) Level 3 (≥20 years) Age at first exposure: Level 1 (none) Level 2 (<25 years) Level 3 (≥25 years) **Other exposures**: wood dust, solvents, and smoking.	Level 2 OR = 2.7 (1.2–6.2) [# not given] Duration (overall): Level 1 OR = 1.0 (Ref. value) [# not given] Level 2 OR = 2.8 (0.83–9.7) [# not given] Level 3 OR = 2.6 (0.87–7.7) [# not given] Duration (excluding 10 yrs before diagnosis): Level 1 OR = 1.0 (Ref. value) [# not given] Level 2 OR = 4.7 (1.1–20) [# not given] Level 3 OR = 1.7 (0.65–6.0) [# not given] Cumulative exposure: Level 1 OR = 1.0 (Ref. value) [# not given] Level 2 OR = 4.0 (0.92–17) [# not given] Level 3 OR = 2.2 (0.80–5.8) [# not given] Time since first exposure: Level 1 OR = 1.0 (Ref. value) [# not given] Level 2 OR = 2.3 (0.52–10) [# not given] Level 3 OR = 2.8 (1.1–7.6) [# not given] Age at first exposure: Level 1 OR = 1.0 (Ref. value) [# not given] Level 2 OR = 2.6 (1.1–6.5) [# not given] Level 3 OR = 3.1 (0.39–24) [# not given] No notable findings were reported between formaldehyde exposure and the risk of nasopharyngeal cancer when considering an induction period of 10 years.
Reference: Vaughan et al. (2000)	**Exposure assessment:** Occupational histories obtained from interviews of cases and controls and identified job	**Internal comparisons:** **All histological types:** Exposure to formaldehyde:

Study	Exposures	Results: effect estimate (95% CI) [# of Cases]
Population: Males and females between the ages of 18 and 74 who were diagnosed with nasopharyngeal cancer between April 1987 and July 1993 and identified from five population-based cancer registries in the United States. Interviews were completed for 82% of eligible cases and 76% of eligible controls. **Outcome definition:** Diagnosis of nasopharyngeal (any histological type) was based on clinical records from cancer registries. Histological typing was reported and included for analysis with 28% diagnosed with undifferentiated and nonkeratinizing carcinomas, 60% with differentiated squamous cell carcinomas, and 12% with epithelial carcinomas (not otherwise specified[NOS]). **Design:** Population-based case-control study of 196 cases of nasopharyngeal cancer. 244 controls identified from random digit dialing in the same geographic regions and frequency matched by age, sex, and cancer registry. **Analysis:** ORs calculated by logistic regression and adjusted for age, sex, race, SEER site, cigarette usage, proxy status, and education. An induction period of 10 years was also utilized to account for latency in evaluating duration and cumulative exposure. Results with and without this 10-year lag period were similar. **Confidence in effect estimates:**[a]  **MEDIUM ↓** (Potential bias toward the null) **IB**: Exposure Group B	title, typical activities/duties, type of industry, and start and stop dates. Exposure was estimated by industrial hygienists by linking occupational history with participants' self-reported exposure information. Probability of exposure: definitely not or unlikely (<10%), possible (≥10 and <50%), probable (≥50 and <90%), and definite (≥90%). Jobs with potential exposure assigned estimated concentration levels based on TWA8: low (<0.10 ppm), moderate (≥0.10 and <0.50 ppm), and high (≥0.50 ppm). Multiple exposure metrics including probability of exposure and cumulative exposure were evaluated. **Duration and timing:** Duration of exposure was evaluated. **Variation in exposure:** Exposure to formaldehyde: Level 1 (never) Level 2 (ever) Maximum exposure: Level 1 (<0.10 ppm) Level 2 (0.10 to 0.50 ppm) Level 3 (>0.50 ppm) Duration: Level 1 (1 to 5 years) Level 2 (6 to 17 years) Level 3 (>18 years) **Other exposures:** Wood dust. [As noted in Appendix A.5.9: Wood dust evaluated as an independent risk factor for NPC controlling for formaldehyde and it was not a risk factor in this data set.]	Level 1 OR = 1.0 (Ref. value) [117] Level 2 OR = 1.3 (0.8–2.1) [79] Maximum exposure: Level 1 OR = 1.4 (0.8–2.4) [60] Level 2 OR = 0.9 (0.4–2.3) [14] Level 3 OR = 1.6 (0.3–7.1) [5] *p*-trend (exposed) = 0.57 Duration: Level 1 OR = 0.8 (0.4–1.6) [24] Level 2 OR = 1.6 (0.7–3.4) [26] Level 3 OR = 2.1 (1.0–4.5) [29] *p*-trend (exposed) = 0.07 **Epithelial (NOS)** Exposure to formaldehyde: Level 1 OR = 1.0 (Ref. value) [12] Level 2 OR = 3.1 (1.0–9.6) [12] Maximum exposure: Level 1 OR = 4.0 (1.2–13.1) [11] Level 2 OR = 1.5 (0.2–13.9) [1] Level 3 no cases *p*-trend (exposed) = 0.46 Duration: Level 1 OR = 2.0 (0.4–9.8) [4] Level 2 OR = 4.0 (0.9–18.6) [3] Level 3 OR = 4.2 (0.8–21.5) [5] *p*-trend (exposed) = 0.036 **Differentiated Squamous Cell** Exposure to formaldehyde: Level 1 OR = 1.0 (Ref. value) [69] Level 2 OR = 1.5 (0.8–2.7) [49] Maximum exposure: Level 1 OR = 1.6 (0.8–3.0) [35] Level 2 OR = 1.2 (0.4–3.3) [10] Level 3 OR = 2.1 (0.4–12.3) [4] *p*-trend (exposed) = 0.32 Duration: Level 1 OR = 0.8 (0.3–2.0) [12] Level 2 OR = 1.8 (0.7–4.3) [17] Level 3 OR = 2.5 (1.1–5.9) [20] *p*-trend (exposed) = 0.033 **Undifferentiated and nonkeratinizing** Exposure to formaldehyde: Level 1 OR = 1.0 (Ref. value) [36] Level 2 OR = 0.9 (0.4–2.0) [18] Maximum exposure: Level 1 OR = 1.0 (0.4–2.4) [14] Level 2 OR = 0.5 (0.1–3.1) [3] Level 3 OR = 1.5 (0.2–14.7) [1] *p*-trend (exposed) = 0.72 Duration: Level 1 OR = 0.7 (0.3–2.2) [8]

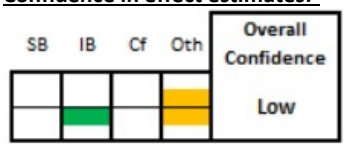
Study	Exposures	Results: effect estimate (95% CI) [# of Cases]
		Level 2 OR = 1.0 (0.2–3.9) [6] Level 3 OR = 1.2 (0.3–4.8) [4] *p*-trend (exposed) = 0.82
Reference: Vaughan et al. (2000)	**Exposure assessment:** Occupational histories obtained from interviews of cases and controls and identified job title, typical activities/duties, type of industry, and start and stop dates. Exposure was estimated by industrial hygienists by linking occupational history with participants' self-reported exposure information. Probability of exposure: definitely not or unlikely (<10%), possible (≥10 and <50%), probable (≥50 and <90%), and definite (≥90%). Jobs with potential exposure assigned estimated concentration levels based on 8-h TWA: low (<0.10 ppm), moderate (≥10 and <50 ppm), and high (≥50 ppm). Multiple exposure metrics including probability of exposure and cumulative exposure were evaluated. **Duration and timing:** Duration of exposure was evaluated. **Variation in exposure:** Exposure to formaldehyde: Level 1 (never) Level 2 (ever) Duration: Level 1 (1 to 5 years) Level 2 (6 to 17 years) Level 3 (>18 years) Cumulative exposure: Level 1 (0.05 to 0.40 ppm-yrs) Level 2 (>0.4 to 1.10 ppm-yrs) Level 3 (>1.10 ppm-yrs) **Other exposures**: Wood dust was evaluated but not found to be a confounder.	**Internal comparisons:** **Excluding undifferentiated and nonkeratinizing histological types** **Possible, probable or definite exposure** Exposure to formaldehyde: Level 1 OR = 1.0 (Ref. Value [# not given] Level 2 OR = 1.6 (1.0–2.8) [61] Duration: Level 1 OR = 0.9 (0.4–2.1) [16] Level 2 OR = 1.9 (0.9–4.4) [20] Level 3 OR = 2.7 (1.2–6.0) [25] *p*-trend (exposed) = 0.014 Cumulative exposure: Level 1 OR = 0.9 (0.4–2.0) [15] Level 2 OR = 1.8 (0.8–4.1) [22] Level 3 OR = 3.0 (1.3–6.6) [24] *p*-trend (exposed) = 0.033 **Probable or definite exposure** Exposure to formaldehyde: Level 1 OR = 1.0 (Ref. Value) [# not given] Level 2 OR = 2.1 (1.1–4.2) [27] Duration: Level 1 OR = 2.0 (0.8–5.0) [12] Level 2 OR = 3.3 (0.9–11.8) [9] Level 3 OR = 1.6 (0.5–5.6) [6] *p*-trend (exposed) = 0.069 Cumulative exposure: Level 1 OR = 1.9 (0.7–4.9) [12] Level 2 OR = 2.6 (0.7–9.5) [7] Level 3 OR = 2.2 (0.7–7.0) [8] *p*-trend (exposed) = 0.13 **Definite exposure** Exposure to formaldehyde: Level 1 OR = 1.0 (Ref. Value) [# not given] Level 2 OR = 13.3 (2.5–70) [10] Duration: Level 1 OR = not reported [5] Level 2 OR = not reported [2] Level 3 OR = not reported [3] *p*-trend (exposed) <0.001 Cumulative exposure: Level 1 OR = not reported [4] Level 2 OR = not reported [2] Level 3 OR = not reported [4] *p*-trend (exposed) <0.001

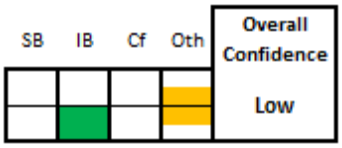
Study	Exposures	Results: effect estimate (95% CI) [# of Cases]
		Results with and without this 10-year lag period were similar.
Reference: West et al. (1993) **Population:** Male and female Filipinos between the ages of 11 and 83 years recruited from the Philippine General Hospital and diagnosed prior to 1992. Among 234 suspicious cases, 9% refused biopsy and were excluded and 104 were pathologically confirmed as cases (Hildesheim et al., 1992), of which 100% agreed to participate. All 104 hospital controls agreed to participate while only 77% of community controls agreed to participate (Hildesheim et al., 1992). **Outcome definition:** Diagnosis of nasopharyngeal was confirmed by histological review for all cases. Histological typing not reported. **Design:** Hospital-based case-control study of 104 predominantly non-Chinese cases of nasopharyngeal cancer. 205 controls (104 hospital and 101 community cases) matched on gender, age, and hospital or neighborhood. **Analysis: RRs estimated by** ORs were calculated by conditional logistic regression and adjusted for education, years since first exposure to dust and exhaust fumes, smoking, antimosquito coils, herbal medicines, and diet including processed meats and fresh fish. **Related studies:** Hildesheim et al. (1992) **Confidence in effect estimates:**[a]  **MEDIUM ↓** (Potential bias toward the null)	**Exposure assessment:** Occupational history obtained by interview for all participants. Occupational exposure to formaldehyde classified by industrial hygienist as likely or unlikely. Multiple exposure metrics including analysis by length of exposure, length of exposure lagged 10 years, TSFE, and age at first exposure were evaluated. **Duration and timing:** Duration of exposure was evaluated. **Variation in exposure:** Time since first exposure: Level 1 (never) Level 2 (<25 years) Level 3 (≥25 years) Antimosquito coil exposure: Level 1 (never) Level 2 (<daily) Level 3 (≥ daily) Length of exposure: Level 1 (never) Level 2 (<15 years) Level 3 (≥15 years) Length of exposure lagged 10 years: Level 1 (no) Level 2 (<15 years) Level 3 (≥15 years) Time since first exposure: Level 1 (never) Level 2 (<25 years) Level 3 (≥25 years) Level 4 (≥35 years) Age at first exposure: Level 1 (never) Level 2 (<25 years) Level 3 (≥25 years) **Other exposures:** dust and exhaust exposure, fresh or salted fish consumption, smoking, antimosquito coils, and herbal medicines. Note: Independent testing of six brands of East Asian mosquito coils evaluated the emission rates of carbonyl compounds in the mosquito smoke and reported that	**Internal comparisons:** Multivariate results from Table 4 in West et al. Time since first exposure: Level 1 OR = 1.0 (Ref. value) [75] Level 2 OR = 1.2 (0.41–3.6) [12] Level 3 OR = 4.0 (1.3–12.3) [14] Antimosquito coil exposure: Level 1 OR = 1.0 (Ref. value) [59] Level 2 OR = 1.4 (0.64–2.8) [24] Level 3 OR = 5.9 (1.7–20.1) [21] **Additional:** Bivariate results adjusted only for dust/exhaust from Table 1 Length of exposure (bivariate): Level 1 OR = 1.0 (Ref. value) [75] Level 2 OR = 2.7 (1.1–6.6) [19] Level 3 OR = 1.2 (0.48–3.2) [8] Length of exposure lagged 10 years (bivariate): (Reference value included eight cases and three controls exposed only in the 10 years before diagnosis) Level 1 OR = 1.0 (Ref. value) [83] Level 2 OR = 1.6 (0.65–3.8) [11] Level 3 OR = 2.1 (0.70–6.2) [8] Age at first exposure (bivariate): Level 1 OR = 1.0 (Ref. value) [75] Level 2 OR = 2.7 (1.1–6.6) [16] Level 3 OR = 1.2 (0.47–3.3) [11] Time since first exposure (bivariate): Level 1 OR = 1.0 (Ref. value) [75] Level 2 OR = 1.3 (0.65–3.8) [12] Level 3 OR = 2.9 (1.1–7.6) [14] Time since first exposure (bivariate): Level 4 OR = 5.6 (0.58–52.9) [5] Authors noted that stronger effects were not evident among those considered most likely to have been exposed or most likely to have been exposed to high doses.

Study	Exposures	Results: effect estimate (95% CI) [# of Cases]
IB: Exposure Group C **Cf**: Controlling for other sources of formaldehyde may have underestimated effect of main formaldehyde exposures.	formaldehyde and acetaldehyde had the highest emission rates (Liu et al., 2003). Among the three experiments on each of the six brands, the range of formaldehyde concentrations was from 0.87 µg/m^3 (0.7 ppb) to 25 µg/m^3 (20 ppb). **[**As noted in Appendix A.5.9, Control for mosquito coils may have underestimated the estimated effect of formaldehyde.**]**	
Reference: Roush et al. (1987b) **Population:** Males identified from the Connecticut Tumor Registry who died of any cause during 1935−1975. **Outcome definition:** Diagnosis of nasopharyngeal cancer based on case registration by the Connecticut Tumor Registry. Clinical records reviewed for >75% of cases. Histological typing not reported. **Design:** Population-based case-control study of 173 male cases of nasopharyngeal cancer. Controls were 605 males dying in Connecticut during the same time period, randomly selected from state death certificates. **Analysis:** ORs calculated by logistic regression and adjusted for age at death, year at death, and availability of occupational information. **Confidence in effect estimates:**[a]  **MEDIUM ↓** (Potential bias toward the null) **IB**: Exposure Group C	**Exposure assessment:** Occupational history obtained by city directories and death certificates, which yielded information on job, industry, employer, and year of employment. Exposure classification scheme based on potential for formaldehyde exposure, probability of exposure for each participant and each job-industry pair, and level of exposure. Probability of exposure defined as unexposed, possibly exposed, probably exposed, or definitely exposed. Level of exposure estimated as zero, low (<1 ppm), and high (≥1 ppm). Among those probably exposed to some level of formaldehyde for most of their working lifetime, the extent and level of exposure were evaluated. **Duration and timing:** Duration of exposure was evaluated. **Variation in exposure:** Exposure level and timing of exposure: Level 1 (unexposed) Level 2 (probably exposed most of working life) Level 3 (probably exposed most of working life and probably exposed 20+ years before death) High exposure level and timing of exposure: Level 1 (unexposed)	Exposure level and timing of exposure: Level 1 OR = 1.0 (Ref. value) [# not given] Level 2 OR = 1.0 (0.6−1.7) [21] Level 3 OR = 1.3 (0.7−2.4) [17] High exposure level and timing of exposure: Level 1 OR = 1.0 (Ref. value) [# not given] Level 2 OR = 1.4 (0.6−3.1) [9] Level 3 OR = 2.3 (0.9−6.0) [7] **Additional:** Age of Death 68+ High exposure level and timing of exposure: Level 3 OR = 4.0 (1.3−12.0) [6]

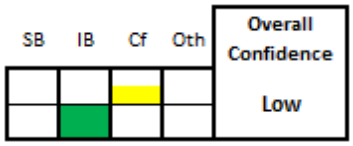
Study	Exposures	Results: effect estimate (95% CI) [# of Cases]
	Level 2 (probably exposed most of working life and probably to high level in some year) Level 3 (probably exposed most of working life and probably exposed to high level 20+ years before death) **Other exposures:** Not evaluated as potential confounders. [As noted in Appendix A.5.9: Exposure to wood dust was not found to be a risk factor for all nasal cancers (NPC + SNC). This suggests a lower potential for confounding by wood dust.]	
Reference: Olsen et al. (1984) **Population:** Male and females linked to the Danish Cancer Registry during 1970−1982. **Outcome definition:** Diagnosis of cancer of the nasopharynx based on ICD code 146 from Registry data. 9% of nasopharyngeal cases were sarcomas and 91% were carcinomas. Sarcomas were excluded but gender-specific case counts were not provided for carcinomas. **Design:** Population-based case-control study of 266 cases of nasopharyngeal cancer. Three controls per case were selected for the same distributions of age, sex, and year of diagnosis as cases. **Analysis:** OR calculated using programs developed by Rothman and Boice (1979). **Confidence in effect estimates:**[a]  **MEDIUM ↓** (Potential bias toward the null) **IB**: Exposure Group C	**Exposure assessment:** Employment histories from 1964 maintained by Danish Cancer Registry. Occupational exposures estimated by industrial hygienists based on industries or occupations considered to have certain or probably exposure. Authors reported that 4.2 and 0.1% of control males and females, respectively, were exposed to formaldehyde. **Duration and timing:** Exposure period starting at 1964. Exposure to formaldehyde may have been between 0 and 20 years depending on when first exposed during the define exposure period. **Variation in exposure:** Occupational exposure: Level 1 (no exposure) Level 2 (ever exposed) Time since first exposure: Level 1 (≤10 years) Level 2 (>10 years) **Coexposures:** Coexposure evaluated included: wood dust, paint, lacquer, and glue. [As noted in Appendix A.5.9 Wood dust is associated with SNC and was evaluated as a potential confounder of NPC but was not a risk factor.]	**Internal comparisons:** Occupational exposure: Men [≈196 (91% of 215)] Level 1 RR = 1.0 (Ref. value) [# not given] Level 2 RR = 0.7 (0.3−1.7) [# not given] Women [≈90 (91% of 99)] Level 1 RR = 1.0 (Ref. value) [# not given] Level 2 RR = 2.6 (0.3−21.9) [# not given] Time since first exposure: No evidence of association (data not shown).

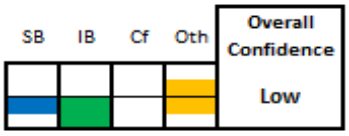
Study	Exposures	Results: effect estimate (95% CI) [# of Cases]
Reference: Coggon et al. (2014) **Population:** 14,008 British men employed in six chemical industry factories which produced formaldehyde. Cohort mortality followed from 1941 through 2012. Cause of deaths was known for 99% of 5,185 deaths through 2000. Similar cause of death information not provided on 7,378 deaths through 2012. Vital status was 98.9% complete through 2003. Similar information not provided on deaths through 2012. **Outcome definition:** Death certificates used to determine cause of deaths from nasopharyngeal cancer. **Design:** Cohort mortality study with external comparison group with a nested case-control study. **Analysis:** SMRs based on English and Welsh age- and calendar-year-specific mortality rates. **Related studies:** Acheson et al. (1984) Gardner et al. (1993) Coggon et al. (2003) **Confidence in effect estimates:**[a]  **LOW ↓** (Potential bias toward the null; low sensitivity) **IB**: Exposure is Group B; Lack of latency analysis. **Oth**: Low power due to rarity of cases.	**Exposure assessment:** Exposure assessment based on data abstracted from company records. Jobs categorized as background, low, moderate, high, or unknown levels. **Duration and timing:** Occupational exposure during 1941–1982. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** Not evaluated. Potential low-level exposure to styrene, ethylene oxide, epichlorhydrin, solvents, asbestos, chromium salts, and cadmium. [As noted in Appendix A.5.9: Styrene is associated with LHP cancers but not URT cancers. Asbestos is associated with URT cancers, but not this outcome. Other coexposures are not known risk factors for this outcome.]	**External comparisons:** Exposed: Observed: 1 deaths Expected: 1.7 deaths $SMR_{Exposed}$ = 0.59 (0.03–2.90) [†] [1] [†]EPA derived confidence intervals for the SMRs using Fischer's Exact method (See Armitage and Cullis (1971); Snedecor and Cochran (1980) for nonzero SMRs and using the Mid-P method See Rothman and Boice (1979).
Reference: Meyers et al. (2013) **Population:** 11,043 workers in 3 U.S. garment plants exposed for at least 3 months. Women comprised 82% of the cohort. Vital status was followed through 2008 with 99.7% completion	**Exposure assessment:** Individual-level exposure estimates for 549 randomly selected workers during 1981 and 1984 with 12–73 within each department. Formaldehyde levels across all departments and facilities were similar.	**External comparisons:** SMR = 0 (0–2.77) [0]

Study	Exposures	Results: effect estimate (95% CI) [# of Cases]
Outcome definition: Death certificates used to determine both the underlying cause of death from nasopharyngeal cancer (ICD code in use at time of death). Histological typing not provided. **Design:** Prospective cohort mortality study with external and internal comparison groups. **Analysis:** SMRs calculated using sex, age, race, and calendar-year-specific U.S. mortality rates. **Related studies:** Stayner et al. (1985) Stayner et al. (1988) Pinkerton et al. (2004) **Confidence in effect estimates:**[a]  **LOW** ↓ (Potential bias toward the null) **IB**: Exposure Group A; Lack of latency analysis. **Oth**: Low power due to rarity of cases.	Geometric TWA8 exposures ranged from 0.09–0.20 ppm. Overall geometric mean concentration of formaldehyde was 0.15 ppm, (GSD 1.90 ppm). Area measures showed constant levels without peaks. Historically earlier exposures may have been substantially higher. **Duration and timing:** Exposure period from 1955 to 1983. Median duration of exposure was 3.3 years. More than 40% exposures <1963. Median time since first exposure was 39.4 years. Duration and timing since first exposure were not evaluated for this cancer. **Variation in exposure:** Not evaluated. **Coexposures:** Study population specifically selected because industrial hygiene surveys at the plants did not identify any chemical exposures other than formaldehyde that were likely to influence findings.	
Reference: Siew et al. (2012) **Population:** All Finnish men born during 1906–1945 who participated in census and were employed in 1970 (*n* = 1.2 million). Vital status was "virtually complete." **Outcome definition:** Diagnosis of cancer reported to the Finnish Cancer Registry. **Design:** Prospective national cohort incidence study with internal comparison groups. **Analysis:** RRs calculated controlling for sex, age, socioeconomic status, period of follow-up, and smoking. **Confidence in effect estimates:**[a]	**Exposure assessment:** Individual-level exposure estimates based on matching occupations listed in the census to the Finnish job-exposure matrix which covers major occupational exposures and provided exposure estimates for formaldehyde. **Duration and timing:** Duration and timing since first exposure were not evaluated. **Variation in exposure:** Exposure to formaldehyde: Level 1 (none) Level 2 (any) **Coexposures:** Wood dust exposures were controlled for in analyses.	**Internal comparisons:** Exposure to formaldehyde: Level 1 RR = 1.00 (Ref. value) [144] Level 2 RR = 0.87 (0.34–2.20) [5]

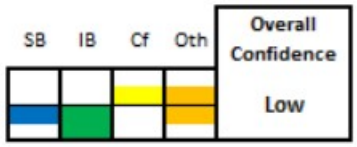
Study	Exposures	Results: effect estimate (95% CI) [# of Cases]
 **LOW ↓** (Potential bias toward the null; low sensitivity) **IB**: Exposure Group D **Oth**: Low power due to rarity of exposure.		
Reference: Yang et al. (2005) **Population:** Taiwanese men and women from 325 families which had two or more nonparent-offspring family members diagnosed with nasopharyngeal cancer (other first-, second-, or third-degree relatives). Cases were identified from the national tumor registry. **Outcome definition:** Diagnosis of incident nasopharyngeal cancer was confirmed by histological review for all cases (*n* = 502). An earlier report on 375 cases from the same series reported >90% diagnosed with nonkeratinizing and undifferentiated carcinomas and 9% with squamous cell carcinoma Hildesheim et al. (2001) **Design:** Family-based case-control study of nasopharyngeal cancer. Cases from high-risk families were compared to two controls groups. Initial set of 375 cases reported by Cheng et al. (1999) had a 99% occupational questionnaire response rate. Similar data were available for 60% of new cases (*n* = 127) with the remainder considered to be missing at random. Overall case response rate is 85%. The Family control groups consisted of up to five unaffected siblings, the parents of affected subjects, or spouses of affected cases' children (*n* = 1,944; participation rate not given). Population controls (*n* = 327; 88% response rate) were originally matched to a subset of cases accrued at an earlier time (*n* = 375) matched	**Exposure assessment:** Occupational history obtained from interviews of cases and controls for jobs held for ≥1 year since age 16 and identified job title, typical activities/duties, type of industry, and tools and/or materials used. Industrial hygienist assigned Standard Industry Classification/Standard Occupational Classification codes to jobs, assigning each a probability and intensity of exposure on a 0 (not exposed) to 9 (strong) scale. Cumulative exposure defined as the product of average intensity and duration. **Duration and timing:** Duration was evaluated as a component of the cumulative exposure score. The timing of exposure was not evaluated. **Variation in exposure:** Intensity scored 0–9 Duration in years Cumulative exposure (Intensity*duration): Level 1 (none) Level 2 (<25) Level 3 (≥25) **Other exposures:** smoking, betel nut use, wood exposure, and salted fish consumption which were not controlled for in the analysis. [As noted in Appendix A.5.9: In this study, smoking was inversely associated with NPC. Since smoking is positively associated with	**Internal Comparisons:** Familial cases (*n* = 502) compared to Family controls (*n* = 1,944) Cumulative exposure: Level 1 OR = 1.0 (Ref. value) [# not given] Level 2 OR = 1.03 (0.60–1.76) [# not given] Level 3 OR = 1.31 (0.87–1.97) [# not given] Familial cases (*n* = 502) compared to population controls (*n* = 327) Cumulative exposure (Intensity*duration): Level 1 OR = 1.00 (Ref. value) [# not given] Level 2 OR = 1.30 (0.70–2.39) [# not given] Level 3 OR = 4.29 (2.45–7.51) [# not given]

Study	Exposures	Results: effect estimate (95% CI) [# of Cases]
on age, sex and residence (Cheng et al., 1999). The same population controls and cases were later augmented with additional cases to encompass the total of 502 cases. **Analysis:** For the Family controls, ORs were calculated by conditional logistic regression matched on family. For the Population controls, OR's were calculated by unconditional logistic regression controlling for age and sex; however, while population controls were originally matched on residence, residence was not controlled for in this later analysis. **Related studies:** Hildesheim et al. (2001); Cheng et al. (1999); Hildesheim et al. (1997) **Confidence in effect estimates:**[a]  **LOW** ↓ (Potential bias toward the null) **IB**: Exposure Group D **SB**: Potential selection bias using next of kin only among the cases which may result in poorer quality exposure data and a bias toward the null. **Cf**: Negative confounding possible. **Oth**: Low sensitivity due to incomplete control of matching factors.	formaldehyde, there may be negative confounding by smoking in this study.]	
Reference: Yu et al. (2004) **Population:** Deceased male and female restaurant workers who died during 1986−1995 and were registered as union members by four major Chinese-style restaurant workers' unions in Hong Kong (*n* = 1,225). **Outcome definition:** Underlying cause of death from nasopharyngeal cancer (ICD-9: 147) obtained from the Hong	**Exposure assessment:** Occupational history obtained from union records. Waiters, waitresses and kitchen workers presumed to be exposed to formaldehyde based on independent studies of air quality from the kitchen exhausts of Hong Kong restaurants (Ho et al., 2006b; EHS Consultants Ltd., 1999) Note: Ho et al. (2006b) reported time-averaged formaldehyde concentrations	**Internal Comparisons:** Male and female (Waiters and waitresses) Wait staff cases compared to kitchen worker controls MOR = 2.53 (1.01−6.36) [21] Male only (Waiters) Wait staff cases compared to kitchen worker controls MOR = 2.61 (1.02−6.69) [17] **External Comparisons:**

Study	Exposures	Results: effect estimate (95% CI) [# of Cases]
Kong Census and Statistics Department (*n* = 29). Cause of death available for more than 80% of restaurant workers. Histological typing not reported. **Design:** Mortality odds ratio where cases are deaths from nasopharyngeal cancer and controls are deaths from all other causes of death after excluding cancer. Internal control group composed of other deceased kitchen workers. External control group composed of all noncancer deaths from the general population in Hong Kong. **Analysis:** Mortality odds ratios (MORs) based on the internal control group were calculated by logistic regression controlling for sex, age at death, year of death, and place of origin. For the external control group, MORs were calculated by logistic regression controlling for sex, age at death, and year of death. **Related studies:** Ho et al. (2006a) EHS Consultants Ltd. (1999) **Confidence in effect estimates:**[a]  **LOW** ↓ (Potential bias toward the null) **IB**: Exposure Group C; Latency not evaluated. **Cf**: Potential confounding by smoking.	at Chinese restaurants in Hong Kong were reported as high as 249 ppb (306 µg/m^3). The Hong Kong Environmental Protection Department survey of indoor air at local restaurants reported a mean formaldehyde concentration of 162 µg/m^3 with a high value of 975 µg/m^3 (EHS Consultants Ltd., 1999). **Duration and timing:** Duration of exposure was evaluated based on length of restaurant union membership. **Variation in exposure:** Cumulative exposure: Level 1 (none) Level 2 (<15 yrs union membership) Level 3 (16–24 yrs union membership) Level 4 (≥25 yrs union membership) **Other exposures:** not evaluated. Wait staff exposed to other sources of formaldehyde such as environmental tobacco smoke, furniture, carpeting, and room partitions made of plywood and fiberboard, which are not shared by kitchen staff. [As noted in Appendix A.5.9: Smoking was evaluated as a potential confounder because 49% of staff smoked compared to 27% of population, but it was insufficient to explain the observed effects.]	Male and female (Waiters and waitresses) Wait staff cases compared to general Hong Kong male and female population controls MOR = 3.28 (2.08–5.16) [21] Male only (Waiters) Wait staff cases compared to general Hong Kong male population controls MOR = 3.02 (1.82–5.00) [17] Male only (Waiters) Cumulative exposure: Level 1 MOR = 1.00 (Ref. Value) [3,225] Level 2 MOR = 2.50 (1.14–5.49) [7] Level 3 MOR = 3.41 (1.56–7.45) [7] Level 4 MOR = 3.75 (1.12–12.54) [3] Female only (Waitresses) Wait staff cases compared to general Hong Kong female population controls MOR = 4.58 (1.63–12.86) [4]
Reference: Hansen and Olsen (1995) **Population:** 2,041 men with cancer who were diagnosed during 1970–1984 and whose longest work experience occurred at least 10 years before cancer diagnosis. Identified from the Danish Cancer Registry and matched with the Danish Supplementary Pension Fund. Ascertainment considered complete.	**Exposure assessment:** Individual occupational histories including industry and job title established through company tax records to the national Danish Product Register. Subject were considered to be exposed to formaldehyde if: (1) they had worked in an industry known to use more than 1 kg formaldehyde per employee per year and (2) subject's longest single work experience (job) in	**External comparisons:** Overall (exposure to formaldehyde ≥10 years prior to cancer diagnosis) SPIR = 1.3 (0.3–3.2) [4]

Study	Exposures	Results: effect estimate (95% CI) [# of Cases]
Pension record available for 72% of cancer cases. **Outcome definition:** Nasopharyngeal cancer (ICD-7: 146) listed on Danish Cancer Registry file. Histological typing not reported. **Design:** Proportionate incidence study with external comparison group. **Analysis:** Standardized proportionate incidence ratio calculated as the proportion of cases for a given cancer in formaldehyde-associated companies relative to the proportion of cases for the same cancer among all employees in Denmark. Adjusted for age and calendar time. **Confidence in effect estimates:**[a]  **LOW** ↓ (Potential bias toward the null) **IB**: Exposure Group D **Oth**: Low power due to rarity of cases.	that industry since 1964 was ≥10 years prior to cancer diagnosis. **Duration and timing:** Exposure period not stated. Based on date of diagnosis during 1970−1984, and the requirement of exposure more than 10 years prior to diagnosis, the approximate period was 1960−1974. **Variation in exposure:** Not evaluated. **Coexposures:** Not evaluated for potential confounding [As noted in Appendix A.5.9: While other coexposures were not evaluated, the overall correlation between coexposures in multiple occupational industries is likely to be low.]	
Reference: Malker et al. (1990) **Population:** Employed Swedish men newly diagnosed with nasopharyngeal cancer identified during 1961−1979 registered by the Swedish Cancer-Environment Registry. **Outcome definition:** Microscopic confirmation obtained for 99.6% of nasopharyngeal cases. Squamous cell carcinomas constituted 48% of cases with 37% classified as unspecified carcinomas, 5% transitional cell carcinomas, and 3% adenocarcinomas. **Design:** Population-based standardized incidence ratio study of 471 incidence cases of nasopharyngeal cancer compared to expected number of cases among men in occupational groups defined by employment in 1960.	**Exposure assessment:** Occupations presumed to be exposed to formaldehyde. **Duration and timing:** Duration and timing of exposure were not evaluated. **Variation in exposure:** Occupation and industry **Coexposures:** Not evaluated as potential confounders. [As noted in Appendix A.5.9: Wood dust is associated with URT cancers and would likely be positively correlated with formaldehyde exposure. Potential for confounding is unknown but could have inflated the observed effect.]	**External comparisons:** Occupation Glassmakers SIR = 6.2 (1.58−16.87)[†] [3] Bookbinders SIR = 6.1 (1.55−16.59)[†] [3] Shoemakers SIR = 3.8 (1.39−8.42)[†] [5] Industry Shoe repair SIR = 4.0 (1.47−8.87)[†] [5] Fiberboard plant SIR = 3.9 (1.24−9.40)[†] [4] [†]EPA derived CIs using the Mid-P Method (See Rothman and Boice, 1979)

Study	Exposures	Results: effect estimate (95% CI) [# of Cases]
Analysis: SIRs calculated as the ratio of observed to expected cases of nasopharyngeal cancer. **Related studies:** Malker et al. (1990) **Confidence in effect estimates:**[a]  **LOW** ↓ (Potential bias toward the null; low sensitivity) **IB**: Exposure Group D; Latency not evaluated. **Cf**: Potential confounding.		
Reference: Vaughan (1989) **Population:** Males and females between the ages of 20 and 74 years residing in a 13-county area identified by the Washington State Cancer Surveillance System during 1980–1983. Participation for all cases was 68.7 and 80.0% for controls. **Outcome definition:** Diagnosis of nasopharyngeal cancer based on review of hospital medical records, surveillance of private radiotherapy and pathology practices, and state death certificates. Nonsquamous cell cancers were excluded from the study. **Design:** Population-based, case-control study of 21 cases with nasopharyngeal cancer. 552 controls were identified by random digit dialing in same geographic area. **Analysis:** ORs were calculated by logistic regression and adjusted for age, gender, and race. Induction periods were evaluated. **Related studies:** Vaughan et al. (1986a, 1986b) **Confidence in effect estimates:**[a]	**Exposure assessment:** Presumed exposure to formaldehyde. Interview-based information on lifetime occupational history by job type and industry. Occupations evaluated for both no lag and 15-year lag time between recent exposure and diagnosis. **Duration and timing:** Duration and timing of exposure were evaluated. **Variation in exposure:** Occupation and industry Duration: Level 1 (unexposed) Level 2 (1 to 9 years) Level 3 (>10 years) **Other exposures:** Not evaluated as potential confounders. [As noted in Appendix A.5.9: Wood dust is associated with risk of sinonasal cancer and was not evaluated as a confounder. ~50% of cases interviews completed by next of kin. May result in poorer quality exposure data and a bias toward the null.]	**Internal comparisons:** Carpenter (lagged 15 years) All Industries: OR = 4.5 (1.1–18.7) [3] All Industries by Duration: Level 1 OR = 1.0 (Ref. value) Level 2 OR = 1.6 (not provided) Level 3 OR = 12.4 (not provided) Chi^2 trend = 8.65 (p = 0.01)[†] Carpenter (lagged 15 years) Construction industry: OR = 6.8 (1.6–28.2) [3] Construction by Duration: Level 1 OR = 1.0 (Ref. value) Level 2 OR = 2.1 (not provided) Level 3 OR = 31.8 (not provided) Chi^2 trend = 14.86 (p = 0.0006)[†] Food Service (lagged 15 years) All Industries: OR = 1.8 (0.6–5.7) [4] All Industries by Duration: Level 1 OR = 1.0 (Ref. value) Level 2 OR = 1.6 (not provided) Level 3 OR = 4.0 (not provided) Chi^2 trend = 1.65 (p = 0.44)[†] Food Service (lagged 15 years) Retail Trade: OR = 1.9 (0.5–6.9) [3]

Study	Exposures	Results: effect estimate (95% CI) [# of Cases]
 **LOW** ↓ (Potential bias toward the null; Low sensitivity) **IB**: Exposure Group D **SB**: Potential selection bias using next of kin only among the cases which may result in poorer quality exposure data and a bias toward the null. **Oth**: Low power due to rarity of cases.		Retail Trade by Duration: Level 1 OR = 1.0 (Ref. value) Level 2 OR = 1.4 (not provided) Level 3 OR = 9.3 (not provided) Chi^2 trend = 2.21 (p = 0.33)† †EPA computed p-value assuming 2 d.f.
Reference: Vaughan et al. (1986a) **Population:** Males and females between the ages of 20 and 74 years residing in a 13-county area identified by the Washington State Cancer Surveillance System during 1980–1983. Participation for all cases was 68.7 and 80.0% for controls. **Outcome definition:** Diagnosis of nasopharyngeal cancer based on review of hospital medical records, surveillance of private radiotherapy and pathology practices, and state death certificates. Histological typing not reported; however, according to Vaughan (1989), 6 cases were nonsquamous cell cancers. **Design:** Population-based, case-control study of 27 cases with nasopharyngeal cancer. 552 controls were identified by random digit dialing in same geographic area. **Analysis:** ORs were calculated by logistic regression and adjusted for cigarette smoking and ethnic origin. Induction periods were evaluated. **Related studies:** Vaughan (1989); Vaughan et al. (1986b) **Confidence in effect estimates:**[a]	**Exposure assessment:** Interview-based information on lifetime occupational exposure to formaldehyde with cases, next of kin, and controls. Exposure from available hygiene data, NIOSH and other data, and NCI job-exposure linkage system. Multiple exposure metrics including intensity, # of years exposed, and exposure score based on the sum of # years spent per job weighted by estimated formaldehyde level were evaluated. Exposure score calculated for both no lag and 15-year lag time between recent exposure and diagnosis. **Duration and timing:** Duration of exposure was evaluated. **Variation in exposure:** Intensity of exposure: Level 1 (background) Level 2 (low) Level 3 (medium or high) Number of years exposed: Level 1 (0 years) Level 2 (1 to 9 years) Level 3 (≥10 years) Exposure score (no lag): Level 1 (0 to 4) Level 2 (5 to 19) Level 3 (≥20) Exposure score (15-year lag): Level 1 (0 to 4) Level 2 (5 to 19) Level 3 (≥20)	**Internal comparisons:** Intensity of exposure: Level 1 OR = 1.0 (Ref. value) [16] Level 2 OR = 1.2 (0.5–3.3) [7] Level 3 OR = 1.4 (0.4–4.7) [4] Number of years exposed: Level 1 OR = 1.0 (Ref. value) [16] Level 2 OR = 1.2 (0.5–3.1) [8] Level 3 OR = 1.6 (0.4–5.8) [3] Exposure score (no lag): Level 1 OR = 1.0 (Ref. value) [21] Level 2 OR = 0.9 (0.2–3.2) [3] Level 3 OR = 2.1 (0.6–7.8) [3] Exposure score (15-year lag): Level 1 OR = 1.0 (Ref. value) [21] Level 2 OR = 1.7 (0.5–5.7) [4] Level 3 OR = 2.1 (0.4–10.0) [2] **Additional:** Excluding Next of Kin Interviews [15] Exposure score (no lag): Level 1 OR = 1.0 (Ref. value) [# not given] Level 2 OR = 1.1 (0.2–5.5) [# not given] Level 3 OR = 2.2 (0.4–10.8) [# not given] Exposure score (15-year lag): Level 1 OR = 1.0 (Ref. value) [# not given] Level 2 OR = 1.4 (0.3–7.3) [# not given] Level 3 OR = 3.1 (0.6–15.4) [# not given]

Study	Exposures	Results: effect estimate (95% CI) [# of Cases]
 **LOW ↓** (Potential bias toward the null) **IB**: Exposure Group D **SB**: Potential selection bias using next of kin only among the cases which may result in poorer quality exposure data and a bias toward the null.	**Other exposures:** Not evaluated as potential confounders. [As noted in Appendix A.5.9: Wood dust is associated with risk of sinonasal cancer and was not evaluated as a confounder. However, as this is a case-control study the correlation between formaldehyde and wood dust is expected to be small and thus wood dust would not be expected to be a confounder.]	
Reference: Vaughan et al. (1986b) **Population:** Males and females between the ages of 20 and 74 years residing in a 13-county area identified by the Washington State Cancer Surveillance System between 1980 and 1983. Participation for all cases was 68.7 and 80.0% for controls. **Outcome definition:** Diagnosis of nasopharyngeal cancer based on review of hospital medical records, surveillance of private radiotherapy and pathology practices, and state death certificates. Histological typing not reported; however, according to Vaughan (1989), 6 cases were nonsquamous cell cancers. **Design:** Population-based, case-control study of 27 cases with nasopharyngeal cancer. 552 controls were identified by random digit dialing in same geographic area. **Analysis:** ORs were calculated by multiple logistic regression and adjusted for cigarette smoking and ethnic origin. **Related studies:** Vaughan (1989); Vaughan et al. (1986a, 1986b) **Confidence in effect estimates:**[a]	**Exposure assessment:** Interview-based information on lifetime occupational history and residential history from cases, next of kin, and controls. Multiple exposure metrics including type of dwelling (i.e., mobile home) and use of particleboard or plywood were evaluated. **Duration and timing:** Exposure period since 1950. Duration of exposure was evaluated. **Variation in exposure:** Lived in a mobile home: Level 1 (no) Level 2 (yes) Lived in a mobile home (lagged 15 years): Level 1 (no) Level 2 (yes) Years of residence in mobile home: Level 1 (0 years) Level 2 (1 to 9 years) Level 3 (≥10 years) Years of exposure to particleboard or plywood: Level 1 (0 years) Level 2 (1 to 9 years) Level 3 (≥10 years) Mobile home exposures (lagged 15 years): Level 1 (none) Level 2 (occupation only) Level 3 (mobile home only) Level 4 (both) Note: The majority (84%) of mobile homes in the United States at about this time were reported to have mean	**Internal comparisons:** Lived in mobile home: Level 1 OR = 1.0 (Ref. value) [19] Level 2 OR = 3.0 (1.2–7.5) [8] Lived in mobile home (lagged 15 years): Level 1 OR = 1.0 (Ref. value) [24] Level 2 OR = 3.0 (0.8–11.2) [3] Years of residence in mobile home: Level 1 OR = 1.0 (Ref. value) [19] Level 2 OR = 2.1 (0.7–6.6) [4] Level 3 OR = 5.5 (1.6–19.4) [4] Years of exposure to particleboard or plywood: Level 1 OR = 1.0 (Ref. value) [17] Level 2 OR = 1.4 (0.5–3.4) [6] Level 3 OR = 0.6 (0.2–2.3) [4] Mobile home exposures (lagged 15 years): Level 1 OR = 1.0 (Ref. value) [15] Level 2 OR = 1.7 (0.5–5.7) [4] Level 3 OR = 2.8 (1.0–7.9) [6] Level 4 OR = 6.7 (1.2–38.9) [2] **Additional:** Excluding Next of Kin Interviews [15] Lived in mobile home: Level 1 OR = 1.0 (Ref. value) [10] Level 2 OR = 2.8 (0.9–8.8) [5]

Study	Exposures	Results: effect estimate (95% CI) [# of Cases]
 **LOW ↓** (Potential bias toward the null) **IB**: Exposure Group D **SB**: Potential selection bias using next of kin only among the cases which may result in poorer quality exposure data and a bias toward the null. **Cf**: Low potential for confounding.	formaldehyde exposures in excess of 100 ppb, with 22% having mean exposures in excess of 500 ppb (Breysse (1984) as cited in WHO (1989). **Coexposures:** Not evaluated. Information on occupational exposures provided in Vaughan et al. (1986a). [As noted in Appendix A.5.9: Wood dust is associated with risk of sinonasal cancer and was not evaluated as a confounder. However, as this is a case-control study the correlation between formaldehyde and wood dust is expected to be small and thus wood dust would not be expected to be a confounder.]	

[a]Evaluation of sources of bias or study limitations (see details in Appendix A.5.9. SB = selection bias; IB = information bias; Cf = confounding; Oth = other feature of design or analysis. Extent of column shading reflects degree of limitation. Direction of anticipated bias indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact would be likely to be away from the null (i.e., spurious or inflated effect estimate).

Sinonasal cancer

Epidemiological evidence

The most specific classification of sinonasal cancer diagnosis commonly reported across the epidemiological literature has been based on the first three digits of the Seventh, Eighth or Ninth Revision of the ICD code (i.e., Malignant neoplasm of nose, nasal cavities, middle ear and accessory sinuses ICD-7/8/9: 160), although some studies did report the histological type of cancer (i.e., squamous cell carcinoma and adenocarcinoma).

Evidence of an association between formaldehyde exposure and the risk of developing or dying from sinonasal cancer was available from 20 epidemiological studies—7 case-control studies (Mayr et al., 2010; D'Errico et al., 2009; Pesch et al., 2008; Luce et al., 2002; Teschke et al., 1997; Roush et al., 1987b; Olsen and Asnaes, 1986) and 12 cohort studies (Coggon et al., 2014; Beane Freeman et al., 2013; Meyers et al., 2013; Siew et al., 2012; Jakobsson et al., 1997; Hansen and Olsen, 1995; Hayes et al., 1990; Bertazzi et al., 1989; Stroup et al., 1986; Levine et al., 1984a; Walrath and Fraumeni, 1984, 1983). One study, (Luce et al., 2002), combined 12 other case-control studies in a pooled analysis of occupational exposures using a common protocol of standardized

questionnaires and standardized exposure classifications.[21] The results of this pooled analysis of original primary data across studies (Luce et al., 2002) are included in place of those from the 12 individual studies that are listed under "Related studies" in Table 1-33 for Luce et al. (2002). The outcome-specific evaluations of confidence in the precise effect estimate of an association from each study are provided in Appendix A.5.9. Three sets of reported results from Mayr et al. (2010), d'Errico et al. (2009), and Harrington and Oakes (1984) were classified as uninformative due to multiple biases and uncertainties; for details see Appendix A.5.9. Details of the reported results of these studies are provided in the evidence table for sinonasal cancer (see Table 1-33) following the causal evaluation.

Consistency of the observed association

Seventeen informative studies reported risks of sinonasal cancer among study subjects with formaldehyde exposure based on occupational history. These studies examined different populations, in different locations, under different exposure settings, and used different study designs. For sinonasal cancer, it is important to consider the histological subtype or types in each report (squamous cell carcinoma, adenocarcinoma, or mixed). The study results presented in Table 1-33 (by confidence level and publication date) detail all of the reported associations. One additional study (Andjelkovich et al., 1995) reported zero cases of SNC among 3,929 U.S. workers exposed to formaldehyde over 83,064 person-years but reported no data on the number of expected cases and thus was not included here.[22]

Sinonasal cancer is exceedingly rare with expected rates of 0.6 cases per 100,000 people each year (Curado et al., 2007). Many of these cohort studies lacked the statistical sensitivity to detect an association with formaldehyde; eight of 12 cohort studies reported zero cases in their study populations and all but one cohort study (Beane Freeman et al., 2013) were classified with low confidence. For such rare cancers, case-control studies can often be the most informative study design.

Of the nine studies that did observe cases of sinonasal cancer, results from six reported increased risks of sinonasal cancer that appeared to be associated with exposure to formaldehyde—four of six sets of results had been classified with *medium* confidence (Beane Freeman et al., 2013; Luce et al., 2002; Roush et al., 1987b; Olsen and Asnaes, 1986) and two with *low* confidence (Teschke et al., 1997; Hansen and Olsen, 1995). Each of the other three sets of

[21]Note the pooled study by Luce et al. (2002) includes data from 12 publications and thus represents substantially more information than a single result. The references for the source data are: Leclerc et al. (1994); Luce et al. (1993); Magnani et al. (1993); Comba et al. (1992a); Comba et al. (1992b); Luce et al. (1992); Zheng et al. (1992); Vaughan and Davis (1991); Bolm-Audorff et al. (1990); Vaughan (1989); Hayes et al. (1986b); Hayes et al. (1986a); Merler et al. (1986); Vaughan et al. (1986a, 1986b); Hardell et al. (1982); Mack and Preston-Martin (Unpub. Data presented in Luce et al. (2002)); Brinton et al. (1985); Brinton et al. (1984).

[22]For Andjelkovich et al. (1995), assuming a rate of SNC for U.S. workers of 0.6 per 100,000 person-years (Curado et al., 2007), the expected number of cases would have been 0.33 and the ~SMR = 0 (95% CI 0, 5.99).

results that did not report some increase in risk associated with formaldehyde exposure had been in the group classified with *low* confidence, in part due to their lack of sensitivity to detect a true effect (Coggon et al., 2014; Siew et al., 2012; Pesch et al., 2008).

As discussed in a following section on the potential for confounding, wood dust is a very strong risk factor for sinonasal cancer and because coexposure to wood dust may also be correlated with formaldehyde exposures (e.g., in carpentry and other woodworking occupations), wood dust could have been a potent confounder that might have caused the reported effects of formaldehyde to appear inflated due to positive confounding. However, the evaluation of studies in Appendix A.5.9 screened each set of results for potential confounding by wood dust and retained only those results that either controlled for coexposures to wood dust using statistical adjustment in regression analyses or by restricting analyses to workers without coexposure to wood dusts (Beane Freeman et al., 2013; Luce et al., 2002; Teschke et al., 1997; Hansen and Olsen, 1995; Roush et al., 1987b; Olsen and Asnaes, 1986), or those results from studies that were unlikely to have had occupational coexposure to wood dusts (Coggon et al., 2014; Siew et al., 2012; Teschke et al., 1997).

As can be seen in Table 1-33, and in Figure 1-21, which shows the *medium* confidence studies, associations were stronger for adenocarcinomas than for squamous cell carcinomas. However, both histological cell type groupings, and a mixed-type group, yielded results which were consistently elevated—with a clear demonstration of statistical significance for the adenocarcinomas.

In summary, the majority of these studies of different populations, in different locations, exposure settings, and using different study designs reported increased risks of sinonasal cancer associated with formaldehyde exposure that was unlikely to have been confounded by coexposure to wood dust.

Strength of the observed association

While reported relative effect estimates were largely elevated above the null value of unity (1.0) across the sets of results that detected cases of sinonasal cancer, the magnitude of the relative effect estimates varied with the quality of the exposure assessment and stratification by histological cell type. The adenocarcinoma results classified with *medium* confidence reported three-fold (and higher) increased risks of sinonasal cancer that appeared to be associated with higher exposure to formaldehyde after controlling for wood dust (Luce et al., 2002; Hansen and Olsen, 1995; Olsen and Asnaes, 1986). Olsen and Asnaes (1986) reported results among men for adenocarcinoma adjusted for wood dust and among those never exposed to wood dust: for ever vs never exposed to formaldehyde, the RR adjusted for ever being exposed to wood dust was 2.2 (95% CI 0.7, 7.2; 17 exposed cases) while the RR for formaldehyde among men never exposed to wood dust was 7.0 (95% CI: 1.1, 43.9; one exposed case after excluded men ever exposed to wood dust). Further restricting formaldehyde exposures to those first exposed more than 10 years prior to cancer incidence, the RR was 9.5 (95% CI 1.6, 57.8; one exposed case). Luce et al. (2002) reported increased risks for men with the highest cumulative formaldehyde exposure adjusted for wood

dusts (OR = 3.0; 95% CI 1.5, 5.7; 91 cases) and for women (OR = 5.8; 95% CI 1.7, 19.4; five cases). Hansen and Olsen (1995), a low confidence study, reported that for formaldehyde exposures more than 10 years prior to cancer incidence, the Standardized Proportional Incidence Ratio was 3.0 (95% CI 1.4, 5.7; nine cases). One adenocarcinoma study that was classified with *low* confidence and was not able to report results by level of formaldehyde exposure, found a decreased risk of sinonasal cancer among woodworkers ever exposed to formaldehyde [Pesch et al. (2008): OR = 0.46; 95% CI 0.14, 1.54]. Pesch et al. (2008) was the only case-control study of sinonasal cancer that relied on prevalent cases and included cases accrued over a 10-year period. Since the controls in Pesch et al. (2008) were accident victims who were frequency matched on age (<60 vs. 60+ years), it is possible that the prevalent cases available at the time of the study could have been selected for survival, which may have resulted in a downward bias and may explain the inverse findings for this study.

The squamous cell carcinoma study results classified with *medium* confidence reported 1.5-to 2-fold increased risks of sinonasal cancer that appeared to be associated with higher exposure to formaldehyde after controlling for wood dust (Luce et al., 2002; Olsen and Asnaes, 1986), although one study result classified with *low* confidence found no association between sinonasal cancer in the 5% of cases "ever" exposed to formaldehyde (Siew et al. (2012): OR = 0.97; 95% CI 0.47, 2.00).

Temporal relationship of the observed association

In each of the studies, the formaldehyde exposures among the study participants started prior to their diagnoses of sinonasal cancer. Three studies provided analyses of the temporal relationship showing some evidence of the effect of TSFE on the risk of dying from sinonasal cancer (Luce et al., 2002; Roush et al., 1987b; Olsen and Asnaes, 1986). Lagging formaldehyde exposures by 10 or 20 years to account for cancer latency increased the observed effects only slightly for adenocarcinoma results (Luce et al., 2002; Olsen and Asnaes, 1986) and for mixed cell type cancers (Roush et al., 1987b); but not for squamous cell carcinomas (Olsen and Asnaes, 1986). It is notable that for nasopharyngeal cancer in the tissue adjacent to the sinonasal tissues, the effect of latency on the temporal relationship between formaldehyde exposure and cancer mortality was generally longer than 25 years. Only one study of sinonasal cancer examined a lag of 20 years (Luce et al., 2002), and none examined the effect of an even longer latency. If the effect of exposure on the occurrence of sinonasal cancer took longer than the 20 years, then differences in results between lagged and unlagged exposure analyses would be consistent with the available epidemiological data.

Exposure-response relationship

Exposure-response relationships were not typically examined in these studies, most likely due to the rarity of cases in all of the studies except in the large, pooled study of information from 12 publications (Luce et al., 2002); see Table 1-33 for details). No results showing associations with

duration of exposure were reported, but Luce et al. (2002) did state that even though their studies reported primarily on cumulative exposure, "All exposure variables (probability, maximum level, and duration) were associated with the risk of adenocarcinoma." The majority of studies reported only comparisons of exposed versus unexposed subjects. Hansen and Olsen (1995) did report an increase in risk among formaldehyde-exposed blue-collar worker (OR = 3.0; 95% CI 1.4, 5.7) compared to exposed white-collar workers whose likely formaldehyde exposures were considered to have been lower (OR = 0.8; 95% CI 0.02, 4.4). Luce et al. (2002) pooled 196 cases of sinonasal adenocarcinoma and 432 cases of squamous cell carcinoma and was able to contrast risks in three levels of exposure probability with the risk in the unexposed. An exposure-response relationship for adenocarcinoma, controlling for coexposure to wood dust, was observed for both men and women (see Table 1-33) with the highest risks among those with the highest probability of exposure. The OR among men with the highest cumulative exposure was 3.0 (95% CI 1.5, 5.7), while it was 5.8 (95% CI 1.7, 19.4) among women. Among men with adenocarcinoma, the odds ratios adjusted for wood dust increased from OR = 0.7 (95% CI: 0.3, 1.9; six cases) among those with 'low' cumulative exposure, to OR = 2.4 (95% CI: 1.3, 4.5; 31 cases) among those with 'medium' cumulative exposure, to OR = 3.0 (95% CI: 1.5, 5.7; 91 cases) among those with 'high' cumulative exposure.

Potential impact of selection bias, information bias, confounding bias, and chance

Selection bias is an unlikely bias in the epidemiological studies of sinonasal cancer as the case-control studies evaluated exposure status without regard to outcome status and most had participation levels of 85–100%, although one case-control study of prevalent cases accrued over long periods of time had lower participation levels (67% in Pesch et al. (2008)). The cohort study (Hansen and Olsen, 1995) included 72% of eligible participants. Selection biases could obscure a truly larger effect of formaldehyde exposure in analyses based on "external" comparisons with mortality in the general population (Hansen and Olsen, 1995), but would not influence analyses using "internal" or matched comparison groups (Pesch et al., 2008; Luce et al., 2002; Roush et al., 1987b; Olsen and Asnaes, 1986). Information bias from the use of indirect exposure measures is unlikely to have resulted in bias away from the null, however random measurement error or nondifferential misclassification is almost certain to have resulted in some bias toward the null among these studies of sinonasal cancer.

Confounding is a potential bias that could arise if another cause of sinonasal cancer were also associated with formaldehyde exposure. Chemicals and other coexposures that have not been independently associated with sinonasal cancer are not expected to confound results. Other known risk factors for sinonasal cancer include wood dust (Hansen and Olsen, 1995; Olsen and Asnaes, 1986), smoking, and alcohol consumption (Vaughan, 1989). While smoking and alcohol may be independent risk factors for sinonasal cancer they are unlikely to be related to formaldehyde exposure and therefore unlikely to be across-the-board confounders. Wood dust, however, is a potential confounder as many wood-related jobs also have exposures to formaldehyde and the

association between wood dust exposure and sinonasal cancer is extremely strong, with relative risks greater than 30-fold (Olsen and Asnaes, 1986).

Wood dust may be an independent risk factor for sinonasal cancer; however, the majority of investigators presented analytic results for formaldehyde among workers who were either not exposed to wood dusts (Hansen and Olsen, 1995; Olsen and Asnaes, 1986), or else controlled for the potential confounding of the effects of wood dust on the risk of sinonasal cancer and did not find wood dust to be a confounder (Luce et al., 2002).

Consistency across multiple studies is demonstrated by a pattern of increased risk in different populations, exposure scenarios, and time periods. Such consistency makes unmeasured confounding an unlikely alternative explanation for the observed associations. This consistency also reduces the likelihood of chance as an alternative explanation by increasing confidence in the statistical strength of the findings through the accumulation of a larger body of similar evidence. The observations of multiple instances of very strong associations in different settings reduce the likelihood that chance, confounding, or other biases can explain the observed associations.

Causal evaluation

The causal evaluation for formaldehyde exposure and the risk of developing or dying from sinonasal cancer placed the greatest weight on four particular considerations: (1) the consistency of the elevated risk across studies (particularly for adenocarcinoma)—including four sets of results classified with *medium* confidence—one of which represents a large pooled analysis of 12 case-control studies with considerably more cases and with greater detail on formaldehyde exposures; (2) the strength of the association with two results classified with *medium* confidence reporting at least a three-fold increase in risk for adenocarcinoma with lower associations for squamous cell carcinoma; (3) the exposure-response relationship in a large pooled analysis of 12 case-control studies showing increased exposure to formaldehyde was associated with increased risk of sinonasal cancer among people with little, or no exposure to wood dust or in analyses that controlled for wood dust; (4) reasonable confidence that alternative explanations have been addressed, including chance, bias, and confounding within individual studies or across studies, although many of the analyses lacked precision due to the rarity of sinonasal cancer. Consistent observations of genotoxicity in exfoliated buccal cells or nasal mucosal cells across several occupational studies involving diverse exposure settings further supports the evidence for sinonasal carcinogenicity in humans.

This evidence was judged to be near the borderline of *robust* evidence and *moderate* evidence, but one additional consideration increased confidence that the evidence was *robust*. The large, pooled analysis using a case-control study design especially suited to identify associations for this extremely rare cancer (Luce et al., 2002) was considered to be especially informative in identifying the effects of formaldehyde on the risks of sinonasal cancer and provided clear evidence of an association of increased risks of sinonasal cancer with formaldehyde exposure – especially for adenocarcinoma.

Conclusion

The available epidemiological studies provide *robust* evidence of an association consistent with causation between formaldehyde exposure and increased risk of sinonasal cancer.

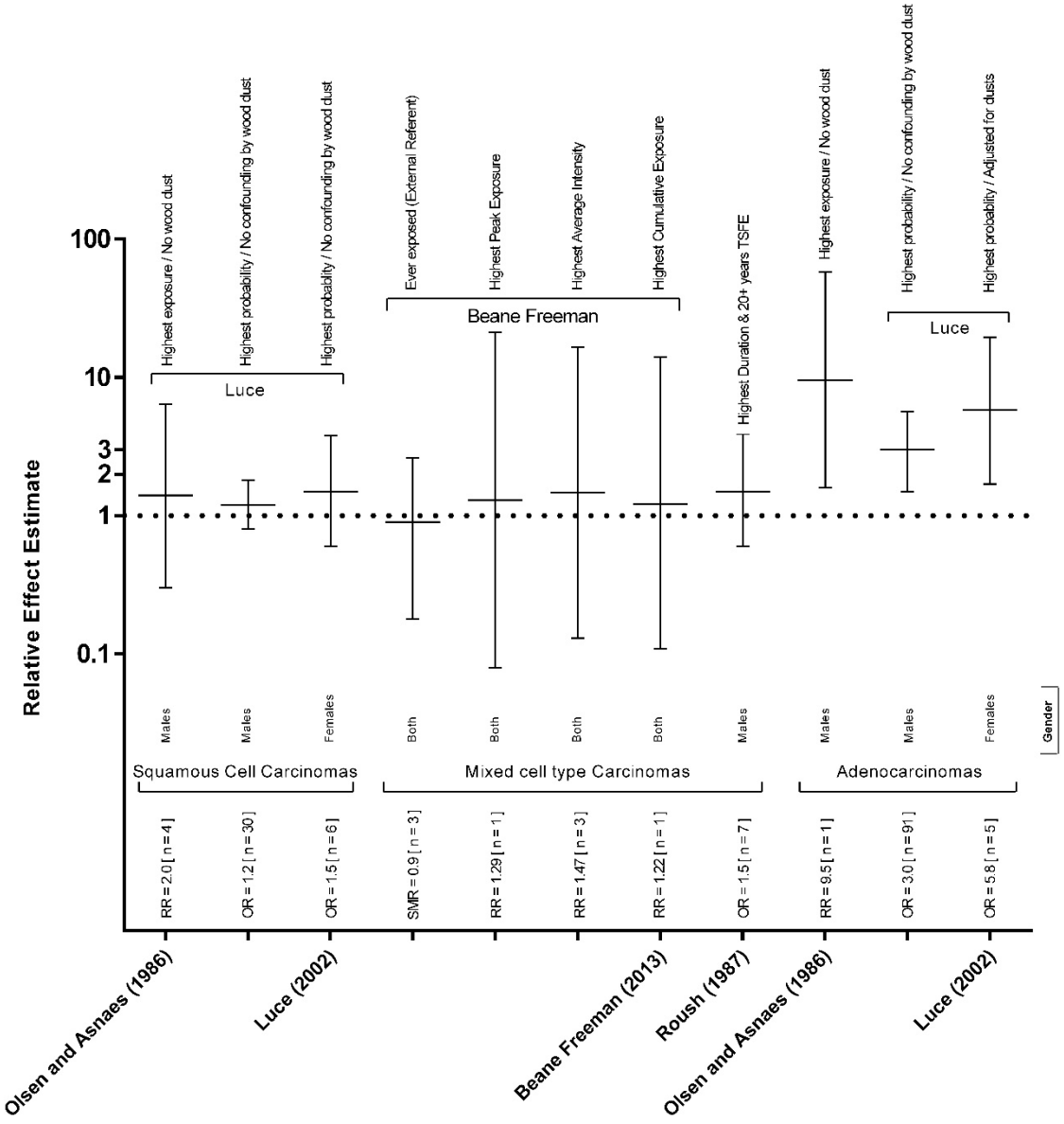


Figure 1-21. Highest (medium) confidence epidemiological studies reporting sinonasal cancer risk estimates.

Results are grouped by histological type as squamous cell carcinomas, mixed cell types, or adenocarcinoma. SMR: standardized mortality ratio. RR: relative risk. OR: odds ratio. TSFE: time since first exposure. For each measure of association, the number of exposed cases is provided in brackets (e.g., [*n* = 4]). For studies reporting results on multiple metrics of exposure, only the highest category of each exposure metric is presented in the figure. Note that two studies (Luce et al., 2002; Olsen and Asnaes, 1986) reported separate results for squamous cell carcinoma and adenocarcinoma and appear

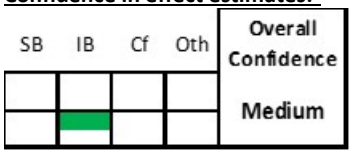
twice in the figure. Also note that the pooled analysis by Luce et al. (2002) includes data from 12 publications and thus represents substantially more information than a single set of results (see Table 1-33 for details).

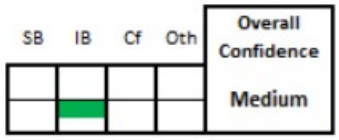
1

Table 1-33. Epidemiological studies of formaldehyde exposure and risk of sinonasal cancers

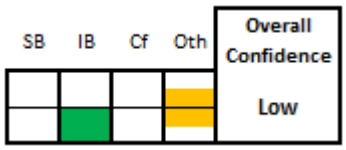
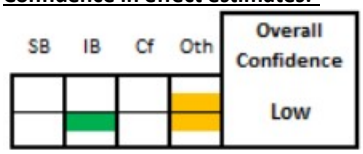
Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Reference: Beane Freeman et al. (2013) **Population:** 25,619 workers employed at 10 formaldehyde-using or formaldehyde-producing plants in the United States followed from either the plant start-up or first employment through 2004. Deaths were identified from the National Death Index with remainder assumed to be living. 676 workers (3%) were lost to follow-up. Vital status was 97.4% complete and only 2.6% lost to follow-up. **Outcome definition:** Death certificates used to determine underlying cause of death from nasal cancer (ICD-8: 160). Histological typing not reported. **Design:** Prospective cohort mortality study with external and internal comparison groups. **Analysis:** RRs estimated using Poisson regression stratified by calendar year, age, sex, and race; adjusted for pay category compared to workers in lowest exposed category. Lagged exposures were evaluated to account for cancer latency. Results were presented for 15-year lag. SMRs calculated using sex, age, race, and calendar-year-specific U.S. mortality rates. **Related studies:** Blair et al. (1986) Hauptmann et al. (2004) Marsh et al. (2007a) Beane Freeman et al. (2009) **Confidence in effect estimates:**[a]  **MEDIUM** ● (No appreciable bias) **IB**: Exposure Group A	**Exposure assessment:** Individual-level exposure estimates based on job titles, tasks, visits to plants by study industrial hygienists who took 2,000 air samples from representative job, and monitoring data from 1960 through 1980. Median TWA (over 8 hours) = 0.3 ppm (range 0.01–4.3). Median cumulative exposure = 0.6 ppm-years (range 0–107.4). Multiple exposure metrics including peak, average, and cumulative exposures were evaluated using categorical and continuous data. **Duration and timing:** Exposure period from <1946 to 1980. Median length of follow-up: 42 years. Median length of employment was 2.6 years (range 1 day–47.7 years). Duration and timing since first exposure were not evaluated. **Variation in exposure:** Peak exposure: Level 1 (>0 to <2.0 ppm) Level 2 (2.0 to <4.0 ppm) Level 3 (≥4.0 ppm) Average intensity: Level 1 (>0 to <0.5 ppm) Level 2 (0.5 to <1.0 ppm) Level 3 (≥1.0 ppm) Cumulative exposure: Level 1 (>0 to <1.5 ppm-yrs) Level 2 (1.5 to <5.5 ppm-yrs) Level 3 (≥5.5 ppm-yrs) Duration of exposure: Level 1 (0 years) Level 2 (>0 to <5 years) Level 3 (5 to <15 years) Level 4 (≥15 years) **Coexposures:** Exposures to 11 other compounds were identified and evaluated as potential confounders and found not be confounders. [As noted in Appendix A.5.9: There was no information on smoking,	**Internal comparisons:** Peak exposure Unexposed RR = 5.67 (0.41–78.89) [2] Level 1 RR = 1.00 (Ref. value) [1] Level 2 RR = 1.53 (0.09–24.68) [1] Level 3 RR = 1.29 (0.08–21.23) [1] *p*-trend (exposed) > 0.5; *p*-trend (all) = 0.37 Average intensity Unexposed RR = 4.31 (0.48–38.67) [2] Level 1 RR = 1.00 (Ref. value) [2] Level 2 RR = 1.47 (0.13–16.50) [1] Level 3 RR = N/A [0] *p*-trend (exposed) > 0.50; *p*-trend (all) = 0.23 Cumulative exposure Unexposed RR = 3.90 (0.41–37.06) [2] Level 1 RR = 1.00 (Ref. value) [2] Level 2 RR = 1.22 (0.11–14.11) [1] Level 3 RR = N/A [0] *p*-trend (exposed) > 0.50; *p*-trend (all) = 0.28 **External comparisons:** $SMR_{Unexposed}$ = 1.93 (0.23–6.98) [2] $SMR_{Exposed}$ = 0.90 (0.18–2.62) [3]

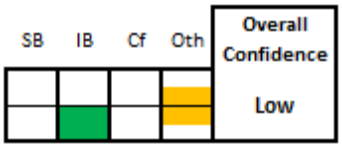
Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Oth: Low power due to rarity of cases.	however, according to Blair et al. (1986), "The lack of a consistent elevation for tobacco-related causes of death, however, suggests that the smoking habits among this cohort did not differ substantially from those of the general population."]	
Reference: Luce et al. (2002) **Population:** Males and females from seven different countries diagnosed with sinonasal cancer during 1968–1990. **Outcome definition:** Diagnoses originally assessed in 12 studies. 195 cases were adenocarcinomas (169 men and 26 women) and 432 were squamous cell carcinomas (330 men and 102 women). **Design:** Pooled analysis of 12 case-control studies that included 627 total cases of sinonasal cancer and 3,136 controls (2,349 men and 787 women). **Analysis:** ORs calculated by unconditional logistic regression. Adenocarcinoma results in men adjusted for age, study, and cumulative exposure to wood and leather dust. All other results adjusted for age and study. **Related studies:** Zheng et al. (1992) Luce et al. (1992) Luce et al. (1993) Leclerc et al. (1994) Bolm-Audorff et al. (1990) Comba et al. (1992a); Comba et al. (1992b) Magnani et al. (1993) Merler et al. (1986) Hayes et al. (1986b) Hayes et al. (1986b); Hayes et al. (1986a) Hardell et al. (1982)	**Exposure assessment:** Detailed occupational history information gathered from interview questionnaires provided the basis for developing an individual's index of exposure to formaldehyde. Standard occupational classification codes and standard industrial classification codes were used to develop a job-exposure matrix in conjunction with available industrial hygiene data. With the given occupational history information of the subjects and the job-exposure matrix, a semiquantitative index of cumulative exposure was determined for each individual calculated as the sum of the job-specific products of probability, level, and duration of exposure over the total work history. Subjects fell into one of four categories of probable exposure (unexposed, low exposure, medium exposure, or high exposure) based upon the job-exposure matrix. **Duration and timing:** Latency was evaluated with 10 and 20-year lags in exposure with somewhat higher effects. Results here are without lagged exposures. **Variation in exposure:** Cumulative exposure: Level 1 (unexposed) Level 2 (low) Level 3 (medium) Level 4 (high) **Coexposures:** Exposures to other compounds were identified and evaluated as potential confounders. Other occupational exposures potentially affecting the risk estimates were controlled for including wood dust, leather dust, textile dust, flour dust, coal dust, crystalline silica,	**Internal comparisons:** **Adenocarcinoma** Men (Adjusted for wood dust) Level 1 OR = 1.0 (Ref. value) [# not given] Level 2 OR = 0.7 (0.3–1.9) [6] Level 3 OR = 2.4 (1.3–4.5) [31] Level 4 OR = 3.0 (1.5–5.7) [91] Women (Not adjusted for wood dust) Level 1 OR = 1.0 (Ref. value) [# not given] Level 2 OR = 0.9 (0.2–4.1) [2] Level 3 no cases Level 4 OR = 6.2 (2.0–19.7) [5] Women (Adjusted for wood dust) Level 1 OR = 1.0 (Ref. value) [# not given] Level 4 OR = 5.8 (1.7–19.4) [5] **Squamous cell carcinoma** Men (Adjusted for wood dust) Level 1 OR = 1.0 (Ref. value) [# not given] Level 2 OR = 1.2 (0.8–1.8) [43] Level 3 OR = 1.1 (0.8–1.6) [40] Level 4 OR = 1.2 (0.8–1.8) [30] Women (Not adjusted for wood dust) Level 1 OR = 1.0 (Ref. value) [# not given] Level 2 OR = 0.6 (0.2–1.4) [6] Level 3 OR = 1.3 (0.6–3.2) [7] Level 4 OR = 1.5 (0.6–3.8) [6] **Additional:** Authors reported that as an additional check for potential residual confounding, the formaldehyde adenocarcinoma results for men were further adjusted for wood dust and that the results were not markedly changed. Among women the result for high probability of formaldehyde exposure was slightly diminished (OR = 5.8; 95% CI: 1.7–19.4).

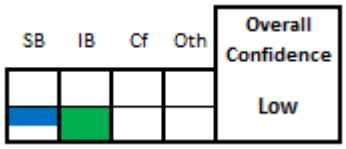
Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Vaughan et al. (1986a, 1986b) Vaughan and Davis (1991) Vaughan (1989) Mack and Preston-Martin (unpub. data) Brinton et al. (1985); Brinton et al. (1984) **Confidence in effect estimates:**[a]  **MEDIUM** ↓ (Potential bias toward the null) **IB**: Exposure Group C	asbestos, and man-made vitreous fibers.	
Reference: Roush et al. (1987b) **Population:** Males identified from the Connecticut Tumor Registry who died of any cause during 1935−1975. **Outcome definition:** Diagnosis of sinonasal cancer based on case registration by the Connecticut Tumor Registry. Clinical records reviewed for >75% of cases. Histological typing not reported. **Design:** Population-based case-control study of 198 male cases of sinonasal cancer. Controls were 605 males dying in Connecticut during the same time period, randomly selected from state death certificates. **Analysis:** ORs calculated by logistic regression and adjusted for age at death, year at death, and availability of occupational information.	**Exposure assessment:** Occupational history obtained by city directories and death certificates, which yielded information on job, industry, employer, and year of employment. Exposure classification scheme based on potential for formaldehyde exposure, probability of exposure for each participant and each job-industry pair, and level of exposure. Probability of exposure defined as unexposed, possibly exposed, probably exposed, or definitely exposed. Level of exposure estimated as zero, low (<1 ppm), and high (≥1 ppm). Among those probably exposed to some level of formaldehyde for most of their working lifetime, the extent and level of exposure were evaluated. **Duration and timing:** Duration of exposure was evaluated. **Variation in exposure:** Exposure level and timing of exposure: Level 1 (unexposed) Level 2 (probably exposed most of working life)	**Internal comparisons:** Exposure level and timing of exposure: Level 1 OR = 1.0 (Ref. value) [# not given] Level 2 OR = 0.8 (0.5−1.8) [21] Level 3 OR = 1.0 (0.5−1.8) [16] High exposure level and timing of exposure: Level 1 OR = 1.0 (Ref. value) [# not given] Level 2 OR = 1.0 (0.5−2.2) [9] Level 3 OR = 1.5 (0.6−3.9) [7]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Confidence in effect estimates:[a]  **MEDIUM** ↓ (Potential bias toward the null) **IB**: Exposure Group C	Level 3 (probably exposed most of working life and probably exposed 20+ years before death) High exposure level and timing of exposure: Level 1 (unexposed) Level 2 (probably exposed most of working life and probably to high level in some year) Level 3 (probably exposed most of working life and probably exposed to high level 20+ years before death) **Coexposures:** Not evaluated. [As noted in Appendix A.5.9: Exposure to wood dust was not found to be a risk factor for all nasal cancers (NPC + SNC). This suggests a lower potential for confounding by wood dust.]	
Reference: Olsen and Asnaes (1986) **Population:** Identified from the Danish Cancer Registry between 1970 and 1982. Exposures to formaldehyde and wood dust were identified too rarely to allow for risk estimation. **Outcome definition:** Diagnosis of cancer of the nasal cavity (ICD-7 160.0) or sinuses (ICD-7 160.2–160.9) was histologically confirmed. Of all male cases for cancer of the nasal cavity and paranasal sinuses (*n* = 310), 69% were squamous cell carcinoma and lymphoepithelioma, 13% were adenocarcinoma, 6% were sarcoma, 5% were malignant melanoma, and 7% were of other histological type. **Design:** Case-control study of 254 men with sinonasal cavity and paranasal cancers (215 with squamous cell carcinoma/lymphoepithelioma and 39 with adenocarcinomas). 2,465 controls with other cancers matched for gender, age, and year of diagnosis.	**Exposure assessment:** Employment histories from 1964 maintained by Danish Cancer Registry estimated by industrial hygienists. Occupational exposures estimated by industrial hygienists based on industry or occupations considered to have certain or probably exposure. Authors reported that 4.2% of control males exposed to formaldehyde. Multiple exposure metrics including known exposure and duration since first exposure were evaluated. **Duration and timing:** Exposure period starting at 1964. **Variation in exposure:** Exposure to formaldehyde: Level 1 (Unexposed) Level 2 (Exposed) Exposure to formaldehyde and wood dust: Level 1 (unexposed to either) Level 2 (exposed to formaldehyde and unexposed to wood dust)	**Internal comparisons:** **Adenocarcinoma** Exposure to formaldehyde controlling for wood dust: Level 1 RR = 1.0 (Ref. value) [10] Level 2 RR = 2.2 (0.7–7.2) [17] Exposure to formaldehyde and wood dust: Level 1 RR = 1.0 (Ref. value) [8] Level 2 RR = 7.0 (1.1–43.9) [1] Level 3 RR = 24.0 (7.6–75.6) [2] Level 4 RR = 39.5 (22.0–70.8) [16] ≥10 years since 1st exposure to formaldehyde and wood dust: Level 1 RR = 1.0 (Ref. value) [6] Level 2 RR = 9.5 (1.6–57.8) [1] Level 3 RR = 36.8 (13.5–96.0) [3] Level 4 RR = 44.1 (22.2–87.8) [11] **Squamous cell carcinoma and lymphoepithelioma** Exposure to formaldehyde controlling for wood dust: Level 1 RR = 1.0 (Ref. value) [113] Level 2 RR = 2.3 (0.9–5.8) [13]

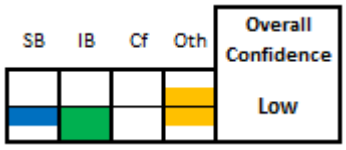
Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Analysis: The Mantel-Haenszel summary estimates of the relative risk were used to account for possible confounding since the subjects were stratified according to several variables. **Related studies:** Olsen and Jensen (1984) **Confidence in effect estimates:**[a]  **MEDIUM ↓** (Potential bias toward the null) **IB**: Exposure Group C	Level 3 (unexposed to formaldehyde and exposed to wood dust) Level 4 (exposed to both) ≥10 years since 1st exposure to formaldehyde and wood dust: Level 1 (unexposed to either) Level 2 (exposed to formaldehyde and unexposed to wood dust) Level 3 (unexposed to formaldehyde and exposed to wood dust) Level 4 (exposed to both) **Coexposures:** Exposure to wood dust was identified and evaluated as a potential confounder and as an effect modifier.	Exposure to formaldehyde and wood dust: Level 1 RR = 1.0 (Ref. value) [113] Level 2 RR = 2.0 (0.7–5.9) [4] Level 3 no cases Level 4 RR = 1.6 (0.8–3.3) [9] ≥10 years since 1st exposure to formaldehyde and wood dust: Level 1 RR = 1.0 (Ref. value) [81] Level 2 RR = 1.4 (0.3–6.4) [2] Level 3 no cases Level 4 RR = 1.8 (0.7–4.4) [6]
Reference: Coggon et al. (2014) **Population:** 14,008 British men employed in six chemical industry factories which produced formaldehyde. Cohort mortality followed from 1941 through 2012. Cause of deaths was known for 99% of 5,185 deaths through 2000. Similar cause of death information not provided on 7,378 deaths through 2012. Vital status was 98.9% complete through 2003. Similar information not provided on deaths through 2012. **Outcome definition:** Death certificates used to determine cause of deaths from nasal cancer. Histological typing not reported. **Design:** Cohort mortality study with external comparison group. **Analysis:** SMRs based on English and Welsh age- and calendar-year-specific mortality rates. **Related studies:** Acheson et al. (1984) Gardner et al. (1993) Coggon et al. (2003) **Confidence in effect estimates:**[a]	**Exposure assessment:** Exposure assessment based on data abstracted from company records. Jobs categorized as background, low, moderate, high, or unknown levels. **Duration and timing:** Occupational exposure during 1941–1982. Duration was evaluated as "more," or "less," than one year only among the 'High' exposure group. Timing since first exposure was not evaluated. **Variation in exposure:** Highest exposure level attained Level 1 (Background) Level 2 (low/moderate) Level 3 (High) **Coexposures:** Not evaluated. Potential low-level exposure to styrene, ethylene oxide, epichlorhydrin, solvents, asbestos, chromium salts, and cadmium. **[**As noted in Appendix A.5.9: Styrene is associated with LHP cancers but not URT cancers. Asbestos is associated with URT cancers, but not this outcome. Other coexposures are not known risk factors for this outcome.**]**	**External comparisons:** Overall: SMR = 0.71 (0.09–2.55) [2] Exposed: Level 1 SMR = 1.08 (0.03–6.01) [1] Level 2 SMR = 1.01 (0.03–5.62) [1] Level 3 SMR = 0 (0–4.03) [0]

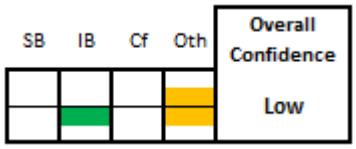
Study	Exposures	Results: effect estimate (95% CI) [# of cases]
 **LOW ↓** (Potential bias toward the null; low sensitivity) **IB**: Exposure is Group B; lack of latency analysis. **Oth**: Low power due to rarity of cases.		
Reference: Meyers et al. (2013) **Population:** 11,043 workers in 3 U.S. garment plants exposed for at least 3 months. Women comprised 82% of the cohort. Vital status was followed through 2008 with 99.7% completion **Outcome definition:** Death certificates used to determine both the underlying cause of death from nasal cancer (ICD-code in use at time of death). Histological typing not provided. **Design:** Prospective cohort mortality study with external and internal comparison groups. **Analysis:** SMRs calculated using sex, age, race, and calendar-year-specific U.S. mortality rates. **Related studies:** Pinkerton et al. (2004) Stayner et al. (1985) Stayner et al. (1988) **Confidence in effect estimates:**[a]  **LOW ↓** (Potential bias toward the null) **IB**: Exposure Group A; lack of latency analysis. **Oth**: Low power due to rarity of cases.	**Exposure assessment:** Individual-level exposure estimates for 549 randomly selected workers during 1981 and 1984 with 12–73 within each department. Formaldehyde levels across all departments and facilities were similar. Geometric TWA8 exposures ranged from 0.09 to 0.20 ppm. Overall geometric mean concentration of formaldehyde was 0.15 ppm, (GSD 1.90 ppm). Area measures showed constant levels without peaks. Historically earlier exposures may have been substantially higher. **Duration and timing:** Exposure period from 1955 to 1983. Median duration of exposure was 3.3 years. More than 40% exposures <1963. Median time since first exposure was 39.4 years. Duration and timing since first exposure were not evaluated for this cancer. **Variation in exposure:** Not evaluated. **Coexposures:** Study population specifically selected because industrial hygiene surveys at the plants did not identify any chemical exposures other than formaldehyde that were likely to influence findings. [As noted in Appendix A.5.9: There was no information on smoking in this analysis, however, according to Leclerc et al. (1997), "the overall prevalence of cigarette smokers was … similar to those reported in a 1980 survey of adult Americans, in which 29.2% of females and 38.3% of males over the age of 20 were current cigarette smokers."	**External comparisons:** SMR = 0 (0–3.89) [0]

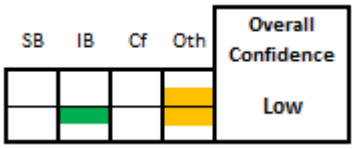
Study	Exposures	Results: effect estimate (95% CI) [# of cases]
	Therefore, confounding was considered to be unlikely.	
Reference: Siew et al. (2012) **Population:** All Finnish men born during 1906–1945 who participated in census and were employed in 1970 (*n* = 1.2 million). Vital status was "virtually complete." **Outcome definition:** Diagnosis of nasal squamous cell cancer reported to the Finnish Cancer Registry. **Design:** Prospective national cohort incidence study with internal comparison groups. **Analysis:** RRs calculated controlling for sex, age, socioeconomic status, period of follow-up, and smoking. **Confidence in effect estimates:**[a]  **LOW** ↓ (Potential bias toward the null; low sensitivity) **IB**: Exposure Group D **Oth**: Low power due to rarity of exposure.	**Exposure assessment:** Individual-level exposure estimates based on matching occupations listed in the census to the Finnish job-exposure matrix which covers major occupational exposures and provided exposure estimates for formaldehyde. **Duration and timing:** Duration and timing since first exposure were not evaluated. **Variation in exposure:** Exposure to formaldehyde: Level 1 (none) Level 2 (any) **Coexposures:** Wood dust exposures were controlled for in formaldehyde analyses.	**Internal comparisons:** Exposure to formaldehyde: Level 1 RR = 1.00 (Ref. value) [158] Level 2 RR = 0.97 (0.47–2.00) [9]
Reference: Pesch et al. (2008) **Population:** Male workers insured by a liability insurance association for the German wood-working industries with an occupational disease during 1994–2003. Of 129 cases of sinonasal adenocarcinoma identified, 86 cases (67%) agreed to participate (including 29 next of kin). 204 controls (75%) participated (including 69 next of kin). **Outcome definition:** Cases were ever employed in German wood industries and diagnosed with histopathologically confirmed sinonasal adenocarcinoma. **Design:** Insurer-based case-control study of 86 cases of sinonasal adenocarcinoma. Controls were 204	**Exposure assessment:** Occupational history information gathered from structured questionnaires. Because next of kin information on exposure to wood additives was considered poor, the probability of exposure to formaldehyde was rated by an expert team as none, low, medium, or high. In Germany, legislation or new formulations altered potential formaldehyde exposure in 1985 (likely lowering them). Final analyses classified exposure as unexposed, any probability of exposure before 1985, or any probability of exposure in 1985 or afterwards.	**Internal comparisons:** Exposure level: Level 1 OR = 1.0 (Ref. value) [39] Level 2 OR = 0.46 (0.14–1.54) [8] Level 3 OR = 0.94 (0.47–1.9) [39]

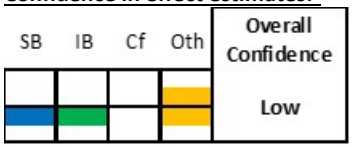
Study	Exposures	Results: effect estimate (95% CI) [# of cases]
workers with accidents between home and work or falls during working shifts. Controls were frequency matched on age with 60 years as the stratification point. **Analysis:** ORs calculated using logistic regressions controlling for age (<60 vs. 60+), region, interviewee, and average wood dust exposure. All temporal exposure variables were lagged by 5 years. **Confidence in effect estimates:**[a]  **LOW** ↓ (Potential bias toward the null) **IB**: Exposure Group B; latency evaluated only for 5 years. **SB**: Potential selection issue due to use of prevalent cases.	**Duration and timing:** Duration of formaldehyde exposure was not evaluated. **Variation in exposure:** Exposure level: Level 1 (unexposed) Level 2 (any exposure <1985) Level 3 (any exposure ≥1985) **Coexposures:** Wood dust exposures were controlled for in formaldehyde analyses.	
Reference: Jakobsson et al. (1997) **Population:** 727 male employees of two plants producing stainless steel sinks and saucepans employed at least one year during 1927–1981 with minimum 15-year follow-up. **Outcome definition:** Incidence of sinonasal cancer from the Swedish Tumor Registry (ICD-7:160). **Design:** Cohort incidence study with external comparison group. **Analysis:** SIRs calculated using sex, age, and calendar-year-expected number of cases from the national population. **Confidence in effect estimates:**[a]  	**Exposure assessment:** Workers grind stainless steel with grinding plates made of formaldehyde resins which may release formaldehyde when heated during grinding operations. **Duration and timing:** Occupational exposure preceding death during 1927–1981. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** Coexposures may have included chromium, nickel, and abrasive dusts including silicon carbide, aluminum oxide, silicon dioxide, and clay. [As noted in Appendix A.5.9: Nickel and chromium are associated with URT cancers and would likely be positively correlated with formaldehyde exposure. Potential for confounding is unknown but could have inflated the observed effect.	**External comparisons:** Observed: 0 Expected: 0.5 SIR = 0 (0–8.0) [0]

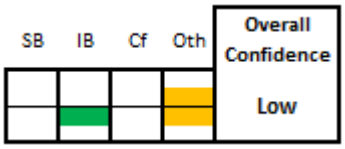
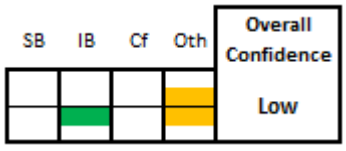
Study	Exposures	Results: effect estimate (95% CI) [# of cases]
LOW ↓ (Potential bias toward the null; low sensitivity) **IB**: Exposure Group D **Cf**: Potential confounding **Oth**: Low power due to rarity of cases.	Other coexposures are not known risk factors for these outcomes. No mention of exposure to wood dust.]	
Reference: Teschke et al. (1997) **Population:** 48 incident cases of nasal cancers (31% female) older than 19 years and registered by the British Columbia Cancer Agency during 1990–1992. Controls were randomly selected from age and sex strata of voter lists of the same time period (frequency matched). 6 of original 54 cases (11%) were excluded for lack of interview as were 36 of 195 eligible controls (18%). **Outcome definition:** Incidence of sinonasal cancer from the British Columbia Cancer Agency (ICD-O:160.0, 160.2, 160.9). Histological types: 23 squamous cell carcinomas (48%), seven melanomas, seven lymphomas, two adenocarcinomas (4%), two adenoid cystic carcinomas, and seven other histologies with one case each. **Design:** Population-based case-control study of nasal cancer. **Analysis:** ORs controlled for sex, age, and smoking. **Confidence in effect estimates:**[a]  **LOW ↓** (Potential bias toward the null; Low sensitivity) **IB**: Exposure Group C **Cf**: Potential confounding by acid mists. **Oth**: Low power due to rarity of exposure.	**Exposure assessment:** Detailed occupational history information gathered from interview questionnaires. 57 Occupational groups assessed. Investigators discussed that textile workers, pulp and paper mill workers, and chemical and biological laboratory personnel may have formaldehyde exposures. **Duration and timing:** Duration of exposure was not evaluated. Timing of exposure was evaluated for nasal cancer with results for 20-year latency presented. **Variation in exposure:** Ever employed in occupational group: Level 1 (never) Level 2 (ever) **Coexposures:** Not evaluated. [As noted in Appendix A.5.9: Potential confounders for these outcomes include chlorophenols, acid mists, dioxin, and perchloroethylene and would likely be positively correlated with formaldehyde exposure. However, on acids mists are associated with URT cancers. Potential for confounding is unknown but could have inflated the observed effect.]	**External comparisons:** All histological types: Textile workers (all) Level 1 OR = 1.0 (Ref. value) [3] Level 2 OR = 7.6 (1.4–56.6) [6] Textile workers (most recent 20 years removed) Level 1 OR = 1.0 (Ref. value) [3] Level 2 OR = 5.0 (0.8–43.0) [4] Pulp and paper mill workers (all) Level 1 OR = 1.0 (Ref. value) [3] Level 2 OR = 3.1 (0.4–25.4) [3] Pulp and paper mill workers (20-yr lag) Level 1 OR = 1.0 (Ref. value) [3] Level 2 OR = 3.1 (0.4–25.4) [3] Chemical and biological lab workers (all) Level 1 OR = 1.0 (Ref. value) [8] Level 2 OR = 0.7 (0.1–4.0) [2] Chemical and biological lab workers (20-yr lag) Level 1 OR = 1.0 (Ref. value) [7] Level 2 OR = 0.9 (0.1–5.3) [2] Squamous cell carcinoma: Textile workers (all) Level 1 OR = 1.0 (Ref. value) [not given] Level 2 OR = 5.3 (0.2–5.3) [not given]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Reference: Hansen and Olsen (1995) **Population:** 2,041 men with cancer who were diagnosed during 1970–1984 and whose longest work experience occurred at least 10 years before cancer diagnosis. Identified from the Danish Cancer Registry and matched with the Danish Supplementary Pension Fund. Ascertainment considered complete. Pension record available for 72% of cancer cases. **Outcome definition:** Nasal cavity cancer (ICD-7: 160) listed on Danish Cancer Registry file. Of all male cases (*n* = 13), histological types of nasal cavity tumors included four squamous cell carcinomas, three adenocarcinomas, one adenoid cystic carcinoma, one melanoma, and one unknown type. Tumors of the maxillary sinus included two squamous cell carcinomas and one anaplastic carcinoma. Overall, there were six squamous cell carcinomas (46%) and two adenocarcinomas (15%). **Design:** Proportionate incidence study with external comparison group. **Analysis:** Standardized proportionate incidence ratio calculated as the proportion of cases for a given cancer in formaldehyde-associated companies relative to the proportion of cases for the same cancer among all employees in Denmark. Adjusted for age and calendar time. **Confidence in effect estimates:**[a]  **LOW** ↓ (Potential bias toward the null) **IB**: Exposure Group D	**Exposure assessment:** Individual occupational histories including industry and job title established through company tax records to the national Danish Product Register. Subject were considered to be exposed to formaldehyde if: (1) they had worked in an industry known to use more than 1 kg formaldehyde per employee per year; and (2) subjects longest single work experience (job) in that industry since 1964 was ≥10 years prior to cancer diagnosis. All subjects were stratified based on job title as either low exposure (white collar worker), above background exposure (blue collar worker), or unknown (job title unavailable). **Duration and timing:** Exposure period not stated. Based on date of diagnosis during 1970–1984, and the requirement of exposure more than 10 years prior to diagnosis, the approximate period was 1960–1974. **Variation in exposure:** Exposure to formaldehyde: Level 1 (unknown) Level 2 (low formaldehyde exposure) Level 3 (formaldehyde exposure, no wood dust) Level 4 (formaldehyde and wood dust exposure) **Coexposures:** Exposure to wood dust was evaluated as a potential confounder of sinonasal cancer. Authors excluded wood dust exposed Cases from Level 3 analyses.	**External comparisons:** Overall (exposure to formaldehyde ≥10 years prior to cancer diagnosis) SPIR = 2.3 (1.3–4.0) [13] Exposure to formaldehyde: Level 1 SPIR = 1.0 (0.03–6.1) [1] Level 2 SPIR = 0.8 (0.02–4.4) [1] Level 3 SPIR = 3.0 (1.4–5.7) [9] Level 4 SPIR = 5.0 (0.5–13.4) [2]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Reference: Hayes et al. (1990) **Population:** 4,046 deceased U.S. male embalmers and funeral directors, derived from licensing boards and funeral director associations in 32 states and the District of Columbia who died during 1975–1985. Death certificates obtained for 79% of potential study subjects (*n* = 6,651) with vital status unknown for 21%. **Outcome definition:** Death certificates and licensing boards used to determine cause of death from sinonasal cancer (ICD-8: 160). **Design:** Proportionate mortality cohort study with external comparison group. **Analysis:** PMRs calculated using sex, race, age, and calendar-year-expected numbers of deaths from the U.S. population. **Confidence in effect estimates:**[a]  **LOW** ↓(Potential bias toward the null; Low sensitivity) **IB**: Exposure Group A; latency not evaluated. **Oth**: Potential undercounting of cases. Low power due to rarity of cases.	**Exposure assessment:** Presumed exposure to formaldehyde tissue fixative. Exposure based on occupation which was confirmed on death certificate. Authors subsequently measured personal embalming exposures ranging from 0.98 ppm (high ventilation) to 3.99 ppm (low ventilation) with peaks up to 20 ppm. Authors state that major exposures are to formaldehyde and possibly glutaraldehyde and phenol. **Duration and timing:** Occupational exposure preceding death during 1975–1985. Of 115 deaths from LHP cancer, 66 (57%) were aged 60–74 years. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** Not evaluated. **[**As noted in Appendix A.5.9: Coexposures may have included: phenol, methyl alcohol, glutaraldehyde, mercury, arsenic, zinc, and ionizing radiation. Anatomists may also be coexposed to stains, benzene, toluene xylene, stains, chlorinated hydrocarbons, dioxane, and osmium tetroxide. Radiation exposure likely to be poorly correlated with formaldehyde. Benzene is not associated with URT cancer.**]**	**External comparisons:** Observed: 0 cases Expected: 1.7 cases PMR = 0 (0–1.76) † [0] **Additional:** By Race White PMR = 0 (0–2.00) † [0] Non-White PMR = 0 (0–14.98) † [0] †**Note:** EPA derived CIs using the Mid-P Method (See Rothman and Boice, 1979)
Reference: Bertazzi et al. (1986) **Population:** 1,332 male workers ever employed in the plant between 1959 and 1980. Deaths were identified from vital statistics offices. Vital status was 98.6% complete. **Outcome definition:** Nasal cancer listed as cause of death on death certificates.	**Exposure assessment:** Individual-level exposure estimates based on occupational histories. Over the whole cohort, approximately 28% of person time was estimated to be exposed to formaldehyde. **Duration and timing:** Occupational exposure preceding death during 1959–1980. Duration and timing since	**External comparisons:** Observed: 0 Expected: 0.0327 SMR = 0 (0–91.61) † [0] †**Note:** EPA derived CIs using the Mid-P Method (See Rothman and Boice, 1979)

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Design: Cohort mortality study with external comparison group. **Analysis:** SMRs calculated using sex, age, and calendar-year-expected number of deaths from the local population. **Confidence in effect estimates:**[a]  **LOW ↓** (Potential bias toward the null; low sensitivity) **IB**: Exposure Group B **Oth**: Low power due to rarity of cases.	first exposure were not evaluated for nasal cancer. **Variation in exposure:** Not evaluated. **Coexposures:** Not evaluated. **[**As noted in Appendix A.5.9: Other exposures included styrene, xylene, toluene, and methyl isobutyl ketone. Styrene is associated with LHP cancers but not URT cancers. Other coexposures are not known risk factors for this outcome.**]**	
Reference: Stroup et al. (1986) **Population:** 2,239 white male members of the American Association of Anatomists from 1888 to 1969 who died during 1925–1979. Death certificates obtained for 91 with 9% lost to follow-up. **Outcome definition:** Cancer of the nasal cavity and sinuses listed as cause of death on death certificates. **Design:** Cohort mortality study with external comparison group. **Analysis:** SMRs calculated using sex, race, age, and calendar-year-expected number of deaths from the U.S. population. **Confidence in effect estimates:**[a]  **LOW ↓** (Potential bias toward the null; Low sensitivity) **IB**: Exposure Group A; latency not evaluated **Oth**: Low power due to rarity of cases.	**Exposure assessment:** Presumed exposure to formaldehyde tissue fixative. **Duration and timing:** Occupational exposure during 1925–1979. Median birth year was 1912. By 1979, 33% of anatomists had died. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** Not evaluated. **[**As noted in Appendix A.5.9: Coexposures may have included: phenol, methyl alcohol, glutaraldehyde, mercury, arsenic, zinc, and ionizing radiation. Anatomists may also be coexposed to stains, benzene, toluene xylene, stains, chlorinated hydrocarbons, dioxane, and osmium tetroxide. Radiation exposure likely to be poorly correlated with formaldehyde. [Benzene is not associated with URT cancer.]	**External comparisons:** SMR = 0 (0–7.2) [0]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Reference: Levine et al. (1984a) **Population:** 1,477 male undertakers first licensed during 1928–1977 with mortality follow-up from 1950 to 1977. Vital status was 96% complete with cause of death available for 94%. **Outcome definition:** Cancer of the nasal cavity and sinuses listed as underlying cause of death on death certificates (ICD-8: 160). **Design:** Cohort mortality study with external comparison group. **Analysis:** SMRs calculated using sex, age, and calendar-year-expected number of deaths from the Canadian population. **Confidence in effect estimates:**[a]  **LOW** ↓ (Potential bias toward the null; Low sensitivity) **IB**: Exposure Group A; latency not evaluated. **SB**: Healthy worker effect **Oth**: Low power due to rarity of cases.	**Exposure assessment:** Presumed exposure to formaldehyde tissue fixative. **Duration and timing:** Occupational exposure during 1928–1977. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** Not evaluated. **[**As noted in Appendix A.5.9: Coexposures may have included: phenol, methyl alcohol, glutaraldehyde, mercury, arsenic, zinc, and ionizing radiation. Anatomists may also be coexposed to stains, benzene, toluene xylene, stains, chlorinated hydrocarbons, dioxane, and osmium tetroxide. Radiation exposure likely to be poorly correlated with formaldehyde. Benzene is not associated with URT cancer.**]**	Observed: 0 Expected: 0.2 PMR = 0 (0–14.98)† [0] †**Note:** EPA derived CIs using the Mid-P Method (See Rothman and Boice, 1979)
Reference: Walrath and Fraumeni (1984) **Population:** 1,007 deceased white male embalmers from the California Bureau of Funeral Directing and Embalming who died during 1925–1980. Death certificates obtained for all. **Outcome definition:** Nasal cancer listed as cause of death on death certificates. **Design:** Proportionate mortality cohort study with external comparison group.	**Exposure assessment:** Presumed exposure to formaldehyde tissue fixative. **Duration and timing:** Occupational exposure preceding death during 1916–1978. Birth year ranged from 1847–1959. Median age of death was 62 years. Most deaths were among embalmers with active licenses. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** Not evaluated.	**External comparisons:** Observed: 0 Expected: 0.6 PMR = 0 (0–4.99)† [0] †**Note:** EPA derived CIs using the Mid-P Method (See Rothman and Boice, 1979)

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Analysis: PMRs calculated using sex, race, age, and calendar-year-expected number of deaths from the U.S. population. **Confidence in effect estimates:**[a]  **LOW ↓** (Potential bias toward the null; low sensitivity) **SB:** Potential selection bias: due to incomplete death certificate ascertainment. **IB**: Exposure Group A; latency not evaluated. **Oth**: Low power due to rarity of cases.	**[**As noted in Appendix A.5.9: Coexposures may have included: phenol, methyl alcohol, glutaraldehyde, mercury, arsenic, zinc, and ionizing radiation. Anatomists may also be coexposed to stains, benzene, toluene xylene, stains, chlorinated hydrocarbons, dioxane, and osmium tetroxide. Radiation exposure likely to be poorly correlated with formaldehyde. Benzene is not associated with URT cancer.**]**	
Reference: Walrath and Fraumeni (1983) **Population:** 1,132 deceased white male embalmers licensed to practice during 1902–1980 in New York who died during 1925–1980 identified from registration files. Death certificates obtained for 75% of potential study subjects (*n* = 1,678). **Outcome definition:** Nasal cancer listed as cause of death on death certificates. **Design:** Proportionate mortality cohort study with external comparison group. **Analysis:** PMRs calculated using sex, race, age, and calendar-year-expected numbers of deaths from the U.S. population. **Confidence in effect estimates:**[a]  **LOW ↓** (Potential bias toward the null; low sensitivity) **SB**: Potential selection bias: due to incomplete death certificate ascertainment.	**Exposure assessment:** Presumed exposure to formaldehyde tissue fixative. **Duration and timing:** Occupational exposure preceding death during 1902–1980. Median year of birth was 1901. Median year of initial license was 1931. Median age at death was 1968. Expected median duration of exposure was 37 years. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** Not evaluated. **[**As noted in Appendix A.5.9: Coexposures may have included: phenol, methyl alcohol, glutaraldehyde, mercury, arsenic, zinc, and ionizing radiation. Anatomists may also be coexposed to stains, benzene, toluene xylene, stains, chlorinated hydrocarbons, dioxane, and osmium tetroxide. Radiation exposure likely to be poorly correlated with formaldehyde. Benzene is not associated with URT cancer.**]**	**External comparisons:** Observed: 0 Expected: 0.5 PMR = 0 (0–5.99)† [0] †**Note:** EPA derived CIs using the Mid-P Method (See Rothman and Boice, 1979)

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
IB: Exposure Group A; latency not evaluated. **Oth**: Low power due to rarity of cases.		

[a]Evaluation of sources of bias or study limitations (see details in Appendix A.5.9). SB = selection bias; IB = information bias; Cf = confounding; Oth = other feature of design or analysis. Extent of column shading reflects degree of limitation. Direction of anticipated bias indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact would be likely to be away from the null (i.e., spurious or inflated effect estimate).

Oropharyngeal/Hypopharyngeal cancer

Epidemiological evidence

Oropharyngeal and hypopharyngeal cancer is commonly reported across the epidemiological literature based on the Seventh, Eighth, or Ninth Revision of the ICD code (ICD-7/8/9: 146 and ICD-7/8/9: 148, respectively). Two studies reported specifically on hypopharyngeal cancer risks (Marsh et al., 2007b; Laforest et al., 2000), and one study reported specifically on oropharyngeal cancer risks (Marsh et al., 2007b). The results from five other studies (of three populations) allowed for grouping these two adjacent tissue sites for analyses to examine the risks of pharyngeal cancers below the nasopharynx (Marsh et al., 2002; Gustavsson et al., 1998; Vaughan, 1989; Vaughan et al., 1986a, b).

Overall, evidence describing an association between formaldehyde exposure and the risk of developing or dying from oropharyngeal/hypopharyngeal cancer was available from nine reports on six distinct study populations—four reports on three cohort studies (Coggon et al., 2014; Meyers et al., 2013; Marsh et al., 2007b; Marsh et al., 2002) and five reports on three case-control studies (Laforest et al., 2000; Gustavsson et al., 1998; Vaughan, 1989; Vaughan et al., 1986a, b). No studies with data specific to these pharyngeal cancer sites were excluded. The outcome-specific evaluations of confidence in the precise effect estimate of an association from each study are provided in Appendix A.5.9). Details of the reported results of *high*, *medium*, and *low* confidence are provided in the evidence table for oropharyngeal/hypopharyngeal cancer (see Table 1-34) following the causal evaluation.

Consistency of the observed association

The nine papers describing six populations reported the risks of oropharyngeal/hypopharyngeal cancer among study subjects who had a high likelihood of formaldehyde exposure (e.g., based on occupational history). The study results presented in Table 1-34 (by confidence level and publication date) detail all of the reported associations. Results are plotted in Figure 1-22 with results grouped by cancer site as "Oropharyngeal only," "Undifferentiated oropharyngeal/hypopharyngeal," or "Hypopharyngeal only."

Based on results for overall SMRs for all workers (both exposed and unexposed) compared to external referent populations in three cohort studies (all classified with *medium* confidence), the effect estimates were generally elevated and ranged in magnitude between 1.1 and 2.01, but none had sufficient statistical power to exclude the null. The effect estimate for oropharyngeal cancer alone was 1.95 (Marsh et al., 2007b); 95% CI 0.63, 4.56); for the combination of oropharyngeal and hypopharyngeal cancer, the effect estimates were 1.1 (Meyers et al., 2013); 95% CI 0.40, 2.39) and 1.29 (Coggon et al., 2014); 95% CI 0.76, 2.05), respectively; and for hypopharyngeal cancer alone the effect estimate was 2.01 (Marsh et al., 2007b); 95% CI 0.87, 3.96). The only case-control study results classified with *medium* confidence (Laforest et al., 2000) reported effect estimates by the probability of exposure with an OR = 1.35 for "Ever" exposure to formaldehyde associated with hypopharyngeal cancer (95% CI 0.86, 2.14), but for cases with >50% probability of formaldehyde exposure the OR was 3.78 (95% CI 1.50, 9.49). The results from the two case-control studies classified with *low* confidence (Gustavsson et al., 1998), and the three Vaughan reports (Vaughan, 1989; Vaughan et al., 1986a, b) were largely surrounding the null.

Subgroup analyses provide some indication of increased risk when a latency period was accounted for. Increased risks of oropharyngeal/hypopharyngeal cancer were also reported by Marsh et al. (2002) among workers with at least 10 years of formaldehyde exposure (SMR = 2.48; 95% CI 0.63, 6.75)—especially for those with at least 10 years of exposures greater than 0.2 ppm (SMR = 4.94; 95% CI 1.25, 13.38). After excluding those with <10% probability of being exposed to formaldehyde, Laforest et al. (2000) found that for those with at least 20 years of exposure, the OR was 2.70 (95% CI 1.08, 6.73).

Overall, the findings were heterogeneous. Results from the two case-control studies classified with *low* confidence Gustavsson et al. (1998) and the Vaughan papers (Vaughan, 1989; Vaughan et al., 1986a, b) did not show increased risks, although Gustavsson et al. (1998) did not assess differences by exposure concentration or duration. The Vaughan analyses (Vaughan, 1989; Vaughan et al., 1986a, b) did examine differences in exposures but did not observe consistently increased risks. As with the Gustavsson et al. (1998) study, the Meyers et al. (2013) cohort study did not assess differences in exposure concentration or duration and found only a minimally increased risk. Coggon et al. (2014) did report results for duration greater than 1 year but did not observe consistently increased risks, and Vaughan et al. (1986b) did not observe an increased risk of oropharyngeal/hypopharyngeal cancer for living more than 10 years in a mobile home (although the corresponding OR for NPC was 5.5). Two other *medium* confidence results from Marsh et al. (2002) and Laforest et al. (2000) did observe increased risks associated with >10 and >20 years of exposure duration.

Strength of the observed association

Summary effect estimates (SMR or RR) ranged from 1.01 (Gustavsson et al., 1998) to slightly more than a doubling of the relative effect estimates (Marsh et al., 2007b). Only one study (Marsh et al., 2007b) reported a summary effect estimate (for cancers of the oropharynx,

hypopharynx and unspecified pharynx) that excluded the null (OR = 1.98; 95% CI 1.17, 3.15). The magnitude of the relative effect estimates varied but did not appear to depend on the specific non-nasopharyngeal cancer site. Marsh et al. (2002) provided specific SMRs for oropharyngeal (ICD-9: 146), hypopharyngeal (ICD-9: 148), and "pharyngeal cancer, unspecified" (ICD-9: 149), which were very similar at 1.95, 2.01, and 2.11 respectively. Exposure level-specific estimated risks ranged from 0.8 for the highest residential duration of exposure to particleboard (Vaughan et al., 1986b) up to 4.94 for workers exposed to concentrations of formaldehyde greater than 200 ppb for more than 10 years.

Temporal relationship of the observed association

In each of the studies, the formaldehyde exposures among the study participants started before their diagnoses of oropharyngeal/hypopharyngeal cancer. Only one study (Vaughan et al., 1986a) reported results for formaldehyde exposure lagged by 15 years to account for latency and did not find higher risks. It is notable that for nasopharyngeal cancer in the tissue neighboring the oropharynx, the latency between formaldehyde exposure and cancer mortality was generally longer than 25 years (see Section 1.2.5 Nasopharyngeal cancer); thus, studies without similar follow-up time and appropriately lagged exposure may be insufficiently sensitive.

Marsh et al. (2002) reported on the effect of time since first employment in a formaldehyde-related occupation as a proxy for latency. Those data (see Table 1-34) indicate that the risk of workers with 20–29 years at a chemical plant producing or using formaldehyde had an SMR = 1.50 (95% CI 0.48, 3.61), while workers with more than 30 years' tenure had a higher risk (SMR = 2.69; 95% CI 1.31, 4.94). Extended duration of exposure can also be a reasonable proxy for latency. Compared to unexposed workers, Laforest et al. (2000) reported increasing risks with increasing duration of exposure for all workers (regardless of their probability of exposure) reaching an OR = 1.51 (95% CI 0.78, 2.92) for those with more than 20 years' exposure to formaldehyde with an even more pronounced effect of extended duration among those workers with the higher probabilities of exposure (OR = 2.70; 95% CI 1.08, 6.73).

Exposure-response relationship

Only three study populations were available for evaluating exposure-response relationships between formaldehyde and increased risk of oropharyngeal/hypopharyngeal cancer. The paired studies by Vaughan et al. (1986a, b) did not show evidence of an exposure-response relationship with the same exposure metrics as they did for nasopharyngeal cancer. Conversely, Laforest et al. (2000) reported a clear exposure-response trend for increasing probability of formaldehyde exposure ($p < 0.005$) and for increasing duration of formaldehyde exposure among subjects with at least 10% probability of exposure ($p < 0.04$), with some indication of a trend with increasing cumulative exposure ($p < 0.14$). Marsh et al. (2002) also found higher risks at higher durations of exposure.

Potential impact of selection bias, information bias, confounding bias, and chance

Selection bias is an unlikely bias in the epidemiological studies of oropharyngeal/hypopharyngeal cancer as the cohort study followed by Marsh et al. (2007b; 2002) included 98% of eligible participants and lost relatively few participants over the course of mortality follow-up, and the case-control study by Laforest et al. (2000) evaluated exposure status without regard to outcome status and had participation levels of 80% for cases and 86% for controls. Information bias is unlikely to have resulted in bias away from the null; however, random measurement error or nondifferential misclassification is almost certain to have resulted in some bias toward the null among these studies of oropharyngeal/hypopharyngeal cancer. For example, regarding one particular analysis from Marsh et al. (2002), the authors reported risks for exposure greater than 700 ppb of formaldehyde that might have been useful for comparison with the risk for exposure of greater than 200 ppb; however, by comparing risk above 700 ppb to risk among "unexposed" workers (with exposures ranging from 0 to 699 ppb), information bias was likely induced, which may have attenuated that risk and made the inclusion of this result unsuitable for exposure-response evaluation.

Confounding is a potential bias that could arise if another cause of oropharyngeal/hypopharyngeal cancer is also associated with formaldehyde exposure. There does not appear to be any evidence of confounding that would provide an alternative explanation for the observed association of formaldehyde exposure with increased risk of oropharyngeal/hypopharyngeal cancer seen across these studies. Chemical and other coexposures that have not been independently associated with oropharyngeal/hypopharyngeal cancer are not expected to confound results. Other known risk factors for oropharyngeal/hypopharyngeal cancer include smoking and alcohol consumption (Vaughan, 1996). While these other exposures may be independent risk factors for oropharyngeal/hypopharyngeal cancer, smoking and alcohol consumption are unlikely to be generally related to occupational and residential formaldehyde exposures and are therefore unlikely to be across-the-board confounders. This is especially true for studies comparing risks within a cohort of workers who may be more similar to each other in smoking status than they are compared to an external population. This is relevant to the NCI cohort which Beane Freeman (2013) noted had a high prevalence of current or former smokers across all levels of formaldehyde exposure (i.e., smoking prevalence was likely independent of formaldehyde exposure and not a confounder). However, the Marsh reports on one plant in this cohort (Marsh et al., 2007b; Marsh et al., 2002) compared the risk of those workers to an external population which might have had lower prevalences of smoking allow for a greater potential for confounding by smoking in those reports.

Overall, the findings were heterogeneous with no association observed in study results of *low* confidence and a mix of positive associations and null findings in study results of *medium* confidence. For oropharyngeal/hypopharyngeal cancer, the lack of consistency weakens the etiologic conclusion. However, the observations of increased risks across multiple *medium*

confidence results, as well as two identified exposure-response relationships with increased duration of formaldehyde exposure is suggestive of an association.

Causal evaluation and conclusion

The causal evaluation for formaldehyde exposure and the risk of developing or dying from oropharyngeal/hypopharyngeal cancer placed the greatest weight on three particular considerations: (1) the observations of increased risks in two *medium* confidence studies with the ability to evaluate multiple metrics of formaldehyde exposure, but little other evidence of increases in risk across one other *medium* and two *low* confidence results; (2) the variable strength of the association across studies and metrics with several results near the null and two *medium* confidence studies reporting three-fold to five-fold increases in risk among groups with the highest exposure probability or duration; and (3) exposure-response relationships using multiple metrics of exposure from one study showing that increased exposure to formaldehyde was associated with increased risk of developing oropharyngeal/hypopharyngeal cancer. Although consistent observations of genotoxicity in exfoliated buccal cells or nasal mucosal cells have been observed across several occupational studies, these data were not interpreted as sufficient to further strengthen the judgment on the human evidence of cancers of the oropharynx and, more indirectly, the hypopharynx.

Conclusion

The available epidemiological studies provide *slight* evidence of an association between formaldehyde exposure and increased risk of oropharyngeal/hypopharyngeal cancer.

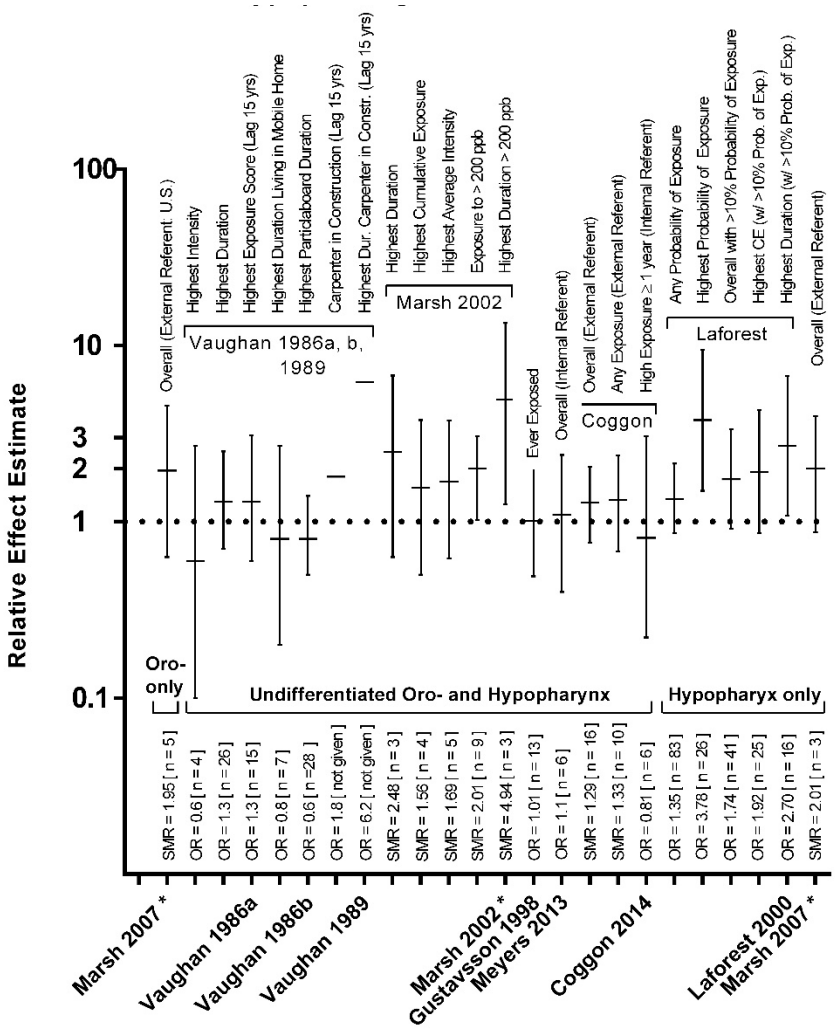
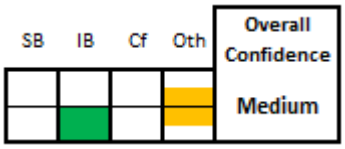
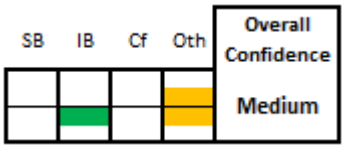


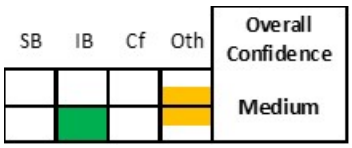
Figure 1-22. Epidemiological studies reporting oropharyngeal or hypopharyngeal cancer risk estimates.

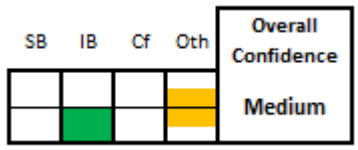
Results are grouped by cancer site as oropharyngeal only, oropharyngeal grouped with hypopharyngeal and unspecified pharyngeal, or hypopharyngeal only. SMR: standardized mortality ratio. RR: relative risk. OR: odds ratio. CE: cumulative exposure. For each measure of association, the number of exposed cases is provided in brackets (e.g., [*n* = 6]). For studies reporting results on multiple metrics of exposure, only the highest category of each exposure metric is presented in the figure. Data from Marsh et al. (2007b; 2002) are based on the same study subjects; however, exposure-response data were only included in the 2002 study, and the 2007 study had more recent comparisons with external referents.

Table 1-34. Studies of formaldehyde exposure and risk of cancer of oropharynx/hypopharynx

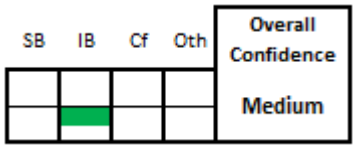
Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Reference: Coggon et al. (2014) **Population:** 14,008 British men employed in six chemical industry factories which produced formaldehyde. Cohort mortality followed from 1941 through 2012. From Coggon et al. (2003), cause of death was known for 99% of 5,185 deaths through 2000. Similar cause of death information not provided on 7,378 deaths through 2012. Vital status was 98.9% complete and only 1.1% lost to follow-up through 2003. Similar information not provided on deaths through 2012. **Outcome definition:** Death certificates used to determine cause of deaths from pharyngeal cancer minus deaths from nasopharyngeal cancer. **Design:** Cohort mortality study with external comparison group with a nested case-control study. **Analysis:** SMRs based on English and Welsh age- and calendar-year-specific mortality rates. **Related studies:** Acheson et al. (1984) Gardner et al. (1993) Coggon et al. (2003) **Confidence in effect estimates:**[a]  **MEDIUM ↓** (Potential bias toward the null) **IB**: Exposure is Group B; lack of latency analysis.	**Exposure assessment:** Exposure assessment based on data abstracted from company records. Jobs categorized as background, low, moderate, high, or unknown levels. **Duration and timing:** Occupational exposure during 1941–1982. Duration was evaluated as more, or less, than one year only among the "High" exposure group. Timing since first exposure was not evaluated. **Variation in exposure:** Duration of "High" exposures Level 1 (Background) Level 2 (<1 year) Level 3 (1 year or more) **Coexposures:** Not evaluated. Potential low-level exposure to styrene, ethylene oxide, epichlorhydrin, solvents, asbestos, chromium salts, and cadmium. **[**As noted in Appendix A.5.9: Styrene is associated with LHP cancers but not URT cancers. Asbestos is associated with URT cancers, but not this outcome. Other coexposures are not known risk factors for this outcome.**]**	**External comparisons:** For NPC (p.1,307): 1 observed case with exposure above background vs. 1.7 expected. For all pharyngeal cancers (see Table 3 in Coggon et al.): 17 cases observed in all subjects vs. 14.1 expected. 11 cases with exposures above background v. 9.2 expected. Therefore, for OHPC: 10 observed cases with exposure above background vs. 7.5 expected. 16 observed cases in all subjects vs. 12.4 expected. $SMR_{All\ Subjects}$ = 1.29 (0.76–2.05)† [16] $SMR_{Exposed}$ = 1.33 (0.68–2.38)† [10] **Internal comparisons:** Since the 1 NPC case had "low/Moderate exposure," the all-pharyngeal-cancer results in Table 6 in Coggon et al. (2014) for "High exposure" are OHPC. Duration of 'High' exposures Level 1 OR = 1.00 (Ref. value) [10] Level 1 OR = 0.63 (0.13–3.03) [3] Level 2 OR = 0.81 (0.22–3.05) [6] †**Note:** EPA derived CIs using the Mid-P Method (See Rothman and Boice, 1979)
Reference: Meyers et al. (2013)	**Exposure assessment:** Individual-level exposure estimates for 549 randomly selected workers during 1981 and	**External comparisons:** SMR = 1.1 (0.40–2.39) [6]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Population: 11,043 workers in 3 U.S. garment plants exposed for at least 3 months. Women comprised 82% of the cohort. Vital status was followed through 2008 with 99.7% completion. **Outcome definition:** Death certificates used to determine both the underlying cause of death from nasopharyngeal cancer (ICD code in use at time of death). Histological typing not provided. **Design:** Prospective cohort mortality study with external and internal comparison groups. **Analysis:** SMRs calculated using sex, age, race, and calendar-year-specific U.S. mortality rates. **Related studies:** Pinkerton et al. (2004) Stayner et al. (1985) Stayner et al. (1988) **Confidence in effect estimates:**[a]  **MEDIUM ↓** (Potential bias toward the null) **IB**: Exposure Group A; latency not evaluated.	1984. Geometric TWA8 exposures ranged from 0.09–0.20 ppm. Overall geometric mean concentration of formaldehyde was 0.15 ppm, (GSD 1.90 ppm). Area measures showed constant levels without peaks. Historically earlier exposures may have been substantially higher. **Duration and timing:** Exposure period from 1955 to 1983. Median duration of exposure was 3.3 years. More than 40% exposures <1963. Median time since first exposure was 39.4 years. Duration and timing since first exposure were not evaluated for this cancer. **Variation in exposure:** Not evaluated. **Coexposures:** Study population specifically selected because industrial hygiene surveys at the plants did not identify any chemical exposures other than formaldehyde that were likely to influence findings.	
Reference: Marsh et al. (2007b); Marsh et al. (2002) is described on the next pages. **Population:** 7,328 workers employed at formaldehyde-using plant in the United States followed from 1945 through 2003. Vital status was identified from the National Death Index, private businesses, or state and local agencies, and was 98% complete and 1.4% lost to follow-up. Among the deceased, the cause of death was available for 95.2%.	**Exposure assessment:** Worker-specific exposure from job-exposure matrix based on available sporadic sampling data from 1965 to 1987, job descriptions, and verbal job descriptions by plant personnel and industrial hygienists. Exposures ranked on a 7-point scale with exposure range assigned to each rank. 17% of jobs validated with company monitoring data; remaining 83% based on professional judgment. Assumed pre-1965 exposure levels same as post-1965 levels.	**External comparisons:** Oropharyngeal cancer U.S. referent SMR = 1.95 (0.63–4.56)[5] County referent SMR = 1.71 (0.56–4.00)[5] Hypopharyngeal cancer U.S. referent SMR = 2.01 (0.87–3.96)[3] County referent SMR = 1.88 (0.81–3.70)[3] Pharyngeal cancer excluding nasopharyngeal U.S. referent SMR = 1.98 (1.17–3.15)[16] County referent SMR = 1.71 (1.01–2.72)[16]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
This population was from one plant from Beane Freeman et al. (2009). **Outcome definition:** Death certificates used to determine underlying cause of death from oropharyngeal/hypopharyngeal cancer according to the ICD-9 codes (146, 148). **Design:** Cohort mortality study with external comparison groups. **Analysis:** SMRs calculated by dividing the number of observed deaths by the number of expected deaths. Expected deaths were the product of death rate (at national, state, or local level) and person-years accumulated by all the members of the cohort. SMRs made age, race, gender, and period specific to reduce bias and to generate tabular information by these variables. Mortality was compared with death rates in two Connecticut counties and the United States. These results are shown in Table 2 in Marsh et al. (2007b). **Related studies:** Hauptmann et al. (2004) Marsh et al. (2002; 1996; 1994) **Confidence in effect estimates:**[a]  **MEDIUM ↓** (Potential bias toward the null; low sensitivity) **IB**: Exposure Group B; lack of latency analysis. **Oth**: Low power due to rarity of cases.	Exposure assessment did not include the same industrial hygiene sampling conducted by Stewart et al. (1986) used in the Beane Freeman (2013; 2009) analyses which included this plant. Exposure estimates generated by this method were 10 times lower on average than those estimated by the NCI. Multiple exposure metrics including, known exposure, average intensity and cumulative exposures were evaluated. **Duration and timing:** Duration of exposure was evaluated. **Variation in exposure:** None. **Coexposures:** Coexposures previously identified in Marsh et al. (1996) included product and nonproduct particulates and airborne pigments. **[**As noted in Appendix A.5.9: Marsh et al. (2002) attempted to evaluate smoking but data were incomplete. No other potential confounders were evaluated. Beane Freeman et al. (2013; 2009) evaluated 11 potential confounders among a set of 10 plants that included this one and did not find any confounding.**]**	
Reference: Marsh et al. (2002) **Population:** 7,328 workers employed at formaldehyde-using plant in the United States followed from 1945 through 1998. Vital status was identified from the National Death Index, private businesses, or state and	**Exposure assessment:** Worker-specific exposure from job-exposure matrix based on available sporadic sampling data from 1965 to 1987, job descriptions, and verbal job descriptions by plant personnel and industrial hygienists. Exposures ranked on a 7-point scale with exposure range assigned to each rank.	**External comparisons:** Oropharyngeal cancer U.S. referent SMR = 2.17 (0.71–5.07) [5] County referent SMR = 1.80 (0.58–4.19) [5] Hypopharyngeal cancer U.S. referent SMR = 2.25 (0.46–6.58) [3] County referent SMR = 1.52 (0.31–4.43) [3]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
local agencies, and was 98.4% complete and 1.6% lost to follow-up. This population was from one plant from Beane Freeman et al. (2009). **Outcome definition:** Death certificates used to determine underlying cause of death from oropharyngeal/hypopharyngeal cancer according to the ICD-9 codes (146, 148). **Design:** Cohort mortality study with external comparison groups. **Analysis:** SMRs calculated by dividing the number of observed deaths by the number of expected deaths. Expected deaths were the product of death rate (at national, state, or local level) and person-years accumulated by all the members of the cohort. SMRs made age, race, sex, and period specific to reduce bias and to generate tabular information by these variables. Mortality was compared with death rates in two Connecticut counties and the United States. These results are shown in Table 2 in Marsh et al. (2002). **Related studies:** Beane Freeman et al. (2013; 2009) Marsh et al. (2007b; 1996; 1994) **Confidence in effect estimates:**[a]  **MEDIUM ↓** (Potential bias toward the null; low sensitivity) **IB**: Exposure Group B; lack of latency analysis. **Oth**: Low power due to rarity of cases.	17% of jobs validated with company monitoring data; remaining 83% based on professional judgment. Assumed pre-1965 exposure levels same as post-1965 levels. Exposure assessment did not include the same industrial hygiene sampling conducted by Stewart et al. (1986) used in the Beane Freeman (2013; 2009) analyses which included this plant, Exposure estimates generated by this method were 10 times lower on average than those estimated by the NCI. Multiple exposure metrics including, known exposure, average intensity and cumulative exposures were evaluated. **Duration and timing:** Duration of exposure was evaluated. **Variation in exposure** (*from Table 3 in Marsh et al. (2002)*)**:** For all variations in exposure: Level 1 (unexposed) Exposure to formaldehyde: Level 2 (exposed) Duration of exposure to formaldehyde: Level 2 (0 to <1 years) Level 3 (1 to 9 years) Level 4 (>10 years) Cumulative exposure to formaldehyde: Level 2 (0 to <0.004 ppm-yrs) Level 3 (0.004 to 0.219 ppm-yrs) Level 4 (>0.22 ppm-yrs) Average intensity exposure: Level 2 (0 to <0.03 ppm) Level 3 (0.03 to 0.159 ppm) Level 4 (>0.16 ppm) Exposure to formaldehyde >0.2 ppm: Level 2 (exposed) Duration of exposure to >0.2 ppm: Level 2 (0 to <1 years) Level 3 (1 to 9 years) Level 4 (>10 years) **Coexposures:** Coexposures previously identified in Marsh et al. (1996)	Pharyngeal cancer, unspecified U.S. referent SMR = 2.11 (0.85–4.35) [7] County referent SMR = 1.89 (0.76–3.89) [7] Oropharyngeal/Hypopharyngeal cancer Exposure to formaldehyde: Level 1 SMR = 1.24‡ (0.21–4.10)† [2] Level 2 SMR = 1.83‡ (1.02–3.05)† [13] Duration of formaldehyde exposure: Level 1 SMR = 1.24‡ (0.21–4.10)† [2] Level 2 SMR = 1.75‡ (0.77–3.46)† [7] Level 3 SMR = 1.58‡ (0.40–4.32)† [3] Level 4 SMR = 2.48‡ (0.63–6.75)† [3] Cumulative exposure to formaldehyde: Level 1 SMR = 1.24‡ (0.21–4.10)† [2] Level 2 SMR = 3.20‡ (1.17–7.10)† [5] Level 3 SMR = 1.28‡ (0.40–3.07)† [4] Level 4 SMR = 1.56‡ (0.50–3.77)† [4] Average intensity exposure: Level 1 SMR = 1.24‡ (0.15–4.49)† [2] Level 2 SMR = 1.96‡ (0.72–4.33)† [5] Level 3 SMR = 1.91‡ (0.49–5.20)† [3] Level 4 SMR = 1.69‡ (0.62–3.74)† [5] Exposure to formaldehyde >0.2 ppm: Level 1 SMR = 1.51‡ (0.21–4.10)† [6] Level 2 SMR = 2.01‡ (1.02–3.05)† [9] Duration of exposure to >0.2 ppm: Level 1 SMR = 1.51‡ (0.21–4.10)† [6] Level 2 SMR = 1.72‡ (0.47–4.16)† [4] Level 3 SMR = 1.30‡ (0.22–4.29)† [2] Level 4 SMR = 4.94‡ (1.25–13.38)† [3] ‡**Note:** EPA derived SMRs for the combination of oropharyngeal, hypopharyngeal and unspecified pharyngeal cancer by subtracting the number of observed and expected nasopharyngeal cancer from the same counts for all pharyngeal cancers. †**Note:** EPA derived CIs using the Mid-P Method (See Rothman and Boice, 1979)

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
	included product and nonproduct particulates and airborne pigments.	
Reference: Marsh et al. (2002)	**Exposure assessment:** Worker-specific exposure from job-exposure matrix based on available sporadic sampling data from 1965 to 1987, job descriptions, and verbal job descriptions by plant personnel and industrial hygienists. Exposures ranked on a 7-point scale with exposure range assigned to each rank. 17% of jobs validated with company monitoring data; remaining 83% based on professional judgment. Assumed pre-1965 exposure levels same as post-1965 levels. Exposure estimates generated by this method were 10 times lower on average than those estimated by the NCI. Multiple exposure metrics including, known exposure, average intensity, and cumulative exposures were evaluated. **Duration and timing:** Duration of exposure was evaluated. **Variation in work *history*** *(from Table 3 in* Marsh et al. (2002)*)*: For all variations in exposure: Level 1 (unexposed) Exposure to formaldehyde: Level 2 (exposed) Work history: Level 1 (short-term workers: <1 year) Level 2 (long-term workers: 1+ year) Year of hire: Level 1 (1941–1946) Level 2 (1947–1956) Level 3 (1957+) Duration of employment: Level 1 (unexposed) Level 2 (<1 year) Level 3 (1+ years)	**External comparisons:** Exposure to formaldehyde >0.7 ppm: Level 1 SMR = 1.86‡ (1.01–3.16)† [12] Level 2 SMR = 1.46‡ (0.37–3.98)† [3] Duration of exposure to >0.7 ppm: Level 1 SMR = 1.86‡ (1.01–3.16)† [12] Level 2 SMR = 1.49‡ (0.25–4.93)† [2] Level 3 SMR = 1.41‡ (0.07–6.95)† [1] Work history: Level 1 SMR = 2.82‡ (1.31–5.37)† [8] Level 2 SMR = 1.70‡ (0.74–3.37)† [7] Year of hire: Level 1 SMR = 0.46‡ (0.11–10.73)† [1] Level 2 SMR = 2.49‡ (1.35–4.23)† [12] Level 3 SMR = 1.14‡ (0.19–3.78)† [2] Duration of employment: Level 1 SMR = 1.83‡ (0.85–3.47)† [8] Level 2 SMR = 1.77‡ (0.56–4.27)† [4] Level 3 SMR = 1.62‡ (0.41–4.41)† [3] Time since first employment: Level 1 SMR = 0.82‡ (0.14–2.71)† [2] Level 2 SMR = 1.50‡ (0.48–3.61)† [4] Level 3 SMR = 2.69‡ (1.31–4.94)† [9] ‡**Note:** EPA derived SMRs for the combination of oropharyngeal, hypopharyngeal and, unspecified pharyngeal cancer by subtracting the number of observed and expected nasopharyngeal cancer from the same counts for all pharyngeal cancers. †**Note:** EPA derived CIs using the Mid-P Method (See Rothman and Boice, 1979)

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
	Time since first employment: Level 1 (<20 year) Level 2 (20−29 years) Level 3 (30+ years)	
Reference: Laforest et al. (2000) **Population:** Males diagnosed with primary hypopharyngeal squamous cell cancers between January 1989 and May 1991 and identified through 15 French hospitals. Interviews completed for 79.5% of eligible cases and 86% of eligible controls. **Outcome definition:** Diagnosis of laryngeal and hypopharyngeal cancers was histologically confirmed. **Design:** Hospital-based case-control study of 201 hypopharyngeal cancers. 296 hospital controls frequency matched on age. **Analysis:** ORs were calculated by unconditional logistic regression and adjusted for age, alcohol, and smoking. Induction periods of 5, 10, and 15 years was also utilized to account for latency in evaluating risk. **Confidence in effect estimates:**[a]  **Medium** ↓ (Potential bias toward the null) **IB**: Exposure Group C	**Exposure assessment:** Occupational history obtained by interview. Exposure assessment based on job-exposure matrix that included level and probability of exposure, duration, and cumulative exposure to formaldehyde. Multiple exposure metrics including known exposure, probability of exposure, and cumulative exposure were evaluated. **Duration and timing:** Duration of exposure was evaluated. **Variation in exposure:** All subjects Exposure to formaldehyde: Level 1 (never exposed) Level 2 (ever exposed) Probability of exposure: Level 1 (never exposed) Level 2 (<10%) Level 3 (10 to 50%) Level 4 (>50%) Duration of exposure: Level 1 (never exposed) Level 2 (<7 years) Level 3 (7 to 20 years) Level 4 (>20 years) Cumulative exposure: Level 1 (never exposed) Level 2 (low, <0.02) Level 3 (medium, 0.02 to 0.09) Level 4 (high, >0.09) Subjects with a probability of exposure >10% Exposure to formaldehyde: Level 1 (never exposed) Level 2 (ever exposed) Duration of exposure: Level 1 (never exposed) Level 2 (≤7 years) Level 3 (7 to 20 years) Level 4 (>20 years) Cumulative exposure: Level 1 (never exposed) Level 2 (low)	**Internal comparisons:** All subjects Exposure to formaldehyde: Level 1 OR = 1.00 (Ref. value) [118] Level 2 OR = 1.35 (0.86−2.14) [83] Probability of exposure: Level 1 OR = 1.00 (Ref. value) [118] Level 2 OR = 1.08 (0.62−1.88) [42] Level 3 OR = 1.01 (0.44−2.31) [15] Level 4 OR = 3.78 (1.50−9.49) [26] *p*-trend (all) < 0.005 Cumulative exposure: Level 1 OR = 1.00 (Ref. value) [118] Level 2 OR = 1.03 (0.51−2.07) [23] Level 3 OR = 1.57 (0.81−3.06) [32] Level 4 OR = 1.51 (0.74−3.10) [28] Duration of exposure: Level 1 OR = 1.00 (Ref. value) [118] Level 2 OR = 1.09 (0.50−2.38) [18] Level 3 OR = 1.39 (0.74−2.62) [37] Level 4 OR = 1.51 (0.78−2.92) [28] Subjects with a probability of exposure >10% Exposure to formaldehyde: Level 1 OR = 1.00 (Ref. value) [118] Level 2 OR = 1.74 (0.91−3.34) [41] Cumulative exposure: Level 1 OR = 1.00 (Ref. value) [118] Level 2 OR = 0.78 (0.11−5.45) [3] Level 3 OR = 1.77 (0.65−4.78) [13] Level 4 OR = 1.92 (0.86−4.32) [25] *p*-trend (all) < 0.14 Duration of exposure: Level 1 OR = 1.00 (Ref. value) [118] Level 2 OR = 0.74 (0.20−2.68) [6] Level 3 OR = 1.65 (0.67−4.08) [19] Level 4 OR = 2.70 (1.08−6.73) [16] *p*-trend (all) < 0.04

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
	Level 3 (medium) Level 4 (high) **Other exposures:** asbestos, coal dust, leather dust, wood dust, flour dust, silica, and textile dust. **[**As noted in Appendix A.5.9: Of these, only coal dust significantly increased the risk of hypopharyngeal cancer in this study but coal dust and asbestos were controlled for in the OHPC analysis.**]**	Introduction of induction times as described did not substantially change the results.
Reference: Gustavsson et al. (1998) **Population:** Males between the ages of 40 and 79 years residing in Sweden identified by hospitals reports or regional cancer registries during 1988−1990. Interviews completed for 90% of cases and 85% of controls. **Outcome definition:** Diagnosis of cancer of the pharyngeal caner based on ICD-9 codes 146 (oropharynx) and 148 (hypopharynx) but not including code 147 (nasopharynx) on weekly reports from departments of otorhinolaryngology, oncology, and surgery and from regional cancer registries. **Design:** Community-based, case-control study of 138 cases of squamous cell carcinoma of the oropharynx/hypopharynx. 641 controls were randomly identified from population registers and frequency matched by region and age. **Analysis:** RRs were calculated by unconditional logistic regression and adjusted for region, age, drinking, and smoking. **Confidence in effect estimates:**[a]  	**Exposure assessment:** Occupational history obtained by interview and yielded information on all jobs held >1 year, starting and stopping times, job title, tasks, and company. Histories reviewed by industrial hygienist who coded jobs based on intensity and probability of exposure to 17 occupational factors. Exposure assessments estimated intensity on a 4-point scale and probability of exposure as point estimates. Cumulative exposure calculated as the product of exposure intensity, probability of exposure, and duration of exposure, and by adding contributions over entire work history. **Duration and timing:** Duration of exposure was evaluated. **Variation in exposure:** Exposure to formaldehyde: Level 1 (never) Level 2 (ever) **Other exposures:** polycyclic aromatic hydrocarbons, asbestos, general dust, wood dust, quartz, metal dust, oil mist, welding fumes, manmade mineral fibers, paper dust, textile dust, hexavalent chromium, phenoxy acids, nickel, acid mist, and leather dust. [As noted in Appendix A.5.9: Of these, only leather dust was a risk factor but only five cases were exposed.]	**Internal comparisons:** Exposure to formaldehyde: Level 1 OR = 1.00 (Ref. value) [# not given] Level 2 OR = 1.01 (0.49−2.07) [13]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
LOW ↓ (Potential bias toward the null; low sensitivity) **IB**: Exposure Group B Latency not evaluated. **Oth**: Low power due to rarity of exposure.		
Reference: Vaughan (1989) **Population:** Males and females between the ages of 20 and 74 years residing in a 13-county area identified by the Washington State Cancer Surveillance System during 1980–1983. Participation for all cases was 68.7 and 80.0% for controls. **Outcome definition:** Diagnosis of nasopharyngeal cancer based on review of hospital medical records, surveillance of private radiotherapy and pathology practices, and state death certificates. Nonsquamous cell cancers were excluded from the study. **Design:** Population-based, case-control study of 183 cases with oro pharyngeal/hypopharyngeal cancer. 552 controls were identified by random digit dialing in same geographic area. **Analysis:** ORs were calculated by logistic regression and adjusted for gender, cigarette smoking, and alcohol. Induction periods were evaluated. **Related studies:** Vaughan et al. (1986a, 1986b) **Confidence in effect estimates:**[a]  **LOW ↓** (Potential bias toward the null) **IB**: Exposure Group D **SB**: Potential selection bias due to use of next of kin.	**Exposure assessment:** Presumed exposure to formaldehyde. Interview-based information on lifetime occupational history by job type and industry. Occupations evaluated for both no lag and 15-year lag time between recent exposure and diagnosis. **Duration and timing:** Duration and timing of exposure were evaluated. **Variation in exposure:** Occupation and industry Duration: Level 1 (unexposed) Level 2 (1 to 9 years) Level 3 (>10 years) **Other exposures:** Not evaluated. **[**As noted in Appendix A.5.9: Wood dust is associated with risk of sinonasal cancer and was not evaluated as a confounder. However, as this is a case-control study the correlation between formaldehyde and wood dust is expected to be small and thus wood dust would not be expected to be a confounder.**]**	**Internal comparisons:** Carpenter (lagged 15 years) All Industries: OR = 1.3 (0.5–3.4) [11] All Industries by Duration: Level 1 OR = 1.0 (Ref. value) Level 2 OR = 0.6 (not given) Level 3 OR = 2.2 (not given) Carpenter (lagged 15 years) Construction industry: OR = 1.8 (0.7–4.8) [10] Construction by Duration: Level 1 OR = 1.0 (Ref. value) Level 2 OR = 0.7 (not given) Level 3 OR = 6.2 (not given)

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Reference: Vaughan et al. (1986a) **Population:** Males and females between the ages of 20 and 74 years residing in a 13-county area identified by the Washington State Cancer Surveillance System between 1980 and 1983. Participation for all cases was 69 and 80% for controls. Interviews completed for 71% of cases and 83% of controls. **Outcome definition:** Diagnosis of oropharynx/hypopharynx cancer (ICD codes 146 and 148) based on review of hospital medical records, surveillance of private radiotherapy and pathology practices, and state death certificates. **Design:** Population-based, case-control study of 205 incident cases with cancer of the oropharynx/hypopharynx including unspecified pharyngeal sites. 552 controls were identified by random digit dialing in same geographic area. **Analysis:** ORs were calculated by logistic regression and adjusted for cigarette smoking, alcohol consumption, sex, and age. An induction period of 15 years was also utilized to account for latency in evaluating exposure score. **Related studies:** Vaughan et al. (1986b) **Confidence in effect estimates:**[a]  **LOW ↓** (Potential bias toward the null) **IB**: Exposure Group D **SB**: Potential selection bias due to use of next of kin.	**Exposure assessment:** Interview-based information on lifetime occupational exposure to formaldehyde with cases, next of kin, and controls. Exposure from available hygiene data, NIOSH and other data, and NCI job-exposure linkage system. Multiple exposure metrics including intensity, # of years exposed, and exposure score based on the sum of # years spent per job weighted by estimated formaldehyde level were evaluated. Exposure score calculated for both no lag and 15-year lag time between recent exposure and diagnosis. **Duration and timing:** Duration of exposure was evaluated. **Variation in exposure:** Intensity: Level 1 (background) Level 2 (low) Level 3 (medium) Level 4 (high) Number of years exposed: Level 1 (0 years) Level 2 (1 to 9 years) Level 3 (≥10 years) Exposure score (no lag): Level 1 (0 to 4) Level 2 (5 to 19) Level 3 (≥20) Exposure score (15-year lag): Level 1 (0 to 4) Level 2 (5 to 19) Level 3 (≥20) **Coexposures:** Not evaluated. [As noted in Appendix A.5.9: Wood dust is associated with risk of sinonasal cancer and was not evaluated as a confounder. However, as this is a case-control study the correlation between formaldehyde and wood dust is expected to be small and thus wood dust would not be expected to be a confounder.]	**Internal comparisons:** Intensity: Level 1 OR = 1.0 (Ref. value) [147] Level 2 OR = 0.8 (0.5−1.4) [41] Level 3 OR = 0.8 (0.4−1.7) [13] Level 4 OR = 0.6 (0.1−2.7) [4] Number of years exposed: Level 1 OR = 1.0 (Ref. value) [147] Level 2 OR = 0.6 (0.3−1.0) [32] Level 3 OR = 1.3 (0.7−2.5) [26] Exposure score (no lag): Level 1 OR = 1.0 (Ref. value) [170] Level 2 OR = 0.6 (0.3−1.2) [14] Level 3 OR = 1.5 (0.7−3.0) [21] Exposure score (15-year lag): Level 1 OR = 1.0 (Ref. value) [174] Level 2 OR = 0.9 (0.4−1.8) [16] Level 3 OR = 1.3 (0.6−3.1) [15]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Reference: Vaughan et al. (1986b) **Population:** Males and females between the ages of 20 and 74 years residing in a 13-county area identified by the Washington State Cancer Surveillance System between 1980 and 1983. Participation for all cases was 68.7 and 80.0% for controls. Interviews completed for 71% of cases and 83% of controls. **Outcome definition:** Diagnosis of oropharynx/hypopharynx cancer (ICD codes 146 and 148) based on review of hospital medical records, surveillance of private radiotherapy and pathology practices, and state death certificates. **Design:** Population-based, case-control study of 205 incident cases with cancer of the oropharynx/hypopharynx including unspecified pharyngeal sites. 552 controls were identified by random digit dialing in same geographic area with one control per case randomly selected from all the eligible persons in the household and frequency matched for gender and age. **Analysis:** ORs were calculated by multiple logistic regression and adjusted for cigarette smoking, alcohol consumption, sex, and age. **Related studies:** Vaughan et al. (1986a) **Confidence in effect estimates:**[a]  **LOW ↓** (Potential bias toward the null) **IB**: Exposure Group D **SB**: Potential selection bias due to use of next of kin.	**Exposure assessment:** Interview-based information on lifetime occupational history and residential history from cases, controls, and next of kin for deceased cases. Multiple exposure metrics including type of dwelling (i.e., mobile home) and use of particleboard or plywood were evaluated. **Duration and timing:** Exposure period since 1950. Duration of exposure was evaluated. **Variation in exposure:** Residence in mobile home: Level 1 (0 years) Level 2 (1 to 9 years) Level 3 (≥10 years) Years of exposure to particleboard or plywood: Level 1 (0 years) Level 2 (1 to 9 years) Level 3 (≥10 years) **Coexposures:** Not evaluated. Information of occupational exposures provided in Vaughan et al. (1986a) [As noted in Appendix A.5.9: Wood dust is associated with risk of sinonasal cancer and was not evaluated as a confounder. However, as this is a case-control study the correlation between formaldehyde and wood dust is expected to be small and thus wood dust would not be expected to be a confounder.]	**Internal comparisons:** Residence in mobile home: Level 1 OR = 1.0 (Ref. value) [177] Level 2 OR = 0.9 (0.5−1.8) [21] Level 3 OR = 0.8 (0.2−2.7) [7] Years of exposure to particleboard: Level 1 OR = 1.0 (Ref. value) [137] Level 2 OR = 1.1 (0.7−1.9) [40] Level 3 OR = 0.8 (0.5−1.4) [28]

[a]Evaluation of sources of bias or study limitations (see details in Appendix A.5.9). SB = selection bias; IB = information bias; Cf = confounding; Oth = other feature of design or analysis. Extent of column shading reflects degree of limitation. Direction of anticipated bias indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact would be likely to be away from the null (i.e., spurious or inflated effect estimate).

Laryngeal cancer

Epidemiological evidence

Evidence describing an association between formaldehyde exposure and the risk of developing or dying from laryngeal cancer was available from 18 studies—13 cohort studies (Coggon et al., 2014; Beane Freeman et al., 2013; Meyers et al., 2013; Band et al., 1997; Jakobsson et al., 1997; Andjelkovich et al., 1995; Hansen and Olsen, 1995; Hansen et al., 1994; Hayes et al., 1990; Stroup et al., 1986; Levine et al., 1984a; Walrath and Fraumeni, 1984, 1983) and five case-control studies (Shangina et al., 2006; Berrino et al., 2003; Laforest et al., 2000; Gustavsson et al., 1998; Wortley et al., 1992). Two reported results were classified as uninformative. Berrino et al. (2003) was classified as uninformative due to likely confounding by highly correlated coexposures, one of which was a stronger risk factor for laryngeal cancer in that study than was formaldehyde (i.e., solvents). Hansen et al. (1994) was classified as uninformative due to likely information bias stemming from the rarity of exposure among cases in that cohort. The outcome-specific evaluations of confidence in the precise effect estimate of an association from each study are provided in Appendix A.5.9. Details of the reported results of *high*, *medium*, and *low* confidence are provided in the evidence table for laryngeal cancer (see Table 1-35) following the causal evaluation.

Consistency of the observed association

The results of the 16 informative studies were not consistent. The study results presented in Table 1-35 (by confidence level and publication date) detail all of the reported associations. Only one set of results was classified with *high* confidence (Beane Freeman et al., 2013), and those results surrounded the null with a modest increase in risk overall with SMR = 1.23 (95% CI 0.91, 1.67), and at the highest level of average intensity of exposure a RR = 1.73 (95% CI 0.83, 3.60), and conversely, a modest decrease in risk at the highest level of peak exposure with RR = 0.72 (95% CI 0.32, 1.65), and a stronger decreased risk at the highest level of duration of exposure with RR = 0.33 (95% CI 0.10, 1.11). Of the five sets of results classified with *medium* confidence (Coggon et al., 2014; Shangina et al., 2006; Laforest et al., 2000; Wortley et al., 1992; Hayes et al., 1990), only two reported clearly increased risks; Shangina et al. (2006) showed an association with the highest level of cumulative exposure (OR = 3.12, 95% CI 1.23, 7.91) and Wortley et al. (1992) showed an association among those with at least 10 years of exposure and the highest peak exposures (OR = 4.3, 95% CI 1.0, 18.7). Coggon et al. (2014) found modestly increased risk for the cohort as a whole (SMR = 1.22, 95% CI 0.76, 1.84) and higher risks among those workers who had ever been "highly" exposed (SMR = 1.96, 95% CI 0.98, 3.50). They did not find greater risk among those who had been "highly" exposed for more than 1 year (SMR = 1.30,

95% CI 0.39, 4.38). The results from Laforest et al. (2000) and Hayes et al. (1990) did not show consistently increased risks. The study results classified with *low* confidence were consistently around the null. Results are plotted in Figure 1-23.

Strength of the observed association

Summary effect estimates for the association between formaldehyde exposure and the relative effect estimates of developing or dying from laryngeal cancer ranged from 0.33 to 4.3 and generally clustered around the null. The study results classified with *low* confidence were all limited to summary estimates without examination of exposures levels within the exposed study subjects. The results classified with *medium* confidence differentiated the risks by levels of exposure, and these results showed somewhat higher effect estimates among the most highly exposed groups, but these effect estimates were largely less than a doubling of risk. There were two results of *medium* confidence that reported more than a tripling of risk (Shangina et al., 2006; Wortley et al., 1992). However, the one set of results classified with *high* confidence (Beane Freeman et al., 2013) did not report a consistent pattern of increased risk.

Specificity of the observed association

Only the specific diagnosis of laryngeal cancer was considered here. The most specific level of laryngeal cancer diagnosis that is commonly reported across the epidemiological literature has been based on the first three digits of the Eighth or Ninth Revision of the ICD code (i.e., Laryngeal cancer ICD-9: 161).

Temporal relationship of the observed association

In each of the studies, the formaldehyde exposures among the study participants started prior to their diagnoses of laryngeal cancer and in the studies that ascertained individual-level exposures, the estimation of formaldehyde exposures was based on job titles and done in a blinded fashion with respect to outcome status. While several of the studies did report results with lagged exposures to account for potential latency effects, none of the 16 studies provided details of analyses of a temporal relationship between the timing of exposure using different lags and the diagnoses of laryngeal cancer or deaths from laryngeal cancer. However, Shangina et al. (2006) did state that a 20-year lag in exposure was assessed but did not report those details for formaldehyde; and Wortley et al. (1992) reported that a 10-year lag in exposure 'only slightly' increased the estimated effects.

Exposure-response relationship

The strongest evidence of an exposure-response was reported by Shangina et al. (2006), who found that among cases of "Ever" exposed to formaldehyde, the OR = 1.68 (95% CI 0.85, 3.31), those cases with the highest tertile of cumulative exposure had an OR = 3.12 (95% CI 1.23, 7.91). Shangina et al. (2006) also reported suggestions of trends for increased risk with increasing tertiles

of duration of exposure ($p < 0.06$) and with increasing tertile of cumulative exposure ($p < 0.07$). Wortley et al. (1992) also found higher risks among the most highly exposed with an OR = 4.3 (95% CI 1.0, 18.7). However, Beane Freeman et al. (2013) did not find consistent evidence of an exposure-response relationship for increasing peak exposure ($p > 0.5$), for increasing average intensity ($p = 0.44$), but did find a significant trend ($p = 0.02$) with cumulative exposure that may have been decreasing in nature with lower risks at higher exposures.

Potential impact of selection bias, information bias, confounding bias, and chance

For laryngeal cancer, the reliance of cohort studies on death certificates to detect cancers with relatively high survival underestimated the actual incidence of those cancers. Five-year survival rates are about 60% (see Appendix A.5.9). This may have resulted in undercounting of incident cases and underestimates of effect estimates in cohort studies compared to general populations. Selection bias could have somewhat obscured a truly larger effect of formaldehyde exposure on the risk of death from laryngeal cancer and may explain the preponderance of effect estimates near the null. The case-control studies Shangina et al. (2006), Laforest et al. (2000), Gustavsson et al. (1998), and Wortley et al. (1992), because they recruited incident cases, were less prone to such a bias. Information bias may distort findings when subjects' true personal exposures are inaccurately assigned. Random measurement error typically results in a bias toward the null, thereby obscuring any real effect by underestimating the effect's magnitude. Confounding is another potential bias that could arise if another cause of laryngeal cancer was statistically associated with formaldehyde exposure. However, there does not appear to be any evidence of negative confounding that could have obscured a real but unobserved effect. Overall, bias is considered to be an unlikely alternative cause for the isolated reports of increased risks of laryngeal cancer associated with formaldehyde exposures.

Causal evaluation

The causal evaluation for formaldehyde exposure and the risk of developing or dying from laryngeal cancer placed the greatest weight on five particular considerations: (1) the *s*uggestive associations reported for two *medium* confidence studies (Shangina et al., 2006; Wortley et al., 1992); (2) the suggestive exposure-response relationships of increased risk with increased formaldehyde exposure, specifically by Shangina et al. (2006), but the lack of support for exposure-response from other studies including the single set of results classified with *high* confidence which found a significant downward trend in risks with increasing exposure (Beane Freeman et al., 2013); (3) the moderate survival rate for laryngeal cancer (60%), which may indicate that mortality data are not as good a proxy for incidence data for this cancer type; and (4) the absence of evidence to evaluate the potential risk to sensitive populations or lifestages.

Conclusion

- The available epidemiological studies provide *indeterminate* evidence to assess the potential for an association between formaldehyde exposure and an increased risk of laryngeal cancer.

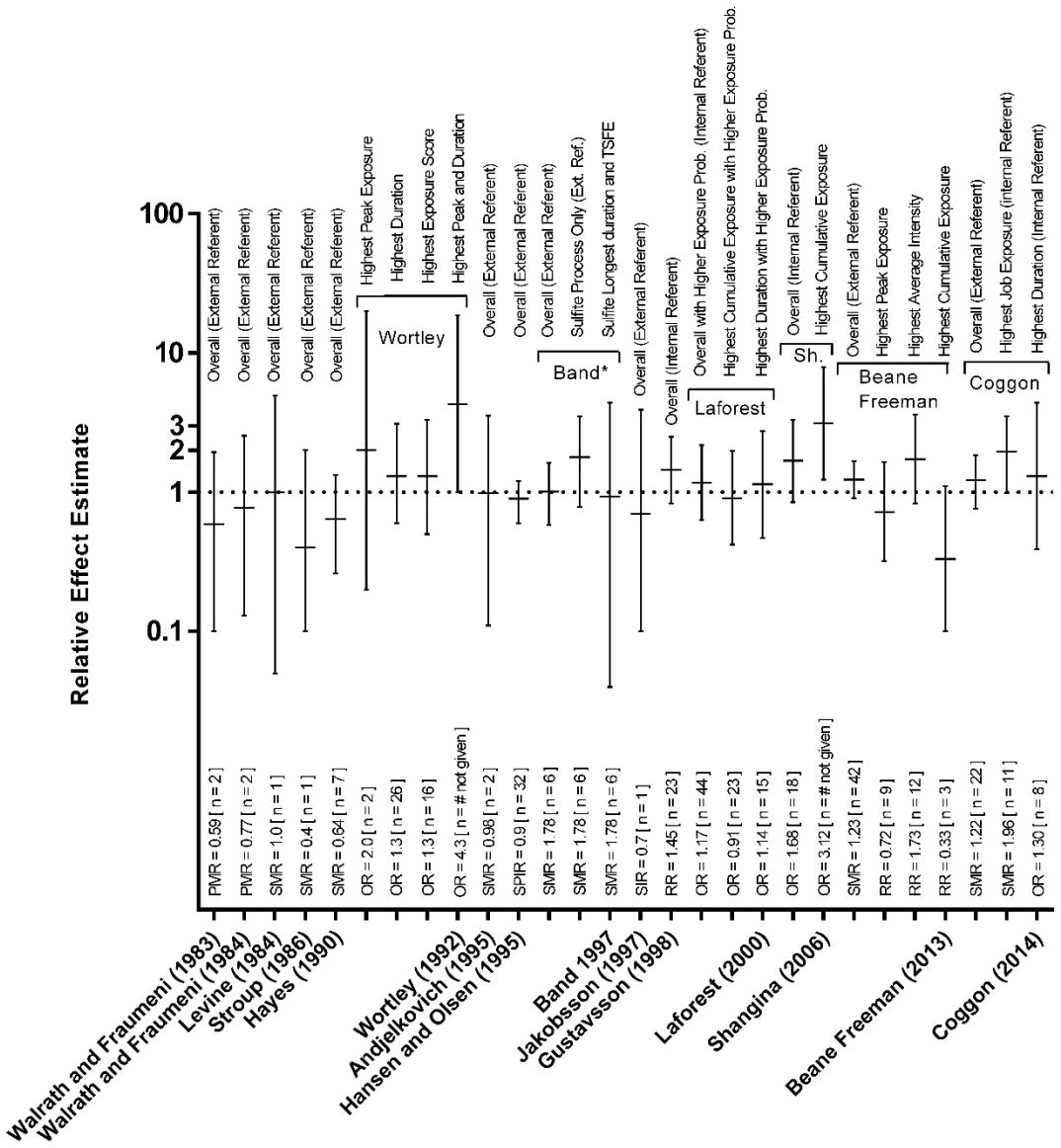
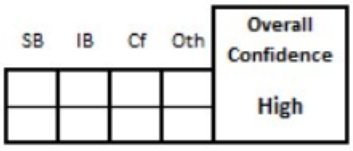


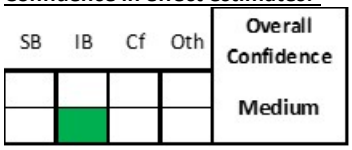
Figure 1-23. Epidemiological studies reporting laryngeal cancer risk estimates.

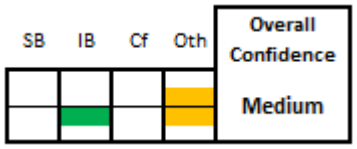
For each measure of association, the number of exposed cases is provided in brackets (e.g., [*n* = 1]). For studies reporting results on multiple metrics of exposure, only the highest category of each exposure metric is presented in the figure. Note that the confidence intervals for Band et al. (1997) are 90%, not 95%. Abbreviations: SMR = standardized mortality ratio; RR = relative risk; OR = odds ratio. SPIR = standardized proportional incidence ratio.

Table 1-35. Epidemiological studies of formaldehyde exposure and risk of laryngeal cancer

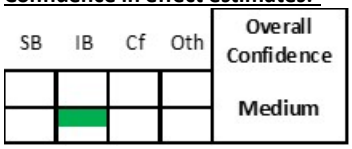
Study	Exposures	Results: effect estimate (95% CI) [# of cases]

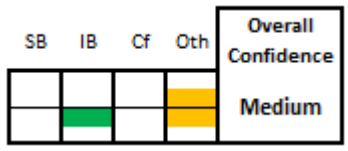
Reference: Beane Freeman et al. (2013)
Population: 25,619 workers employed at 10 formaldehyde-using or formaldehyde-producing plants in the United States followed from either the plant start-up or first employment through 2004. Deaths were identified from the National Death Index with remainder assumed to be living. 676 workers (3%) were lost to follow-up. Vital status was 97.4% complete and only 2.6% lost to follow-up.
 	
Outcome definition: Death certificates used to determine underlying cause of death from laryngeal cancer (ICD-8: 161). Histological typing not reported.
 	
Design: Prospective cohort mortality study with external and internal comparison groups.
 	
Analysis: RRs estimated using Poisson regression stratified by calendar year, age, sex, and race; adjusted for pay category compared to workers in lowest exposed category. Lagged exposures were evaluated to account for cancer latency. Results were presented for 15-year lag.
 	
SMRs calculated using sex, age, race, and calendar-year-specific U.S. mortality rates.
 	
Related studies:
Hauptmann et al. (2004)
Beane Freeman et al. (2009)
 	
Confidence in effect estimates:[a]
 
 	
HIGH ●
IB: Exposure: Group A
	Exposure assessment: Individual-level exposure estimates based on job titles, tasks, visits to plants by study industrial hygienists who took 2,000 air samples from representative job, and monitoring data from 1960 through 1980.
	
	Median TWA (over 8 hours) = 0.3 ppm (range 0.01−4.3). Median cumulative exposure = 0.6 ppm-years (range 0−107.4).
	
	Multiple exposure metrics including peak, average, and cumulative exposures were evaluated using categorical and continuous data.
	
	Duration and timing: Exposure period from <1946 to 1980. Median length of follow-up: 42 years. Median length of employment was 2.6 years (range 1 day−47.7 years). Duration and timing since first exposure were not evaluated.
	
	Variation in exposure:
	Peak exposure:
	Level 1 (>0 to <2.0 ppm)
	Level 2 (2.0 to <4.0 ppm)
	Level 3 (≥4.0 ppm)
	Average intensity:
	Level 1 (>0 to <0.5 ppm)
	Level 2 (0.5 to <1.0 ppm)
	Level 3 (≥1.0 ppm)
	Cumulative exposure:
	Level 1 (>0 to <1.5 ppm-yrs)
	Level 2 (1.5 to <5.5 ppm-yrs)
	Level 3 (≥5.5 ppm-yrs)
	
	Coexposures: Exposures to 11 other compounds were identified and evaluated as potential confounders.
		Internal comparisons:
		Peak exposure
		Unexposed RR = 0.79 (0.25−2.48) [6]
		Level 1 RR = 1.00 (Ref. value) [17]
		Level 2 RR = 1.52 (0.76−3.05) [16]
		Level 3 RR = 0.72 (0.32−1.65) [9]
		p-trend (exposed) > 0.50;
		p-trend (all) > 0.50
		
		Average intensity
		Unexposed RR = 0.89 (0.29−2.75) [6]
		Level 1 RR = 1.00 (Ref. value) [21]
		Level 2 RR = 1.25 (0.57−2.76) [9]
		Level 3 RR = 1.73 (0.83−3.6) [12]
		p-trend (exposed) = 0.44;
		p-trend (all) = 0.39
		
		Cumulative exposure
		Unexposed RR = 0.67 (0.22−2.00) [6]
		Level 1 RR = 1.00 (Ref. value) [29]
		Level 2 RR = 1.01 (0.49−2.11) [10]
		Level 3 RR = 0.33 (0.10−1.11) [3]
		p-trend (exposed) = 0.02;
		p-trend (all) = 0.03
		
		External comparisons:
		$SMR_{Unexposed}$ = 0.93 (0.42−2.08) [6]
		$SMR_{Exposed}$ = 1.23 (0.91−1.67) [42]

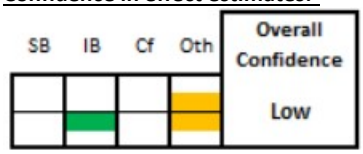
Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Reference: Coggon et al. (2014) **Population:** 14,008 British men employed in six chemical industry factories that produced formaldehyde. Cohort mortality followed from 1941 through 2012. Cause of deaths was known for 99% of 5,185 deaths through 2000. Similar cause of death information not provided on 7,378 deaths through 2012. Vital status was 98.9% complete through 2003. Similar information not provided on deaths through 2012. **Outcome definition:** Death certificates used to determine cause of deaths from laryngeal cancer. **Design:** Cohort mortality study with external comparison group with a nested case-control study. **Analysis:** SMRs based on English and Welsh age- and calendar-year-specific mortality rates. **Related studies:** Acheson et al. (1984) Gardner et al. (1993) Coggon et al. (2003) **Confidence in effect estimates:**[a]  **MEDIUM** ↓ (Potential bias toward the null) **IB**: Exposure: Group B; lack of latency analysis.	**Exposure assessment:** Exposure assessment based on data abstracted from company records. Jobs categorized as background, low, moderate, high, or unknown levels. **Duration and timing:** Occupational exposure during 1941–1982. Duration was evaluated as more, or less, than one year only among the "High" exposure group. Timing since first exposure was not evaluated. **Variation in exposure:** Highest exposure level attained Level 1 (Background) Level 2 (low/moderate) Level 3 (High) Duration of "High" exposures Level 1 (Background) Level 2 (<1 year) Level 3 (1 year or more) **Coexposures:** Not evaluated. Potential low-level exposure to styrene, ethylene oxide, epichlorhydrin, solvents, asbestos, chromium salts, and cadmium. **[**As noted in Appendix A.5.9: Styrene is associated with LHP cancers but not URT cancers. Asbestos is associated with URT cancers, including laryngeal cancer. Authors stated that the extent of coexposures was expected to be low. Potential for confounding may be mitigated by low coexposures. Other coexposures are not known risk factors for this outcome.**]**	**External comparisons:** SMR = 1.22 (0.76–1.84) [22] Highest exposure level attained Level 1 SMR = 0.33 (0.04–1.20) [2] Level 2 SMR = 1.40 (0.64–2.66) [9] Level 3 SMR = 1.96 (0.98–3.50) [11] **Internal comparisons:** Highest exposure level attained Level 1 OR = 1.00 (Ref. value) [14] Level 2 OR = 1.20 (0.53–2.73) [17] Level 3 OR = not given [22] Duration of "High" exposures Level 1 OR = 1.00 (Ref. value) [14] Level 1 OR = 2.02 (0.65–6.27) [14] Level 2 OR = 1.30 (0.39–4.38) [8]
Reference: Shangina et al. (2006) **Population:** Males between the ages of 15 and 79 years residing in four European countries that were diagnosed with laryngeal cancer during 1999–2002 and identified by	**Exposure assessment:** Occupational histories obtained by interview and yielded information on all jobs held >1 year. A general questionnaire obtained information of job titles, tasks, industries, starting and stopping times, full-time/part-time status, working environments, and specific exposures. A specific questionnaire	**Internal comparisons:** Exposure to formaldehyde: Level 1 OR = 1.00 (Ref. value) [298] Level 2 OR = 1.68 (0.85–3.31) [18] Duration of exposure: *p*-trend (all) = 0.06 Cumulative exposure:

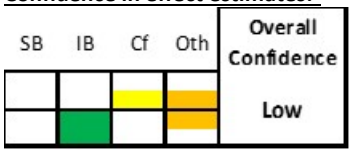
Study	Exposures	Results: effect estimate (95% CI) [# of cases]
study centers in Romania, Poland, Russia, and Slovakia. **Outcome definition:** Diagnosis of laryngeal cancer was histologically or cytologically confirmed and included topographic subcategories from ICD-O code C32 (glottis, supraglottis, subglottis, laryngeal cartilage, overlapping lesion of the larynx, and larynx, unspecified). **Design:** Multicenter case-control study of 316 laryngeal cancer cases. 728 hospital controls were frequency matched by age. **Analysis:** ORs were calculated by unconditional logistic regression and adjusted for age, country, tobacco smoking, and alcohol consumption. An induction period of 20 years was also utilized to account for latency in evaluating risk. **Confidence in effect estimates:**[a]  **MEDIUM** ↓ (Potential bias toward the null) **IB**: Exposure: Group C **Oth**: Low power due to rarity of exposure.	was completed for employment in defined jobs or industries. Exposure assessment based on expert judgment of reported task descriptions. Exposure scored according to intensity, frequency, and confidence. Multiple exposure metrics including known exposure and cumulative exposure were evaluated. **Duration and timing:** Duration of exposure was evaluated. **Variation in exposure:** Exposure to formaldehyde: Level 1 (never) Level 2 (ever) Cumulative exposure (tertiles): Level 1 (Tertile 1 unspecified) Level 2 (Tertile 2 unspecified) Level 3 (≥22,700 mg/m^3-hrs) Duration of exposure (tertiles): Level 1 (Tertile 1 unspecified) Level 2 (Tertile 2 unspecified) Level 3 (Tertile 3 unspecified) Definitions for levels of exposure for duration of exposure to formaldehyde and cumulative exposure not provided by authors except for the lower bound of Tertile 3 for cumulative exposure. **Other exposures:** Not evaluated as confounders. [As noted in Appendix A.5.9: Other exposures that were found to be risk factors included dusts of "hard alloys" (16 cases) and chlorinated solvents (15 cases). Hard-alloy dust and chlorinated solvents were each found in fewer than 6% of cases, the correlation between them is considered to be small enough to make confounding unlikely.]	Level 1 Unspecified Level 2 Unspecified Level 3 OR = 3.12 (1.23–7.91) *p*-trend (all) = 0.07 Duration of exposure: Level 1 Unspecified Level 2 Unspecified Level 3 Unspecified *p*-trend (all) = 0.06 No notable findings were reported between formaldehyde exposure and the risk of laryngeal cancer when considering an induction period of 20 years.
Reference: Laforest et al. (2000)	**Exposure assessment:** Occupational history obtained by interview. Exposure assessment based on job-exposure matrix that included level	**Internal comparisons:** All subjects Exposure to formaldehyde:

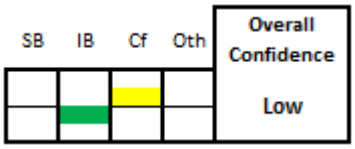
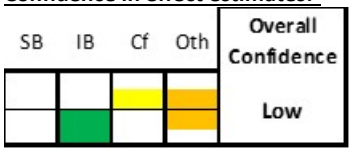
Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Population: Males diagnosed with primary laryngeal squamous cell cancers between January 1989 and May 1991 and identified through 15 French hospitals. Interviews completed for 79.5% of eligible cases and 86% of eligible controls. **Outcome definition:** Diagnosis of laryngeal was histologically confirmed. **Design:** Hospital-based case-control study of 296 laryngeal cancers. 296 hospital controls frequency matched on age. **Analysis:** Ors were calculated by unconditional logistic regression and adjusted for age, alcohol, and smoking. Induction periods of 5, 10, and 15 years was also utilized to account for latency in evaluating risk. **Confidence in effect estimates:**[a] SB: ; IB: ; Cf: ; Oth: ; Overall Confidence: Medium **MEDIUM ↓** (Potential bias toward the null) **IB**: Exposure: Group C	and probability of exposure, duration, and cumulative exposure to formaldehyde. Multiple exposure metrics including known exposure, probability of exposure, and cumulative exposure were evaluated. **Duration and timing:** Duration of exposure was evaluated. **Variation in exposure:** All subjects Exposure to formaldehyde: Level 1 (never exposed) Level 2 (ever exposed) Probability of exposure: Level 1 (never exposed) Level 2 (<10%) Level 3 (10 to 50%) Level 4 (>50%) Duration of exposure: Level 1 (never exposed) Level 2 (<7 years) Level 3 (7 to 20 years) Level 4 (>20 years) Cumulative exposure: Level 1 (never exposed) Level 2 (low, <0.02) Level 3 (medium, 0.02 to 0.09) Level 4 (high, >0.09) Subjects with a probability of exposure >10% Exposure to formaldehyde: Level 1 (never exposed) Level 2 (ever exposed) Duration of exposure: Level 1 (never exposed) Level 2 (≤7 years) Level 3 (7 to 20 years) Level 4 (>20 years) Cumulative exposure: Level 1 (never exposed) Level 2 (low) Level 3 (medium) Level 4 (high) **Other exposures:** asbestos, coal dust, leather dust, wood dust, flour dust, silica, and textile dust. **[**As noted in Appendix A.5.9: Of these, none significantly increased the risk of	Level 1 OR = 1.00 (Ref. value) [194] Level 2 OR = 1.14 (0.76–1.70) [102] Probability of exposure: Level 1 OR = 1.00 (Ref. value) [194] Level 2 OR = 1.16 (0.73–1.86) [58] Level 3 OR = 1.12 (0.55–2.30) [23] Level 4 OR = 1.04 (0.44–2.47) [21] Cumulative exposure: Level 1 OR = 1.00 (Ref. value) [194] Level 2 OR = 1.12 (0.62–2.01) [35] Level 3 OR = 1.44 (0.79–2.63) [38] Level 4 OR = 0.87 (0.45–1.67) [29] Duration of exposure: Level 1 OR = 1.00 (Ref. value) [194] Level 2 OR = 1.42 (0.75–2.68) [35] Level 3 OR = 1.09 (0.62–1.96) [37] Level 4 OR = 0.96 (0.52–1.76) [30] Subjects with a probability of exposure >10% Exposure to formaldehyde: Level 1 OR = 1.00 (Ref. value) [194] Level 2 OR = 1.17 (0.63–2.17) [44] Cumulative exposure: Level 1 OR = 1.00 (Ref. value) [194] Level 2 OR = 0.68 (0.12–3.90) [4] Level 3 OR = 1.86 (0.76–4.55) [17] Level 4 OR = 0.91 (0.42–1.99) [23] Duration of exposure: Level 1 OR = 1.00 (Ref. value) [194] Level 2 OR = 1.68 (0.60–4.72) [15] Level 3 OR = 0.86 (0.33–2.24) [14] Level 4 OR = 1.14 (0.47–2.74) [15] Introduction of induction times as described did not substantially change the results.

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
	laryngeal cancer in this study but coal dust was controlled for in the laryngeal cancer analysis.]	
Reference: Wortley et al. (1992) **Population:** Males and females between the ages of 20 and 74 years residing in western Washington who were diagnosed with laryngeal cancer between September 1983 and February 1987 and identified through the cancer surveillance system of the Fred Hutchinson Cancer Research Center. Interviews completed for 80.8% of eligible cases and 80% of eligible controls. **Outcome definition:** Diagnosis of cancer of the larynx based on ICD codes 161.0−161.9 from cancer registry data. **Design:** Population-based case-control study of 235 cases of laryngeal cancer. 547 controls identified from random digit dialing and were selected for the same distributions of age and sex to the cases. **Analysis:** ORs were calculated by multiple logistic regression and adjusted for smoking, drinking, age, and education. An induction period of 10 years was also utilized to account for latency in evaluating duration and exposure score. **Confidence in effect estimates:**[a]  **MEDIUM** ↓ (Potential bias toward the null) **IB**: Exposure: Group C	**Exposure assessment:** Occupational history obtained by interview for all jobs held for ≥6 months and included job titles, description of tasks performed, and industry. Job titles analyzed by duration of exposure (≤9 year and ≥10 years). Exposures assessment based on job-exposure matrix. Industrial hygienists classified jobs into four levels of exposure to formaldehyde based on judgment of both likelihood and degree of exposure. Exposure score calculated as the weighted sum of years with exposure, with weight based on level of exposure code. Exposure codes defined as: 0 = no, 1 = low, 2 = medium, and 3 = high. Multiple exposure metrics including peak exposure (subject's highest exposure code) and exposure score were evaluated. **Duration and timing:** Duration of exposure was evaluated. **Variation in exposure:** Peak exposure: Level 1 (none) Level 2 (low) Level 3 (medium) Level 4 (high) Duration: Level 1 (<1 years) Level 2 (1 to 9 years) Level 3 (≥10 years) Exposure scores: Level 1 (<5) Level 2 (5 to 19) Level 3 (≥20) Peak and Duration: Level 1 (none) Level 2 (med/high and ≥10 years) Level 3 (high and ≥10 years) **Other exposures:** asbestos, chromium, nickel, cutting oils, and diesel fumes. High-risk occupations (e.g., mechanics,	**Internal comparisons:** Peak exposure: Level 1 OR = 1.0 (Ref. value) [177] Level 2 OR = 1.0 (0.6−1.7) [42] Level 3 OR = 1.0 (0.4−2.1) [14] Level 4 OR = 2.0 (0.2−20) [2] Duration: Level 1 OR = 1.0 (Ref. value) [182] Level 2 OR = 0.8 (0.4−1.3) [27] Level 3 OR = 1.3 (0.6−3.1) [26] Exposure scores: Level 1 OR = 1.0 (Ref. value) [201] Level 2 OR = 1.0 (0.5−2.0) [18] Level 3 OR = 1.3 (0.5−3.3) [16] Peak and Duration Level 1 OR = 1.0 (Ref. value) [177] Level 2 OR = 4.2 (0.9−19.4) [not given] Peak and Duration Level 1 OR = 1.0 (Ref. value) [177] Level 2 OR = 4.2 (0.9−19.4) [not given] Level 3 OR = 4.3 (1.0−18.7) [not given] No notable findings were reported between formaldehyde exposure and the risk of laryngeal cancer when considering an induction period of 10 years.

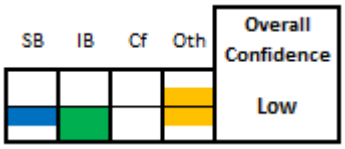
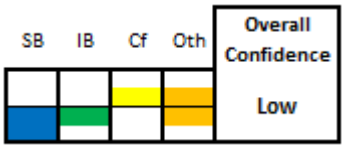
Study	Exposures	Results: effect estimate (95% CI) [# of cases]
	carpenters, painters, textile machine operators) likely had coexposures to unidentified substances. **[**As noted in Appendix A.5.9: This is a case-control study the correlation between formaldehyde and those potential confounders is expected to be small, and thus, wood dust would not be expected to be a confounder.**]**	
Reference: Hayes et al. (1990) **Population:** 4,046 deceased U.S. male embalmers and funeral directors, derived from licensing boards and funeral director associations in 32 states and the District of Columbia who died during 1975−1985. Death certificates obtained for 79% of potential study subjects (*n* = 6,651) with vital status unknown for 21%. **Outcome definition:** Death certificates and licensing boards used to determine cause of death from laryngeal cancer (ICD-8: 161). **Design:** Proportionate mortality cohort study with external comparison group. **Analysis:** PMRs calculated using sex, race, age, and calendar-year-expected numbers of deaths from the U.S. population. **Confidence in effect estimates:**[a]  **MEDIUM ↓** (Potential bias toward the null) **IB**: Exposure Group A; latency not evaluated **Oth**: Potential undercounting of cases.	**Exposure assessment:** Presumed exposure to formaldehyde tissue fixative. Exposure based on occupation which was confirmed on death certificate. Authors subsequently measured personal embalming exposures ranging from 0.98 ppm (high ventilation) to 3.99 ppm (low ventilation) with peaks up to 20 ppm. Authors state that major exposures are to formaldehyde and possibly glutaraldehyde and phenol. **Duration and timing:** Occupational exposure preceding death during 1975−1985. Of 115 deaths from LHP cancer, 66 (57%) were aged 60−74 years. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** Not evaluated. **[**As noted in Appendix A.5.9: Coexposures may have included: phenol, methyl alcohol, glutaraldehyde, mercury, arsenic, zinc, and ionizing radiation. Anatomists may also be coexposed to stains, benzene, toluene xylene, stains, chlorinated hydrocarbons, dioxane, and osmium tetroxide. Radiation exposure likely to be poorly correlated with formaldehyde. Benzene is not associated with URT cancer.**]**	**External comparisons:** PMR = 0.64 (0.26−1.33) [7]

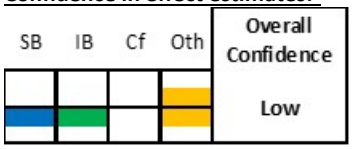
Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Reference: Meyers et al. (2013) **Population:** 11,043 workers in 3 U.S. garment plants exposed for at least 3 months. Women comprised 82% of the cohort. Vital status was followed through 2008 with 99.7% completion. **Outcome definition:** Death certificates used to determine both the underlying cause of death from laryngeal cancer (ICD code in use at time of death). **Design:** Prospective cohort mortality study with external and internal comparison groups. **Analysis:** SMRs calculated using sex, age, race, and calendar-year-specific U.S. mortality rates. **Related studies:** Pinkerton et al. (2004) Stayner et al. (1985) Stayner et al. (1988) **Confidence in effect estimates:**[a]  **LOW** ↓ (Potential bias toward the null; low sensitivity) **IB**: Exposure: Group A; lack of latency analysis. **Oth**: Low power due to rarity of cases.	**Exposure assessment:** Individual-level exposure estimates for 549 randomly selected workers during 1981 and 1984. Geometric TWA8 exposures ranged from 0.09 to 0.20 ppm. Overall geometric mean concentration of formaldehyde was 0.15 ppm, (GSD 1.90 ppm). Area measures showed constant levels without peaks. Historically earlier exposures may have been substantially higher. **Duration and timing:** Exposure period from 1955 to 1983. Median duration of exposure was 3.3 years. More than 40% exposures <1963. Median time since first exposure was 39.4 years. Duration and timing since first exposure were not evaluated for this cancer. **Variation in exposure:** Not evaluated. **Coexposures:** Study population specifically selected because industrial hygiene surveys at the plants did not identify any chemical exposures other than formaldehyde that were likely to influence findings.	**External comparisons:** SMR = 0.77 (0.21−1.97) [4]
Reference: Gustavsson et al. (1998) **Population:** Males between the ages of 40 and 79 years residing in Sweden identified by hospitals reports or regional cancer registries during 1988−1990. Interviews completed for 90% of cases and 85% of controls. **Outcome definition:** Diagnosis of laryngeal cancer based on ICD-9 codes on weekly reports from departments of otorhinolaryngology, oncology, and	**Exposure assessment:** Occupational history obtained by interview and yielded information on all jobs held >1 year, starting and stopping times, job title, tasks, and company. Histories reviewed by industrial hygienist who coded jobs based on intensity and probability of exposure to 17 occupational factors. Exposure assessments estimated intensity on a 4-point scale and probability of exposure as point estimates. Cumulative exposure calculated as the product of exposure	**Internal comparisons:** Exposure to formaldehyde: Level 1 RR = 1.00 (Ref. value) [# not given] Level 2 RR = 1.45 (0.83−2.51) [23]

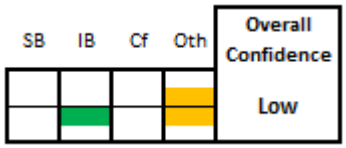
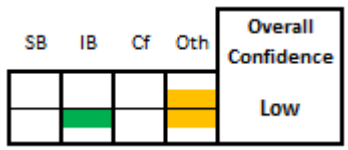
Study	Exposures	Results: effect estimate (95% CI) [# of cases]
surgery and from regional cancer registries. **Design:** Community-based, case-control study of 157 cases of squamous cell carcinoma of the larynx. 641 controls were randomly identified from population registers and frequency matched by region and age. **Analysis:** RRs were calculated by unconditional logistic regression and adjusted for region, age, drinking, and smoking. **Confidence in effect estimates:**[a]  **LOW** ↓ (Potential bias toward the null) **IB**: Exposure: Group B; latency not evaluated. Cf: Potential confounding Oth: Low power	intensity, probability of exposure, and duration of exposure, and by adding contributions over entire work history. **Duration and timing:** Duration of exposure was evaluated. **Variation in exposure:** Exposure to formaldehyde: Level 1 (never) Level 2 (ever) **Other exposures:** polycyclic aromatic hydrocarbons, asbestos, general dust, wood dust, quartz, metal dust, oil mist, welding fumes, manmade mineral fibers, paper dust, textile dust, hexavalent chromium, phenoxy acids, nickel, acid mist, and leather dust. [As noted in Appendix A.5.9: Asbestos and metal dust were both stronger risk factors for laryngeal cancer so there is a potential for confounding.]	
Reference: Band et al. (1997) **Population:** 30,157 male workers in the pulp and paper industry with at least 1-year employment accrued by January 1950. Followed through December 1982. Loss to follow-up was less than 6.5% for workers exposed to the sulfate process (67% of original cohort of 30,157) and less than 20% for workers exposed to the sulfite process. **Outcome definition**: Cause of death obtained from the National Mortality Database based on ICD version in effect at time of death and standardize to ICD-9 version. Larynx: ICD-9 161. **Design:** Cohort mortality study with external comparison group. **Analysis:** SMRs calculated using sex, race, age, and calendar-year-expected	**Exposure assessment:** Occupational data limited to hire and termination dates for all workers and type of chemical process of pulping (sulfate vs. sulfite). No job-specific data available. Presumed exposure to formaldehyde known to be used in the plant. Formaldehyde is known to be an exposure risk for pulp and paper mill workers: job-specific median exposures ranging from 0.04 to 0.4 ppm with peaks as high as 50 ppm (Korhonen et al., 2004). **Duration and timing:** Duration and timing since first exposure were not evaluated. **Variation in exposure:** No variation in formaldehyde exposure was reported. Results presented by pulping process (sulfate vs. sulfite) but neither process uses formaldehyde which is used in paper making.	**External comparisons:** All workers SMR = 1.01 (90% CI 0.58−1.63) [12] **Workers only in sulfite process** All workers SMR = 1.78 (90% CI 0.78−3.52) [8] Work duration <15 years TSFE <15 years SMR = 2.46 (90% CI 0.10−11.63) [1] TSFE ≥15 years SMR = 2.13 (90% CI 0.72−4.87) [4] Work duration ≥15 years TSFE ≥15 years SMR = 0.93(90% CI 0.04−4.38) [1]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
numbers of deaths from the Canadian population. **Confidence in effect estimates:**[a]  **LOW** ↓ (Potential bias toward the null) **IB**: Exposure: Group C **Cf**: Potential confounding	**Coexposures:** Not evaluated as confounders. [As noted in Appendix A.5.9: Potential confounders for these outcomes include chlorophenols, **acid mists**, dioxin, and perchloroethylene and would likely be positively correlated with formaldehyde exposure. Potential for confounding is unknown but could have inflated the observed effect.]	
Reference: Jakobsson et al. (1997) **Population:** 727 male employees of two plants producing stainless steel sinks and saucepans employed at least 1 year during 1927–1981 with minimum 15-year follow-up. **Outcome definition:** Incidence of laryngeal cancer from the Swedish Tumor Registry (ICD-7:161). **Design:** Cohort incidence study with external comparison group. **Analysis:** SIRs calculated using sex, age, and calendar-year-expected number of cases from the national population. **Confidence in effect estimates:**[a]  **LOW** ↓ (Potential bias toward the null; low sensitivity) **IB**: Exposure: Group D **Oth**: Low power due to rarity of cases.	**Exposure assessment:** Workers grind stainless steel with grinding plates made of formaldehyde resins, which may release formaldehyde when heated during grinding operations. **Duration and timing:** Occupational exposure preceding death during 1927–1981. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** Not evaluated as confounders. [As noted in Appendix A.5.9: Nickel and chromium are associated with URT cancers and would likely be positively correlated with formaldehyde exposure. Potential for confounding is unknown but could have inflated the observed effect. Other coexposures are not known risk factors for these outcomes.]	**External comparisons:** SIR = 0.7 (0–3.9) [1]
Reference: Andjelkovich et al. (1995) **Population:** 3,929 automotive industry iron foundry workers exposed from 1960 to 1987 and followed through 1989.	**Exposure assessment:** Individual-level exposure status (Yes/No, Quartile) based on review of work histories by an industrial hygienist. Exposure assessment blinded to outcome.	**External comparisons:** $SMR_{Unexposed}$ = 0.70 (0.01–3.91) [1] $SMR_{Exposed}$ = 0.98 (0.11–3.53) [2]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Outcome definition: Underlying cause of death obtained from Social Security Administration, Pension Benefit Informations, and National Death Index) Larynx: ICD 161 **Design:** Cohort mortality study with external comparison group. **Analysis:** SMRs calculated using sex-, age-, race-, and calendar-year-specific U.S. mortality rates. **Confidence in effect estimates:**[a]  **LOW** ↓ (Potential bias toward the null) **IB**: Exposure: Group B; Latency not evaluated **Cf**: Potential confounding **Oth**: Low power due to rarity of cases.	Independent testing of iron foundries by NIOSH reported a range from 0.02 ppm to 18.3 ppm (cited in WHO (1989) Env. Health Criteria 89: Formaldehyde). **Duration and timing:** Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** Not evaluated. **[**As noted in Appendix A.5.9: Nickel and chromium are associated with URT cancers and would likely be positively correlated with formaldehyde exposure. Potential for confounding is unknown but could have inflated the observed effect. Other coexposures are not known risk factors for these outcomes.**]**	
Reference: Hansen and Olsen (1995) **Population:** 2,041 men with cancer who were diagnosed during 1970−1984 and whose longest work experience occurred at least 10 years before cancer diagnosis. Identified from the Danish Cancer Registry and matched with the Danish Supplementary Pension Fund. **Outcome definition:** Cancer of the larynx (ICD-7: 161) listed on Danish Cancer Registry file. **Design:** Proportionate incidence study with external comparison group. **Analysis:** Standardized proportionate incidence ratio calculated as the proportion of cases for a given cancer in formaldehyde-associated companies relative to the proportion of cases for the same cancer among	**Exposure assessment:** Individual occupational histories including industry and job title established through company tax records to the national Danish Product Register. Subjects whose longest work experience was ≥10 years prior to cancer diagnosis were considered potentially exposed to formaldehyde. All subjects were stratified based on job title as either low exposure (white collar worker), above background exposure (blue collar worker), or unknown (job title unavailable). **Duration and timing:** Exposure period since 1964. **Variation in exposure:** Not evaluated. **Coexposures:** Not evaluated. **[**As noted in Appendix A.5.9: While other coexposures were not evaluated, the overall correlation between	Overall (exposure to formaldehyde ≥10 years prior to cancer diagnosis) SPIR = 0.9 (0.6−1.2) [32]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
all employees in Denmark. Adjusted for age and calendar time. **Confidence in effect estimates:**[a]  **LOW** ↓ (Potential bias toward the null) **IB**: Exposure Group D	coexposures in multiple occupational industries is likely to be low.**]**	
Reference: Stroup et al. (1986) **Population:** 2,239 white male members of the American Association of Anatomists from 1888 to 1969 who died during 1925–1979. Death certificates obtained for 91% with 9% lost to follow-up. **Outcome definition:** Laryngeal cancer (ICD-8: 161) listed as cause of death on death certificates. **Design:** Cohort mortality study with external comparison group. **Analysis:** SMRs calculated using sex, race, age, and calendar-year-expected number of deaths from the U.S. population. **Confidence in effect estimates:**[a]  **LOW** ↓ (Potential bias toward the null) **IB**: Exposure Group A; latency not evaluated **SB**: Healthy worker effect. **Oth**: Low power due to rarity of cases.	**Exposure assessment:** Presumed exposure to formaldehyde tissue fixative. **Duration and timing:** Occupational exposure preceding death during 1925–1979. Median birth year was 1912. By 1979, 33% of anatomists had died. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** Not evaluated. **[**As noted in Appendix A.5.9: Coexposures may have included: phenol, methyl alcohol, glutaraldehyde, mercury, arsenic, zinc, and ionizing radiation. Anatomists may also be coexposed to stains, benzene, toluene xylene, stains, chlorinated hydrocarbons, dioxane, and osmium tetroxide. Radiation exposure likely to be poorly correlated with formaldehyde. Benzene is not associated with URT cancer.]	**External comparisons:** SMR = 0.4 (0–2.0) [1]
Reference: Levine et al. (1984a) **Population:** 1,477 male undertakers licensed with the Ontario Board of Funeral Services from 1928 to 1957 who died during 1950–1977. Vital status was followed through 1977	**Exposure assessment:** Presumed exposure to formaldehyde tissue fixative. **Duration and timing:** Occupational exposure preceding death during	**External comparisons:** Observed: 1 Expected: 1.0 SMR = 1.00 (0.05–4.93)† [1]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
with 96% completion and only 4% lost to follow-up. **Outcome definition:** Death certificates used to determine cause of death from cancer of the larynx (ICD-8: 161). **Design:** Retrospective cohort mortality study with external comparison group. **Analysis:** Ontario mortality rates for <1950 not available for SMR calculations. Expected deaths were determined by applying age- and calendar year-specific mortality rates of Ontario men to the 1950 through 1977 experience of the cohort. **Confidence in effect estimates:**[a]  **Low** ↓ (low sensitivity; potential bias toward the null) **IB**: Exposure Group A; latency not evaluated **SB**: Healthy worker effect. **Oth**: Low power due to rarity of cases.	1950–1977. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** Not evaluated. **[**As noted in Appendix A.5.9: Coexposures may have included: phenol, methyl alcohol, glutaraldehyde, mercury, arsenic, zinc, and ionizing radiation. Anatomists may also be coexposed to stains, benzene, toluene xylene, stains, chlorinated hydrocarbons, dioxane, and osmium tetroxide. Radiation exposure likely to be poorly correlated with formaldehyde. Benzene is not associated with URT cancer.**]**	†EPA derived CIs using the Mid-P Method (See Rothman and Boice, 1979)
Reference: Walrath and Fraumeni (1984) **Population:** 1,007 deceased white male embalmers from the California Bureau of Funeral Directing and Embalming who died during 1925–1980. Death certificates obtained for all. **Outcome definition:** Laryngeal cancer listed as cause of death on death certificates. **Design:** Proportionate mortality cohort study with external comparison group. **Analysis:** PMRs calculated using sex, race, age, and calendar-year-expected number of deaths from the U.S. population.	**Exposure assessment:** Presumed exposure to formaldehyde tissue fixative. **Duration and timing:** Occupational exposure preceding death during 1916–1978. Birth year ranged from 1847 to 1959. Median age of death was 62 years. Most deaths were among embalmers with active licenses. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** Not evaluated. **[**As noted in Appendix A.5.9: Coexposures may have included: phenol, methyl alcohol, glutaraldehyde, mercury, arsenic, zinc, and ionizing radiation.	**External comparisons:** Observed: 2 Expected: 2.6 PMR = 0.77 (0.13–2.54)† [2] †EPA derived CIs using the Mid-P Method (See Rothman and Boice, 1979)

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Confidence in effect estimates:[a]  **LOW ↓** (Potential bias toward the null; low sensitivity) **SB:** Potential selection bias: due to incomplete death certificate ascertainment. **IB**: Exposure Group A; latency not evaluated **Oth**: Low power due to rarity of cases.	Anatomists may also be coexposed to stains, benzene, toluene, xylene, stains, chlorinated hydrocarbons, dioxane, and osmium tetroxide. Radiation exposure likely to be poorly correlated with formaldehyde. Benzene is not associated with URT cancer.**]**	
Reference: Walrath and Fraumeni (1983) **Population:** 1,132 deceased white male embalmers licensed to practice during 1902−1980 in New York who died during 1925−1980 identified from registration files. Death certificates obtained for 75% of potential study subjects (*n* = 1,678). **Outcome definition:** Laryngeal cancer listed as cause of death on death certificates. **Design:** Proportionate mortality cohort study with external comparison group. **Analysis:** PMRs calculated using sex, race, age, and calendar-year-expected numbers of deaths from the U.S. population. **Confidence in effect estimates:**[a]  **LOW ↓** (Potential bias toward the null; Low sensitivity) **SB:** Potential selection bias: due to incomplete death certificate ascertainment. **IB**: Exposure Group A; latency not evaluated **Oth**: Low power due to rarity of cases.	**Exposure assessment:** Presumed exposure to formaldehyde tissue fixative. **Duration and timing:** Occupational exposure preceding death during 1902−1980. Median year of birth was 1901. Median year of initial license was 1931. Median age at death was 1968. Expected median duration of exposure was 37 years. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** Not evaluated. **[**As noted in Appendix A.5.9: Coexposures may have included: phenol, methyl alcohol, glutaraldehyde, mercury, arsenic, zinc, and ionizing radiation. Anatomists may also be coexposed to stains, benzene, toluene xylene, stains, chlorinated hydrocarbons, dioxane, and osmium tetroxide. Radiation exposure likely to be poorly correlated with formaldehyde. Benzene is not associated with URT cancer.**]**	**External comparisons:** Observed: 2 Expected: 3.4 PMR = 0.50 (0.10−1.94)† [2] †EPA derived CIs using the Mid-P Method (See Rothman and Boice, 1979)

[a]Evaluation of sources of bias or study limitations (see details in Appendix A.5.9). SB = selection bias; IB = information bias; Cf = confounding; Oth = other feature of design or analysis. Extent of column shading reflects degree of limitation. Direction of anticipated bias indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact would be likely to be away from the null (i.e., spurious or inflated effect estimate).

Respiratory Tract Cancers in Animal Studies

This section covers precancerous lesions (i.e., dysplasia) and neoplasms (tumors) of the respiratory tract in animal experiments, with most of the available studies focusing on the development of squamous cell carcinomas (SCCs) in the nasal cavity. Considering the long duration necessary for the development of these cancers, the evidence tables of the experimental animal studies are organized by study duration, specifically focusing on chronic exposure (≥1 year) and subchronic exposure (≥3 months) with long-term follow-up (typically assessed after ≥1 year). These studies are further organized by study confidence and species in Table 1-36.

Animal studies investigating formaldehyde-induced respiratory carcinogenesis were carried out primarily in rats and to a lesser extent in mice, hamsters, and nonhuman primates. While the most consistent evidence of formaldehyde-induced respiratory cancers in animals is restricted to the nasal cavity and consists primarily of squamous cell carcinomas (SCCs), other neoplasms that have been observed include carcinomas other than SCCs, sarcomas, papillomas, and adenomas (Kamata et al., 1997; Monticello et al., 1996; Morgan et al., 1986b; Sellakumar et al., 1985; Kerns et al., 1983). Nasal tumors are rare in both mice and rats (Brown, 1990), thus any consistent increase in incidence is notable. Although dysplastic lesions, as well as hyperplasia and squamous metaplasia (see Section 1.2.4), have been observed posterior to the nasal cavity, respiratory tract tumors in these regions have not been reported to be significantly increased by formaldehyde treatment. In chronic studies in rats, carcinogenic effects generally first occur around 12 months in high exposure groups, with increased tumor incidence and decreased latency correlating with increasing exposure concentrations. Two subchronic studies with an extended period of observation also reported an increase in tumor incidence.

Although the bioassays in mice, hamsters, and rats represent similar exposure concentrations and duration of exposure, clear species differences in the severity of lesions are present. Hamsters display little histopathological change whereas rats exhibit gross toxicity and even increased mortality. Mice exhibit a range of effects on the respiratory epithelium, but not to the severity observed in rats. There are significant species differences in the anatomical structure of the airways, and in oral/nasal breathing patterns, including reflex bradypnea (see Appendix A.3 for discussion), all of which may influence areas of formaldehyde absorption or flux into the tissue. The differential toxicity of formaldehyde on the URT in animals may also be due to localized differences in mucus flow and production, as well as differences in the expression or distribution of enzymes involved in formaldehyde detoxification. Overall, as discussed below, inhalation exposure to formaldehyde in experimental animals induces nasal cancer and dysplasia with increasing incidence as a function of exposure duration and concentration at the POE.

Methodological issues considered in evaluation of studies

This section describes histopathological evidence reporting the induction of carcinomas, other neoplasms, and dysplasia in the respiratory tract of experimental animals after formaldehyde exposure. The discussion emphasizes observations of malignant tumors (e.g., adenocarcinomas and carcinomas and squamous cell carcinomas (SCCs), which were those most commonly observed) as representing the most advanced stage of rodent tumor malignancy. Other neoplasms were reported in the database, including adenomas and papillomas. While these neoplasms also represent abnormal changes to the respiratory tissue, the use of benign lesions to characterize potential human cancer risk is more straightforward when chemical-specific data are available to associate such lesions with the development of more malignant lesions along relevant progression pathways. For example, while squamous cell papillomas are benign lesions that could progress to become malignant SCCs in various rodent tissues, this progression through a benign papillomatous stage may not occur in rat nasal passages, whereas SCCs may arise directly from hyperplastic or dysplastic tissue (McConnell et al., 1986). Conversely, nasal polypoid adenomas (representing a different cellular lineage from those developing into SCCs) may progress to adenocarcinomas, which represent the more advanced stage in this cancer continuum. While benign and malignant rodent tumors are considered neoplasms, dysplasia is an example of a dedicated, preneoplastic lesion which may progress to neoplasia, and is therefore informative to the potential for human carcinogenesis. However, dysplasia itself is not cancer per se, but simply one possible stage along the presumed continuum of progressive changes characteristic of epithelial carcinogenesis. Thus, this section prioritizes discussion of incidence data for malignant tumors, representing the most advanced and rare lesions relevant to informing human cancer hazard; discussion of other neoplasms or dysplasia is presented separately, as supporting evidence.

This section describes the incidence, location, and severity of these lesions. Although, generally, the study authors cited in this section did not provide statistical comparisons for the reported lesions data, given the rarity of these neoplasms in unexposed animals (SCCs in particular), any observations of malignant tumors in the respiratory tract are considered to be biologically relevant, abnormal changes. Potential relationships between lesions or the potential for progression of benign lesions to malignant tumors are presented in the MOA discussion that follows. Other respiratory tract lesions that may be relevant to cancer development include hyperplasia and squamous metaplasia, which were discussed in Section 1.2.4.

All subchronic or chronic studies (and an 8-week exposure study in potentially vulnerable mice) in experimental animals that included histopathological evaluations of respiratory tract tissues (i.e., nose/nasal cavity, larynx, trachea, lung) were considered and evaluated (see Appendix A.5.9), noting that evaluations of the pharynx or mouth were uncommon in these studies, probably because experimental rodents are obligate nose-breathers). Histopathological evaluations used standard cross-section levels of the nasal passages that paralleled the evaluations of respiratory tract pathology described in Section 1.2.4 (see Figure 1-14 for example cross-section

levels). This section focuses on studies of *high* and *medium* confidence. Studies interpreted with *low* confidence for these particular endpoints are briefly summarized, but excluded from the evidence tables: This includes all subchronic exposure studies that did not include a follow-up period to allow for the development of respiratory tract cancers, such that the total experimental duration from first exposure to terminal sacrifice was ≥12 months (24 months of observation is preferred).

Synthesis of respiratory tract cancer in animals

Squamous cell carcinomas

Squamous cell carcinomas (SCCs) are the most consistently observed respiratory tract cancer in mice and rats exposed to formaldehyde. These malignant tumors likely arise from squamous cells, a type of differentiated epithelial cell that also comprises the majority of the epidermis ("skin" cells). Formaldehyde-induced SCCs are restricted to the nasal cavity and have not been observed in any other region of the respiratory tract. The most useful and abundant SCC data (i.e., the large majority of studies interpreted with *medium* or *high* confidence) are from studies of exposed rats. Following exposure of rats to formaldehyde for 2 years, an increase in SCCs was observed in 5 of 6 studies (see Table 1-36 and Figure 1-24). These tumors were detected in exposed male and female Fischer 344 (F344) and Sprague Dawley rats, but findings in Wistar rats were less clear (see discussion below). Overall, SCCs were not reproducibly detected below 6 mg/m^3 formaldehyde in rats; however, none of the available rat studies tested exposure between 3 and 6 mg/m^3, introducing uncertainty. Reflecting the rarity of these tumors [rat background incidence averages <0.3% (Brown et al., 1991)], the incidence in control groups across the chronic formaldehyde exposure studies in rats was 0%. Generally, the incidence increased to around 1% at approximately 7 mg/m^3 formaldehyde, and further increased to around 40% as formaldehyde concentrations neared 18 mg/m^3 (Note that for purpose of comparison across studies, Table 1-36 reports incidence rates unadjusted for mortality; see Section 2.2.1 for mortality-adjusted rates. Unadjusted rates are generally underestimates; for example, the adjusted cumulative incidence rate in female rats exposed for 24 months at 17.6 mg/m^3 by Kerns et al. (1983) was reported at 87%).

The data as reported in Kerns et al. (1983) and Monticello et al. (1996) were corrected in a memorandum issued by the CIIT Centers for Health Research, which had sponsored or conducted these studies (Bermudez, 2004). The corrected data are noted in separate rows in Table 1-36. The correction for Kerns et al. (1983) in the CIIT memo (2004) indicates the number of animals examined instead of the number of animals in the experiment. The corrections for Monticello et al. (1996) issued in the CIIT memo (2004) arise from an examination by CIIT scientists of tissues for an additional group of 94 rats from the study that had not been previously examined (as explained

inConolly et al., 2003).[23] These tissues were from the 12-, 18-, and 24-month time points and were distributed approximately evenly across the six exposure concentrations.

[23]Conolly et al. (2003) modeled the dose-response for squamous cell carcinoma (SCC) data by combining the data from Kerns et al. (1983) and Monticello et al. (1996) and the data from these 94 rats. The individual animal data pertaining to the combined data are reported in the Appendix in Conolly et al. (2003). EPA's dose-response analysis used the combined data.

Table 1-36. Squamous cell carcinoma (SCC) incidence in rats[a] exposed to formaldehyde for ≥2 years

	Strain	Sex	Formaldehyde concentration range[b] (specific mg/m3 examined)						
			0	0 < × < 3	3 < × < 6	6 < × < 9	9 < × < 12	12 < × < 15	15 > × > 18.5
High confidence									
Kerns et al. (1983)	F344	M	0/118	0/118 (2.5[c])	—	1/119 (6.9)	—	—	51/117 (17.6)
		F	0/114	0/118 (2.5)	—	1/116 (6.9)	—	—	52/115 (17.6)
Corrected Bermudez (2004)		M and F	0/237	0/239	—	2/235	—	—	83/225
Monticello et al. (1996)	F344	M	0/90	0/90 (0.9); 0/90 (2.5)	—	1/90 (7.4)	—	20/90 (12.2)	69/147 (18.4)
Corrected Bermudez (2004)		M and F	0/104	0/221	—	1/108		22/103	79/161
Wouters en et al. (1989)	Wistar	M	0/26	1/26 (0.1); 1/28 (1.2)	—	—	—	1/26 (12.1)	—
Medium confidence									
Holmstrom et al. (1989c)	Sprague Dawley	F	0/15	—	—	—	—	—	1/16 (15.3)
Kamata et al. (1997)	F344	M	0/32	0/32 (0.4); 0/32 (2.7)	—	—	—	—	13/32 (18.3)
Sellakumar et al. (1985)	Sprague Dawley	M	0/99	—	—	—	—	—	38/100 (18.2)
Formaldehyde range (mg/m^3)			0	0 < × < 3	3 < × < 6	6 < × < 9	9 < × < 12	12 < × < 15	15 > × > 18.5
Total rats examined Range of percentage incidence[d]/study			494 0–0%	534 0–3.8% [e]	0 —	325 0.8–1.1%	0 —	116 3.8–22.2%	527 6.3–46.9%

F344: Fischer 344; M: Male; F: Female; — Concentrations in this range were not examined.

[a]This table is restricted to experimental studies in rats, given toxicokinetic differences across species. A mouse (Kerns et al., 1983) and hamster (Dalbey, 1982) study also meet confidence and exposure duration criteria.

[b]These ranges were arbitrarily chosen to cover the available data and do not have a biological basis.
[c]The specific concentration(s) of formaldehyde tested in the study is in parentheses.
[d]Incidence rates are unadjusted for mortality.
[e]Both SCCs in this concentration range are from Woutersen et al. (1989), which did not observe any increases in SCCs at much higher formaldehyde concentrations in Wistar rats, reducing confidence in these findings.

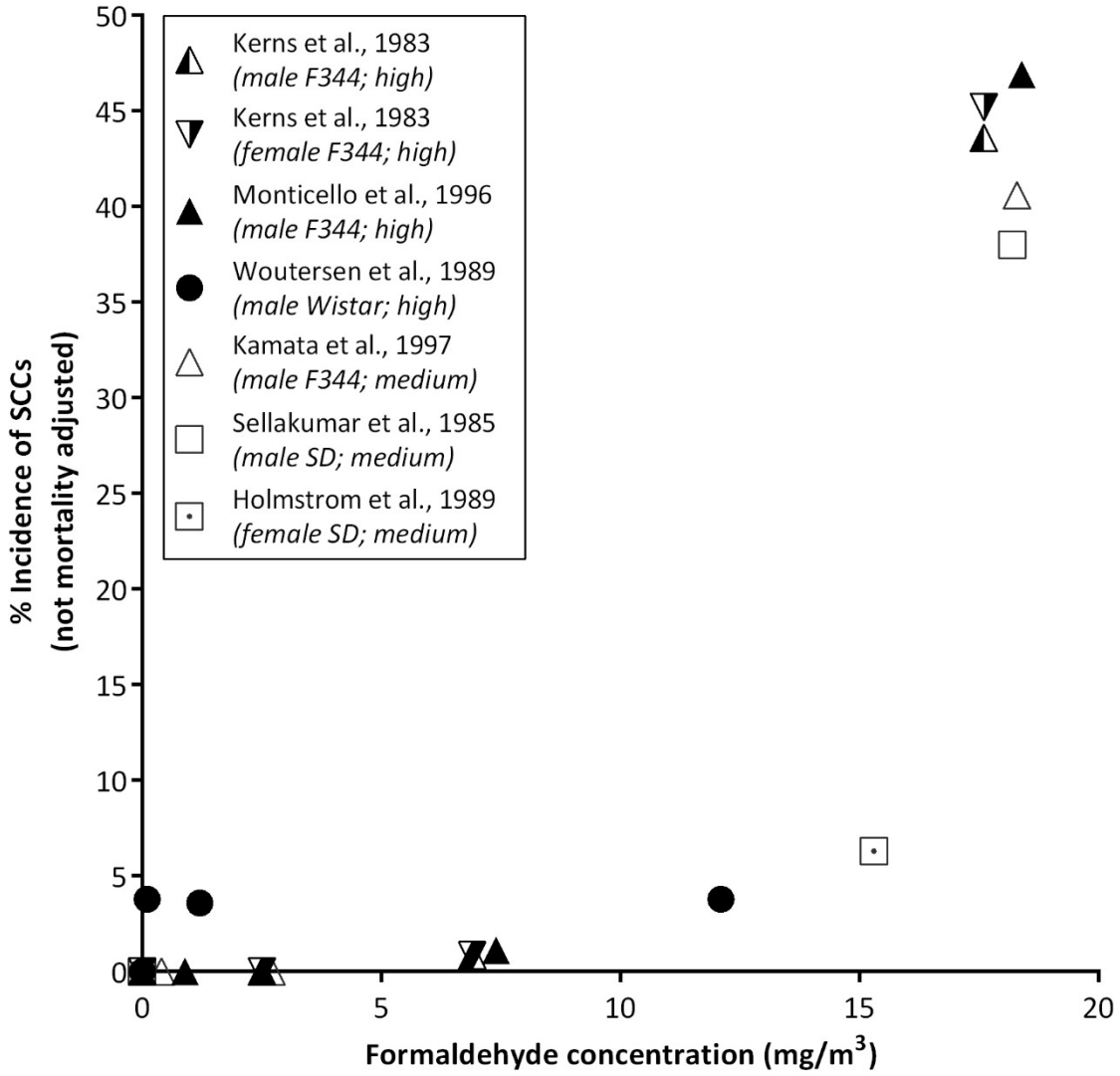


Figure 1-24. Nasal SCCs in rats exposed to formaldehyde for at least 2 years.

Incidence data for squamous cell carcinomas from the *high* and *medium* (unfilled shapes) confidence studies evaluating formaldehyde exposures of at least 2 years.

The data suggest that rats of different strains may vary in their sensitivity to formaldehyde-induced SCCs. The only rat study with 2 years of formaldehyde exposure that did not observe an association of SCCs with increasing formaldehyde exposure was conducted in Wistar rats (Woutersen et al., 1989). Although the authors reported a single SCC in each of the treatment groups (no SCCs were observed in controls), these tumors may not have been related to

formaldehyde exposure as the incidence did not change at higher formaldehyde levels and observations of SCCs occurred at far lower concentrations than in any other rat studies. Consistent with this potential resistance of Wistar rats to formaldehyde-induced SCCs observed by Woutersen et al. (1989), an earlier study from the same laboratory examining Wistar rats at identical formaldehyde concentrations did not detect any SCCs (Appelman et al., 1988); however, the earlier study only exposed and observed animals for 12 months, substantially reducing its ability to detect cancers. Two additional experiments from the same laboratory examined whether subchronic formaldehyde exposure with follow-up for more than 2 years resulted in SCCs in Wistar rats (Woutersen et al., 1989; Feron et al., 1988). Both of these studies observed a single SCC induced in response to formaldehyde exposure at approximately 11 mg/m^3, with an increased incidence of formaldehyde-induced SCCs to 3 of 44 in the study that tested a higher exposure of 24.4 mg/m^3 (Feron et al., 1988). The <4% incidence in Wistar rats exposed to approximately 11 mg/m^3 in these studies contrasts with the 22% incidence observed at this level in F344 rats by Monticello et al. (1996). Taken together, although some of the data with a sufficient duration of observation suggest that formaldehyde exposure can induce a low incidence of SCCs in Wistar rats (Woutersen et al., 1989; Feron et al., 1988), these findings indicate that this strain may be resistant to formaldehyde-induced nasal SCCs, as compared to F344 and Sprague Dawley rats.

The effects of long-term formaldehyde exposure in species other than rats are less well studied, but the available data suggest that rats may be the most sensitive laboratory rodents. The only mouse study testing exposure of at least 2 years (Kerns et al., 1983) provided support for the consistent observations of SCCs in formaldehyde-exposed rats. In this well-conducted (i.e., *high* confidence) study, SCCs were observed at 17.6 mg/m^3, but not at 6.9 or 2.5 mg/m^3 (incidence in controls was 0%). The incidence at 17.6 mg/m^3 was <2% (2/120), in contrast with the >40% incidence detected in F344 rats exposed to similar formaldehyde concentrations by the same study authors (Kerns et al., 1983). The authors also reported that the SCCs in rats were more invasive and severe than those observed in mice. These differences could reflect the use of a mouse strain that might be insensitive to these effects, similar to the above discussion of Wistar rats, but the differences more likely reflect a decreased response due to a lower inhaled dose of formaldehyde resulting from differences in breathing patterns and irritant responses across species (see Appendices A2 and A3). In contrast, no respiratory tract tumors were observed in Syrian golden hamsters exposed to 12.3 mg/m^3 of formaldehyde for a lifetime (Dalbey, 1982), although no other exposure levels were tested to inform whether this species or strain may also be less sensitive than exposed F344 and Sprague Dawley rats, and exposed mice.

In rats and mice, SCC formation appears to be dependent on both the formaldehyde concentration and the duration of exposure and observation. Specifically, higher formaldehyde exposure levels tend to be associated with both an increased incidence and an earlier onset of tumor formation. An example of this was demonstrated in a follow-up to the Kerns et al. (1983) study by Monticello et al. (1996). Monticello et al. (1996) reported that the incidence of SCCs in rats

exposed to 18.4 mg/m^3 formaldehyde was 47%, with the first tumor noted at 12 months. The incidence of SCCs in the 12.2 mg/m^3 exposure group was lower, at 22%, and the tumor latency was longer, with the first SCC observed at 18 months. Of the 90 rats exposed at 7.4 mg/m^3 for 20 months, only one SCC was noted, and no SCCs were detected at 0, 0.85, or 2.52 mg/m^3 over 28 months (Monticello et al., 1996). Initial observations of SCCs varied across the available rat studies, and the study design sometimes prevented an accurate determination of the timing (e.g., microscopic examinations may have been conducted every 6 months, every year, or only after 2 years). However, the first tumor generally was not observed before 12 months of observation, and often took 16 months or longer to develop (see Table 1-37). Consistent with this long latency, SCCs observed in mice took 2 years to develop (Kerns et al., 1983), and no URT neoplasms were observed during 8 months of observation in a short-term, *low* confidence (i.e., due to its 8-week exposure duration and <1 year follow-up) study of potentially sensitive mice (Morgan et al., 2017). In light of these observations, subchronic and shorter-term exposure studies without a long duration of follow-up are not expected to be capable of detecting formaldehyde-induced SCCs. In studies where interim sacrifices were performed and described, longer durations of exposure were generally associated with an increased incidence, severity, and sometimes more posterior location, of the induced SCCs (Monticello et al., 1996; Kerns et al., 1983). These data suggest that longer formaldehyde exposure duration is correlated with a greater incidence and severity of SCCs.[24]

The large bioassay of Kerns et al. (1983) in F344 rats showed no overt differences in the development of SCCs across sexes (i.e., 51/117 in males vs. 52/117 in females at 17.6 mg/m^3). There is some evidence to suggest that male rodents may be more sensitive to these effects. For example, only 1 of 16 female Sprague Dawley rats exposed to 15.3 mg/m^3 developed SCCs (Holmstrom et al., 1989b), whereas slightly higher levels (18.2 mg/m^3) of formaldehyde in another study of male Sprague Dawley rats (Sellakumar et al., 1985) induced more than six times as many SCCs (38/100). In addition, only male mice (2/120), but not female mice (0/120), developed SCCs in a chronic study (Kerns et al., 1983). However, these suggestions of differential sensitivity between sexes are not easily interpreted given the small sample sizes (Holmstrom et al., 1989b) and a low incidence of SCCs in exposed mice (Kerns et al., 1983).

The locations of the induced SCCs were consistent with both the distribution of inhaled formaldehyde and locations of other formaldehyde-induced nasal pathologies (see Section 1.2.4), with SCCs arising from the epithelium lining the airway and not from the underlying glandular epithelium. These tumors were most commonly observed in anterior regions of the nasal cavity, although higher exposure levels sometimes resulted in progression of SCCs to more posterior locations. Morgan et al. (1986b) mapped the location of formaldehyde-induced SCCs from the

[24]While some data exist to suggest that SCCs can be induced following subchronic formaldehyde exposure when observations continue for more than 2 years (Woutersen et al., 1989; Feron et al., 1988), definitive experiments in rats that are sensitive to the development of SCCs have not been performed (e.g., comparing SCC incidence in Sprague Dawley or F344 rats exposed for shorter durations and followed up for >2 years versus rats exposed to the same concentrations for >2 years with no additional follow up).

Kerns et al. (1983) study. In F344 rats, the majority of animals had single tumors, with a little under 20% of each sex with tumors developing multiple neoplasms. More than half (57%) of the SCCs occurred on the lateral side of the nasoturbinate and adjacent lateral wall at the front of the nose (Levels I and II; see Table 1-37); approximately 25% were located on the midventral nasal septum (Levels II and III); and about 10% were on the dorsal septum and roof of the dorsal meatus (Levels I, II, and III). A small number (3%) were found on the maxilloturbinate (Levels II and III), which only involved the medial aspect. Similar observations were reported for other studies of F344 rats (Monticello et al., 1996) and B6C3F1 mice (Kerns et al., 1983). Locations of SCCs in Sprague Dawley and Wistar rats were not as specifically reported in the available studies, but were generally similar, primarily affecting the respiratory epithelium lining the septum and nasoturbinates (Woutersen et al., 1989; Sellakumar et al., 1985).

Other malignant neoplasms

Although the data on other neoplasms are far less robust than those related to SCCs, formaldehyde inhalation also appears to induce other types of malignant nasal tumors. The incidence of these other neoplasms was typically only one, or rarely two, animals in an exposed group (never in controls); however, it is considered highly unlikely that these are incidental, as these rare neoplasms only developed after exposure to the highest formaldehyde concentrations, typically those above 17 mg/m^3 (see Table 1-37). As with SCCs, these neoplasms were limited to the nasal cavity. Carcinomas, which derive from epithelial tissues, were reported in several studies with an observation period greater than 2 years, consistent with the pronounced effect of inhaled formaldehyde on the nasal epithelium. A single nasal carcinoma was observed in both male and female F344 rats (Kerns et al., 1983), a mixed carcinoma was observed in male Sprague Dawley rats (Sellakumar et al., 1985), and a carcinoma in situ was observed in male Wistar rats exposed to 24 mg/m^3 (Feron et al., 1988), but not ≤12.1 mg/m^3 (Woutersen et al., 1989; Appelman et al., 1988; Feron et al., 1988), failed to develop any of these other malignant tumors.

Nonmalignant neoplasms

Several other benign tumors of the respiratory tract have been reported following formaldehyde exposure in rats, but not in other species. These tumors parallel findings for the other observed tumors, in that they are restricted to the nasal cavity and generally take more than 12 months to develop. Overall, these tumors appear to represent an erratic growth of the nasal epithelial tissue (i.e., adenomas and papillomas), with the exception being an ameloblastoma observed at 24 mg/m^3 formaldehyde (Feron et al., 1988), a tumor that presumably secondarily infiltrated the nasal cavity. In male Sprague Dawley rats, 10% of animals (10/100) exposed to 18.2 mg/m^3 for their lifetime developed nasal polyps or papillomas (Sellakumar et al., 1985; Albert et al., 1982), while approximately the same percentage of male F344 rats (3/32) exposed to a near-identical formaldehyde concentration (18.3 mg/m^3) developed squamous cell papillomas (Kamata et al., 1997). Polypoid adenomas have also been consistently observed in response to

formaldehyde exposure. Similar to SCCs, and in contrast to the other malignant tumors discussed above, these neoplasms may be inducible at formaldehyde concentrations below 12 mg/m^3, and perhaps even below 7 mg/m^3, although the data are somewhat more variable as compared to the SCC data (see Table 1-37). Polypoid adenomas were increased compared to controls in male Wistar rats exposed to 11.3 mg/m^3 (Woutersen et al., 1989) or 24.2 mg/m^3 (Feron et al., 1988) for 3 months with follow-up to >2 years, and in chronically exposed F344 rats (Monticello et al., 1996; Kerns et al., 1983). The responses in F344 rats occurred primarily in males and were reported at concentrations as low as 2.5 mg/m^3 (Kerns et al., 1983), although interpretation of the incidence data across exposure levels is not straightforward. Taken together, the data indicate that benign epithelial tumors in the nasal cavity can be induced by formaldehyde exposure.

Dysplasia

Similar to observations of nasal tumors, the incidence of dysplasia in long-term formaldehyde inhalation studies in rats and mice (i.e., chronic or subchronic exposure with observation periods of >12 months) increased in severity and occurred in more distal portions of the nasal cavity with both formaldehyde concentration and duration. Whereas the rat nasal tumor data consistently demonstrated that tumors are restricted to the nasal cavity, one study reported that F344 rats (which appear to be sensitive to these effects) also exhibited mild dysplasia in the trachea (Kerns et al., 1983), although the tracheal lesions were not observed when rats exposed for 2 years were left unexposed for 3 months. The study authors did not observe any tracheal lesions in mice (Kerns et al., 1983). Epithelial dysplasia of the nasal cavity was first noted at 12 months in rats exposed to concentrations as low as 2.5 mg/m^3, and in a "few" mice after 18 or 24 months of exposure at concentrations as low as 6.9 mg/m^3 formaldehyde (Kerns et al., 1983). However, after 24 months of exposure to 17.6 mg/m^3 formaldehyde, the incidence of nasal dysplasia was significantly increased in rats and mice, with greater than 90% of mice exhibiting this lesion (Kerns et al., 1983). The study authors noted that the identification of dysplasia in this study may have been termed metaplasia or hyperplasia by other study authors (Kerns et al., 1983), suggesting that this may represent a sensitive estimate of dysplasia. In another study, a female Sprague Dawley rat exposed to 15.3 mg/m^3 formaldehyde for a lifetime also developed dysplasia of the nasal epithelium (Holmstrom et al., 1989b). In line with the nasal tumor data, studies of Wistar rats and hamsters did not identify dysplastic lesions (see Table 1-37).

Conclusions

Tumors of the respiratory tract (predominantly SCCs but including other epithelial and nonepithelial tumors) were consistently observed in mice and several strains of rats, but not in hamsters, exposed to formaldehyde concentrations above approximately 6–7 mg/m^3. Precancerous dysplastic lesions were induced in rats and mice, sometimes at lower formaldehyde concentrations than those at which malignant tumors were observed. The dysplasia and neoplasms were predominantly localized to anterior regions of the nasal respiratory epithelium, although the

lesions progressed to more posterior locations with increasing duration and concentration of formaldehyde exposure, with one study reporting that dysplasia can develop in portions of the proximal trachea in rats (note: all tumors were limited to the nasal cavity). These lesions were never observed in other respiratory tract regions, such as the larynx and lung, and they generally only developed in animals that were observed for longer than 12 months. Studies of subchronic formaldehyde exposure without follow-up consistently failed to observe dysplasia or neoplasms in the nose, trachea, larynx, or lungs across a range of formaldehyde concentrations in rats (Wilmer et al., 1989; Appelman et al., 1988; Feron et al., 1988; Zwart et al., 1988; Woutersen et al., 1987; Rusch et al., 1983) and mice (Maronpot et al., 1986), and at lower formaldehyde levels (<3.65 mg/m3) in hamsters and cynomolgus monkeys (Rusch et al., 1983). Studies with a long observation period were not identified to inform the possibility of cancer development in nonhuman primates exposed to formaldehyde. The development of these lesions, particularly SCCs, depended on the duration of observation, and based on an increasing incidence and severity of lesions in animals exposed for longer periods of time, the formaldehyde exposure duration. Most notably, the lesion incidence, as well as the tumor invasiveness and latency, was reproducibly shown to worsen with increasing formaldehyde exposure level.

Table 1-37. Respiratory tract cancer—chronic and subchronic (with long-term follow up) exposure in rats, mice, and hamsters

<table>
<tr><th>Reference and study design[a]</th><th>Results</th></tr>
<tr><td colspan="2">Chronic exposure</td></tr>
<tr><td colspan="2">High confidence</td></tr>
<tr><td colspan="2">Rats</td></tr>
<tr><td>Kerns et al. (1983)
Rats: F344; males and females; 119 to 121/sex/group
Test article: Paraformaldehyde
Exposure: 6 hr/d, 5 d/wk for up to 2 yr (recovery: 27 and 30 months) at 0, 2.5, 6.9, or 17.6 mg/m^3
Histopathology [b]: 5 sections of nasal turbinates (Levels I–V) for animals that died or at interval sacrifices (i.e., at months 6, 12, 18, 24, 27, and 30)
Related study/earlier reports: Battelle (1982, 1981); [interim findings presented in Swenberg et al. (1980b)]
Note: viral infection reported (sialodacryoadenitis) at approximately weeks 52–53 (Kerns et al., 1983); the authors attributed transient decreases in body weight to this infection. This infection was not interpreted to affect the reliability of the cancer incidence data, in part</td><td>
<table>
<tr><td colspan="5">Malignant tumors</td></tr>
<tr><td>mg/m^3</td><td>0</td><td>2.5</td><td>6.9</td><td>17.6</td></tr>
<tr><td colspan="5">Squamous cell carcinoma [a]</td></tr>
<tr><td>Male</td><td>0/118</td><td>0/118</td><td>1/119</td><td>51/117</td></tr>
<tr><td>Female</td><td>0/114</td><td>0/118</td><td>1/116</td><td>52/115</td></tr>
<tr><td colspan="5">Nasal carcinoma</td></tr>
<tr><td>Male</td><td>0/118</td><td>0/118</td><td>0/119</td><td>1/117[b]</td></tr>
<tr><td>Female</td><td>0/114</td><td>0/118</td><td>0/116</td><td>1/115</td></tr>
<tr><td colspan="5">Carcinosarcoma</td></tr>
<tr><td>Male</td><td>0/118</td><td>0/118</td><td>0/119</td><td>1/117</td></tr>
<tr><td>Female</td><td>0/114</td><td>0/118</td><td>0/116</td><td>0/115</td></tr>
<tr><td colspan="5">Undifferentiated carcinoma or sarcoma</td></tr>
<tr><td>Male</td><td>0/118</td><td>0/118</td><td>0/119</td><td>2/117[b]</td></tr>
<tr><td>Female</td><td>0/114</td><td>0/118</td><td>0/116</td><td>0/115</td></tr>
<tr><td colspan="5">Other Neoplasms</td></tr>
<tr><td colspan="5">Polypoid adenoma</td></tr>
<tr><td>Male</td><td>1/118</td><td>4/118</td><td>6/119</td><td>4/117</td></tr>
<tr><td>Female</td><td>0/114</td><td>4/118</td><td>0/116</td><td>1/115</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Reference and study design[a]</th><th>Results</th></tr>
<tr><td>because dysplasia and other lesions were already present at 12 months (when the infection began)</td><td>
<table>
<tr><td colspan="5">Epithelial Dysplasia</td></tr>
<tr><td>6 months</td><td>–[c]</td><td>–</td><td>–</td><td>–[d]</td></tr>
<tr><td>12 months</td><td>–[c]</td><td>Level I [e]</td><td rowspan="3">Level I–III[f]</td><td rowspan="3">Level I–V[f]</td></tr>
<tr><td>18 months</td><td>–[c]</td><td>NR</td></tr>
<tr><td>24 months</td><td>–[c]</td><td>Level I</td></tr>
</table>
[a]SCCs became clinically observable in females at ~12 months, and in males at ~14 months; most appeared to originate in the nasoturbinates
[b]A rat in this group also had SCC
[c]Lesion frequency (dysplasia or metaplasia) of <15% at 0 mg/m^3 (Level I)
[d] Although formaldehyde-induced lesions were identified in Level I–III, the authors did not specify them as dysplasia
[e]Squamoid epithelial lining several cells thick with polarity changed from vertical to horizontal was noted and termed dysplasia, but authors acknowledged related changes can be termed hyperplasia or metaplasia
[f]Dysplasia was most intense in Level I. Exposure-related effects were observed in Levels I–III and I–V at 6.9- and 17.6-mg/m^3, respectively, although the specific timing for these lesions was not provided; note: dysplasia was consistently detected earlier than squamous metaplasia
Trachea: at 17.6 mg/m^3, minimal-to-mild dysplasia at 18 months, with greater frequency ($p < 0.05$) in 24-month and unscheduled deaths groups; trachea lesions not observed in postexposure group or at lower levels
</td></tr>
<tr><td>Monticello et al. (1996)
Rats: F344; male; 90–147/group
Test article: Paraformaldehyde
Exposure: 6 hr/d, 5 d/wk for up to 24 months at 0, 0.85, 2.52, 7.40, 12.2, or 18.4 mg/m^3
Histopathology [b]: 6 sections of the nasal cavity</td><td>
<table>
<tr><td colspan="5">Malignant tumors in the nasal cavity[a]</td></tr>
<tr><td></td><td>0, 0.85, or 2.52 mg/m^3</td><td>7.4 mg/m^3</td><td>12.2 mg/m^3</td><td>18.4 mg/m^3</td></tr>
<tr><td>Squamous cell carcinoma[b]</td><td>0/90</td><td>1/90 (1%)</td><td>20/90 (22%)</td><td>69/147 (47%)</td></tr>
<tr><td>Adenocarcinoma</td><td>0/90</td><td>0/90</td><td>1/90</td><td>1/147</td></tr>
<tr><td>Rhabdomyosarcoma</td><td>0/90</td><td>0/90</td><td>1/90</td><td>1/147</td></tr>
<tr><td colspan="5">Other neoplasms</td></tr>
<tr><td>Polypoid adenoma</td><td>0/90</td><td>0/90</td><td>5/90 (6%)</td><td>14/147 (10%)</td></tr>
</table>
[a]Spontaneous buccal SCCs were observed at 0, 2.52, and 18.4 mg/m^3
[b]SCCs that could be localized were identified most often in the anterior or posterior lateral meatus 1/90, 12/90, 17/147 or 0/90, 12/90, 9/147 corresponding to 7.4, 12.2, and 18.4 mg/m^3); SCCs were also observed in the mid- and dorsal septum, as well as the maxilloturbinates, but only at 18.4 mg/m^3; however, most tumors were too large to localize and these often eroded through nasal bone and invaded the subcutis of the dermis. Tumors began appearing ~1 yr at 18.4 mg/m^3 and ~1.5 yr at 12.2 mg/m^3
No tumors observed beyond the respiratory tract
</td></tr>
<tr><td>Sellakumar et al. (1985)
Rats: Sprague Dawley; male; 99–100/group
Test article: Paraformaldehyde (slurry in paraffin oil)
Exposure: 6 hr/d, 5 d/wk for lifetime at 0 or 18.2 mg/m^3 [Note: prior reporting of levels during first 588 days at 17.5 mg/m^3 (Albert et al., 1982)]
Histopathology [b]: multiple sections of the head (from just behind the nostril to the eye orbits), lung, trachea, and larynx
Related study: Albert et al. (1982)</td><td>
<table>
<tr><td></td><td>Colony Control</td><td>Air sham</td><td>18.2 mg/m^3</td></tr>
<tr><td colspan="4">Malignant tumors in the nasal mucosa</td></tr>
<tr><td>Squamous cell carcinoma[a]</td><td>0/100</td><td>0/99[b]</td><td>38/100</td></tr>
<tr><td>Adenocarcinoma</td><td>0/100</td><td>0/99</td><td>0/100</td></tr>
<tr><td>Mixed carcinoma</td><td>0/100</td><td>0/99</td><td>1/100</td></tr>
<tr><td>Fibrosarcoma</td><td>0/100</td><td>0/99</td><td>1/100</td></tr>
<tr><td colspan="4">Other neoplasms in the nasal mucosa</td></tr>
<tr><td>Polyp or papillomas</td><td>0/100</td><td>0/99</td><td>10/100</td></tr>
</table>
[a]Predominantly moderate/well differentiated, keratin obstructed lumen; latency to tumor formation was approximately 603–645 days

No tumors observed in the trachea or lungs
</td></tr>
</table>

<table>
<tr><th>Reference and study design[a]</th><th>Results</th></tr>
<tr><td>Woutersen et al. (1989)
Rats: Wistar; male; 30/group
Test article: Paraformaldehyde
Exposure: 6 hr/d, 5 d/wk for 28 months at 0, 0.1, 1.2, or 12.1 mg/m^3
Histopathology [b]: 6 nasal cross sections
Note: experiments with nasal damage prior to exposure are not presented here</td><td>
<table>
<tr><th colspan="5">*Malignant tumors*</th></tr>
<tr><td></td><td>0 mg/m^3</td><td>0.1 mg/m^3</td><td>1.2 mg/m^3</td><td>12.1 mg/m^3</td></tr>
<tr><td>*Squamous cell carcinoma*</td><td>0/26</td><td>1/26</td><td>1/28</td><td>1/26</td></tr>
<tr><td>*Adenosquamous carcinoma*</td><td>0/26</td><td>0/26</td><td>0/28</td><td>0/26</td></tr>
<tr><td>*Adenocarcinoma*</td><td>0/26</td><td>0/26</td><td>0/28</td><td>0/26</td></tr>
</table>
Note: the specific locations of these tumors was not described</td></tr>
<tr><td colspan="2">***Mice***</td></tr>
<tr><td>Kerns et al. (1983)
Mice: B6C3F1; males and females; 119 to 121/sex/group
Exposure: 6 hr/d, 5 d/wk for up to 24 months (recovery at 27 and 30 months) at 0, 2.5, 6.9, or 17.6 mg/m^3
Test article: Paraformaldehyde
Histopathology [b]: 3 sections of nasal turbinates, defined as Levels II, III, and V for all animals that died or were sacrificed at scheduled intervals (i.e., at month 6, 12, 18, 24, 27, and 30)
Earlier reports: Battelle (1982, 1981)

Main limitations: Lesion incidence NR; only three nasal sections examined</td><td>
<table>
<tr><th colspan="5">*Malignant tumors*</th></tr>
<tr><td></td><td>0 mg/m^3</td><td>2.5 mg/m^3</td><td>6.9 mg/m^3</td><td>17.6 mg/m^3</td></tr>
<tr><td>SCCs at 24 months [a]</td><td>0/~120 (both sexes)</td><td>0/~120 (both sexes)</td><td>0/~120 (both sexes)</td><td>2/~120 male
0/~120 female</td></tr>
<tr><td colspan="5">*Dysplasia* [b]</td></tr>
<tr><td>12 months</td><td>–</td><td>–</td><td>–</td><td>–</td></tr>
<tr><td>18 months</td><td>–</td><td>–</td><td>Level II: “few”</td><td>Level II (~90%)</td></tr>
<tr><td>24 months</td><td>–</td><td>–</td><td>Level II: “few”</td><td>>90%</td></tr>
<tr><td>Recovery (27 months)</td><td>–</td><td>–</td><td>none</td><td>yes (incidence and level NR)</td></tr>
</table>
[a]SCCs were not observed prior to 24 months ($p > 0.05$); both SCCs originated from nasoturbinates; the number of mice evaluated was not specified, but assumed ~120 based on 119–121 mice/group
[b]Unless noted, exact frequency of lesion NR, and sex not specified

No tracheal lesions were observed</td></tr>
<tr><td colspan="2">*Medium confidence*</td></tr>
<tr><td colspan="2">**Rats**</td></tr>
<tr><td>Appelman et al. (1988)
Rats: SPF Wistar; male; 10/group
Test article: Paraformaldehyde
Exposure: 6 hr/d, 5 d/wk for 52 weeks at 0.12, 1.2, or 12.1 mg/m^3
Histopathology [b]: nose (6 standard cross levels), larynx, trachea, and lungs
Note: experiments with nasal damage prior to exposure are not presented here

Main limitations: 1-year short duration to allow for cancer development</td><td>*No dysplasia or nasal neoplasms were observed in nose, larynx, trachea, or lungs with exposure up to 12.1 mg/m^3 for up to 1 year (assumed, based on histopathological evaluation of these tissues, although the study authors did not specifically state these conclusions)*</td></tr>
<tr><td>Holmstrom et al. (1989b)
Rats: Sprague Dawley; female; 15–16/group
Test articles: Paraformaldehyde
Exposure: 6 hr/d, 5 d/wk for 104 weeks at 0 or 15.3 mg/m^3
Histopathology [b]: 5 sections of the nose from the vestibulum to the posterior ethmoturbinatic region, and the lungs
Note: data on wood dust combined with formaldehyde exposure not evaluated</td><td>
<table>
<tr><th colspan="3">*Malignant tumors*</th></tr>
<tr><td></td><td>Air control</td><td>15.3 mg/m^3</td></tr>
<tr><td>Squamous Cell Carcinoma</td><td>0/15</td><td>1/16[a]</td></tr>
<tr><td colspan="3">*Dysplasia*</td></tr>
<tr><td></td><td>0/15</td><td>1/16[b]</td></tr>
</table>
[a]Observed after 21 months after exposure
[b]An addition two rats exhibited pronounced squamous metaplasia with keratinization (7 more exhibited squamous metaplasia)

Note: Mortality was similar in both groups</td></tr>
</table>

<table>
<tr><th>Reference and study design[a]</th><th>Results</th></tr>
<tr><td>Main limitations: Limited reporting; some health issues noted</td><td></td></tr>
<tr><td>Kamata et al. (1997)
Rats: F344; male; 32/group
Test article: Formalin (methanol control)
Exposure: nose-only 6 hr/d, 5 d/wk for up to 28 months at 0, 0.40, 2.67, or 18.27 mg/m^3 (methanol—0, 18.27 mg/m^3 groups, estimated at 5.5 mg/m^3, presumed from percentage methanol in formalin)
Histopathology [b]: nasal region (sections from five anatomical levels) and trachea

Main limitations: small sample size; use of formalin (uncertainties, such as possible differences in tissue formaldehyde due to methanol, remain despite inclusion of a methanol control)</td><td>
<table>
<tr><th></th><th colspan="4">Months (interim sac.)</th><th rowspan="2">Dead</th><th rowspan="2">All</th></tr>
<tr><th></th><th>12</th><th>18</th><th>24</th><th>28</th></tr>
<tr><td colspan="7">*Squamous cell carcinomas at 18.27 mg/m^3 [a]*</td></tr>
<tr><td>*SCCs*</td><td>0/5</td><td>1/5</td><td>0/2</td><td>0/0</td><td>12/20</td><td>13/32[b]</td></tr>
<tr><td colspan="7">*Other malignant tumors at 18.27 mg/m^3 [a]*</td></tr>
<tr><td>*Unclassified sarcoma*</td><td>0/5</td><td>0/5</td><td>0/2</td><td>0/0</td><td>0/20</td><td>0/32</td></tr>
<tr><td>*Sarcoma*</td><td>0/5</td><td>0/5</td><td>0/2</td><td>0/0</td><td>1/20</td><td>1/32</td></tr>
<tr><td colspan="7">*Other neoplasms at 18.27 mg/m^3[a]*</td></tr>
<tr><td>*Squamous cell papilloma*</td><td>0/5</td><td>1/5</td><td>0/2</td><td>0/0</td><td>2/20</td><td>3/32</td></tr>
</table>
[a]No nasal tumors were observed at 0, 0.4, or 2.67 mg/m^3 (note: 1 unclassified sarcoma found in a dead room control group rat); average latency across groups varied from 603 and 645 days
[b]Significant at $p \le 0.01$, compared with the 0 mg/m^3 group.
Note: Most tumors were located in levels B and C (see diagram in left column); large tumors invaded the subcutis through the nasal bones

No tumors were observed in the trachea</td></tr>
<tr><td colspan="2">Hamsters</td></tr>
<tr><td>Dalbey (1982)
Hamsters: Syrian golden; male; 132 untreated controls and 88 exposed
Test article: Paraformaldehyde
Exposure: 5 hr/d, 5 d/wk for a lifetime at 0 or 12.3 mg/m^3
Histopathology [b]: Two transverse sections of the nasal turbinates, and sections of the larynx, trachea, and lungs

Main limitations: minimal sampling, histological evaluation, and reporting
Note: mixture experiment not evaluated</td><td>*No tumors reported in the nose, larynx, lungs, or trachea with a lifetime of exposure to 12.3 mg/m^3*

Note: study authors indicated formaldehyde exposure at 36.9 mg/m^3 amplified diethylnitrosamine-induced respiratory tumors.</td></tr>
<tr><td colspan="2">Subchronic exposure with long-term follow-up</td></tr>
<tr><td colspan="2">High confidence</td></tr>
<tr><td colspan="2">Rats</td></tr>
<tr><td>Woutersen et al. (1989)
Rats: Wistar; male; 30/group
Test article: Paraformaldehyde
Exposure: 6 hr/d, 5 d/wk for 3 months at 0, 0.1, 1.2, or 11.3 mg/m^3; sacrificed at 28 months
Histopathology [b]: 6 nasal cross sections
Note: short duration of exposure</td><td>
<table>
<tr><th></th><th>0 mg/m^3</th><th>0.1 mg/m^3</th><th>1.2 mg/m^3</th><th>11.3 mg/m^3</th></tr>
<tr><td colspan="5">*Malignant tumors*</td></tr>
<tr><td>*Squamous cell carcinoma*</td><td>0/26</td><td>0/30</td><td>0/29</td><td>1/26</td></tr>
<tr><td>*Carcinoma in situ*</td><td>0/26</td><td>0/30</td><td>0/29</td><td>0/26</td></tr>
<tr><td colspan="5">*Other neoplasms*</td></tr>
<tr><td>*Polypoid adenoma*</td><td>0/26</td><td>0/30</td><td>0/29</td><td>1/26</td></tr>
</table>
Note: cross-section locations not specified</td></tr>
<tr><td colspan="2">Medium confidence</td></tr>
<tr><td colspan="2">Rats</td></tr>
</table>

Reference and study design[a]	Results			
Feron et al. (1988) *Rats*: Wistar; male; 45/group *Test article*: Paraformaldehyde *Exposure*: 6 hr/d, 5 d/wk for up to 13 weeks at 0, 11.3–11.9, or 24.2–24.4 mg/m^3; sacrificed at 130 weeks *Histopathology* [b]: 6 standard cross levels of the nose. **Main limitations**: Limited reporting; short duration of exposure		0 mg/m^3	~11.5 mg/m^3	~24 mg/m^3
	Malignant tumors			
	Squamous cell carcinoma:			
	4-wk exposure (wk sacrificed indicated)	0/44	0/44	1/45 (wk 106)
	8-wk exposure	2/45 (wk 94, 130)	1/44 (wk 130)	1/43 (wk 121)
	13-wk exposure	0/45	1/44 (wk 82)	3 or 4/44[a] (wk 63, 112, 114, NR)
	Other malignant tumors with 13 wk exposure [b]*:*			
	Carcinoma in situ:	0/45	0/44	1/44 (wk 81)
	Other neoplasms			
	Ameloblastoma:	0/45	0/44	1/44 (wk 73)
	Polypoid adenoma:			
	4 wk exposure	0/44	0/44	1/45 (wk 110)
	8 wk exposure	0/45	0/44	1/43 (wk 100)
	13 wk exposure	0/45	0/44	0/44
	[a]1 SCC was classified as a "cystic SCC," which may have been derived from the palate, and which the authors did not associate with exposure [b]carcinomas other than SCC were not observed with <13 wk exposure			

Abbreviations: NR = not reported; F = Fischer; hr = hour(s); d = day(s); wk = week(s); yr = year(s).
[a]Analytical formaldehyde levels are presented and, unless otherwise noted, whole-body exposures were used.
[b]The studies used the same sectioning levels described for noncancer lesions in Section 1.2.4 (see Figure 1-14).

Evidence on Mode of Action for Upper Respiratory Tract Cancers

Formaldehyde exposure has been associated with elevated incidence of carcinomas in human URT tissues, with the strongest evidence for nasopharyngeal and sinonasal tumor formation (Tables 1-32 and 1-33). Formaldehyde inhalation reproducibly induces squamous cell carcinomas (SCC) in the nasal passages of F344, Sprague Dawley, and Wistar rats (obligate nose-breathers), as well as polypoid adenomas (PA); SCCs and PAs are both rare tumors in rats, with background frequencies of ≤0.3% and ≤0.04%, respectively (Poteracki and Walsh, 1998; Chandra et al., 1992; Brown et al., 1991). SCCs were also elevated in the anterior nasal passages of chronically exposed B6C3F$_1$ mice [background frequency of 0/2,818; (Brown et al., 1991)], but not in hamsters. Formaldehyde-associated SCCs and PAs originate in the nasoturbinates, maxilloturbinates, or lateral wall of the nasal cavity, and likely arise from the same target cell population (i.e., the nasal respiratory or transitional epithelium). The neoplastic response to formaldehyde exposure in rat nasal epithelium appears to be complex; SCC incidence is dramatically induced at exposure levels associated with other proliferative epithelial pathology, increasing from 1% at 7 mg/m^3 to 60% at 18 mg/m^3 in chronically exposed F344 rats. In contrast, relatively low frequencies of PAs are induced at concentrations ranging from 2.5 to18 mg/m^3, with PA incidence increasing moderately to a maximum of 10% at 18 mg/m^3 (see Table 1-37). SCCs and PAs are similarly induced in Sprague

Dawley rats, and although nasal tumor incidence may be somewhat lower in Wistar rats, studies in the latter strain provide some evidence of tumor induction following subchronic exposure with lifetime follow-up.

Following inhalation exposure at analogous POE tissues in humans (nasal, buccal, and nasopharyngeal epithelium), nonhuman primates (nasal and extranasal respiratory and transitional epithelium, larynx, trachea, and carina), and rodents (nasal respiratory and transitional epithelium), evidence exists supporting the evaluation of a cancer mode of action (MOA). Among a variety of influential forces, two primary mechanistic considerations appear to contribute, both directly and indirectly, to tumorigenesis resulting from formaldehyde exposure at POE tissues: genotoxicity-associated mutagenicity, and cytotoxicity-induced regenerative proliferation. Furthermore, formaldehyde may stimulate nasal epithelial cell proliferation to some extent, even in the absence of frank tissue cytotoxicity. Instead of considering independent, sequential series of key events for each of these mechanistic considerations, evidence for genotoxicity and mutagenicity, cellular proliferation (independent from tissue pathology), and cytotoxicity-induced regenerative tissue proliferation is evaluated in an integrated manner, whereby hypothesized mutagenesis and increased cellular turnover initiate and then augment URT carcinogenesis as a function of exposure duration, periodicity, and tissue dose. This approach is consistent with the observation that, while mitogenesis can drive rodent tumor prevalence, it may not supplant the contribution of mutagenicity to chemically induced carcinogenesis (Ames and Gold, 1990).

Much of the available evidence relevant to these mechanistic considerations is discussed in detail in the prior sections on URT cancer data in human and animal studies, as well as in Sections 1.2.3 and 1.2.4, and in Appendices A.4 and A.5.6. Herein, these findings are summarized and integrated into a proposed cancer MOA network to serve as a framework for the evidence evaluation and MOA analysis (see Figures 1-25–1-27). The evidence is synthesized with an emphasis placed on observations from humans and experimental animals repeatedly exposed to formaldehyde via the inhalation route, evaluated following the Bradford Hill considerations (U.S. EPA, 2005a), and conclusions are discussed in the context of URT carcinogenesis proceeding via this hypothesized, integrated cancer MOA. While evidence from biochemical investigations or cells cultured in vitro is not exhaustively described, pertinent observations are presented when useful in providing a mechanistic interpretation to effects described in vivo, when the available in vivo evidence is limited or nonexistent, or does not inform the effect under consideration. Only results from studies reporting some quantitative estimate of formaldehyde exposure concentration were synthesized, due to a general abundance of information relevant to the mechanistic considerations, and relative paucity of studies failing to provide formaldehyde exposure estimates. Evidence informing other modulating or modifying effects such as immune dysfunction and oxidative stress, DNA repair inhibition, and epigenetic alterations are also discussed briefly (for more detail see Appendices A.4 and A.5.6), while evidence for systemic genotoxicity and immune system effects outside the URT as relevant to carcinogenesis are primarily discussed elsewhere (see Section 1.3.3,

Evidence on mode of action for LHP cancers). While these factors may contribute significantly at various stages of URT carcinogenesis to the mechanistic considerations described above, the limited available data preclude evaluating their independent contribution to the formaldehyde URT cancer MOA. Likewise, while various aspects of this analysis may be directly relevant to formaldehyde exposure by other routes, or cancer at other (i.e., distal) tissue locations, this discussion is focused on cancers at POE tissues (i.e., the URT) following inhalation exposure.

Summary of genotoxicity and mutagenicity

This overall summary is relevant to MOA interpretations for both URT cancers (this section) and lymphohematopoietic cancers (see Section 1.3.3). Formaldehyde is a direct-acting chemical that has been shown to be genotoxic or mutagenic in a variety of in silico and in vitro test systems; experimental animals including mice, rats, and monkeys; as well as in humans. Formaldehyde exposure typically induces genotoxicity, mutagenicity, or related endpoints in a concentration- and duration-dependent manner, including deletions and point mutations; DNA-protein and DNA-DNA crosslinks (DPX and DDC, respectively) and DNA mono (hmDNA) adducts; clastogenic-related effects such as micronuclei (MN) and chromosomal aberration (CA) formation, as well as sister chromatid exchanges (SCEs), single-strand and double-strand breaks (SSBs, DSBs, respectively); and unscheduled DNA synthesis (UDS), DNA repair inhibition, and cellular transformation. For a comprehensive description of the evidence on formaldehyde genotoxicity, see Appendix A.4, which includes a summary table of genotoxicity endpoints investigated across the test systems most relevant to human inhalation exposure and, when possible, separates the results into respiratory- versus nonrespiratory-related tissues or systems.

This evaluation emphasizes the experiments interpreted to best inform the potential for genotoxicity in humans following inhalation exposure to formaldehyde, and therefore focuses on in vivo studies in mammalian species. In addition, the relative importance of the specific genotoxic endpoints was considered when prioritizing results in the synthesis of epidemiological evidence for genotoxicity. For example, it has been shown that increased frequency of CAs and MN are associated with increased cancer mortality, and these endpoints are considered by EPA to be highly relevant to the assessment of genotoxicity in humans (Bonassi et al., 2008; Bonassi et al., 2007; U.S. EPA, 2005a; Bonassi et al., 2004b). SSBs and DSBs in DNA indicate genetic instability and are also considered by EPA to be highly relevant to the assessment of genotoxicity for humans, while increased frequencies of sister chromatid exchange (SCE) are less strongly associated with cancer mortality (Bonassi et al., 2004a).

Inhaled formaldehyde primarily encounters cellular macromolecules at POE tissues, including both nasal and buccal epithelial cells in humans, while preferentially affecting the nasal epithelium in rodents, which are obligate nose-breathers. In these barrier tissues, formaldehyde can interact directly with DNA, resulting in DPX and DDC, DNA mono (hmDNA) adducts, SSBs, MN, and CAs. Furthermore, cells in the lower respiratory tract (LRT) and tissues distal to the initial

point of exogenous formaldehyde exposure, such as peripheral blood lymphocytes (PBLs), are also potential targets of formaldehyde genotoxicity.

Neither DPX nor hmDNA adduct levels have been assessed specifically in nasal or buccal tissues from formaldehyde-exposed human workers, although occupational exposure to formaldehyde was associated with a significant exposure- and duration-related increase in DPX formation in PBLs. Formaldehyde-induced DPXs in the URT of rats and nonhuman primates in a dose-responsive manner across several studies. The predominant location of DPX formation varied due to anatomical differences in the nasal physiology and breathing patterns of primates versus rodents; however, the distribution of DPXs in rat nasal tissues corresponded to sites of tumor incidence, cell proliferation, and cytotoxicity. hmDNA monoadducts have been observed in the nasal epithelium of rats and the maxilloturbinate regions of rhesus monkeys following formaldehyde exposure, as well as in cell-free systems, and cultured cell lines including human nasal epithelial cells.

The majority of occupational studies have associated formaldehyde exposure with increased MN formation in human nasal or buccal epithelial cells, predominantly forming centromere-negative micronuclei suggesting clastogenic effects. Although no MN in nasal tissues were observed in one short-term, high-dose rodent inhalation study, MN were consistently induced in different mammalian cells in vitro. In addition, long-term occupational exposure was associated with significantly increased MN in PBLs, and aneugenicity appears to be the predominant effect in peripheral tissues (see Section 1.3.3). Exposure to formaldehyde also was associated with significantly increased CAs in PBLs of human workers, as well as in rodents from a short-term, high-dose study. Formaldehyde also induced CAs in rat pulmonary lavage cells, as well as hamster and primary human cells in vitro. Exposure-related increases in SSBs were observed in rat nasal tissues in one experimental study and in several studies of PBLs from exposed workers and rodents. Occupational exposure to formaldehyde caused increased mutant p53 protein expression in the serum of exposed workers, while cell lines derived from formaldehyde-induced rat nasal SCCs showed *p53* mutations. Across the available database, formaldehyde consistently induces various endpoints consistent with mutagenicity, such as base pair mutations, deletions, insertions and point mutations, SCEs, SSBs, UDS, and DNA repair inhibition in various cells in vitro, in experimental animal models in vivo, as well as in exposed humans.

Formaldehyde is genotoxic. This conclusion is supported by several streams of evidence including observations of CAs, MN, and SSBs in exposed humans across a range of studies, occupations, and exposure scenarios, with supporting, similar findings in exposed rodents and in vitro systems, and consistent observations of DPXs detected in multiple experimental systems, showing a pattern of concentration-dependent increases. Together, these multiple streams of evidence (from human, animal, in vitro and nonmammalian systems) converge to clearly indicate that formaldehyde is genotoxic in most systems tested, is mutagenic in systems specifically

evaluating genetic or chromosomal mutations, and exhibits strong evidence for mutagenicity in the URT of rodents and humans following inhalation exposure.

Summary and integration of mechanistic pathways into a cancer mode of action

The evidence pertaining to URT carcinogenesis following formaldehyde exposure was assembled into a putative URT cancer MOA network highlighting the potential contributions of genotoxicity and cytotoxicity-induced regenerative proliferation (see Figure 1-25), as well as incorporating the influences of underlying chronic inflammation and epigenetic activity as prime examples of other considerations that can interact with and further modify the primary mechanisms propelling formaldehyde-induced URT cancer, in addition to potentially contributing independently. Table 1-38 presents a concordance summary view of the available evidence (Meek et al., 2014), illustrating the exposure concentration and duration required to either elicit or amplify formaldehyde-associated effects in the URT of F344 rats (the model species most sensitive to SCC development with the most diverse and robust data set available). These rat data are informative of the mechanistic pathways of primary concern, including genotoxicity endpoints as an indicator of mutagenic potential; reports of tissue pathology including hyperplasia, squamous metaplasia, dysplasia, and necrosis; cellular DNA synthesis as an indicator of epithelial proliferation rate (independent of cause); as well as formaldehyde-associated tumor induction (see Section 1.2.5, *Respiratory Tract Cancers in Animal Studies*). These interrelated streams of evidence are summarized separately (below) and then integrated into a composite MOA, which is evaluated in subsequent sections.

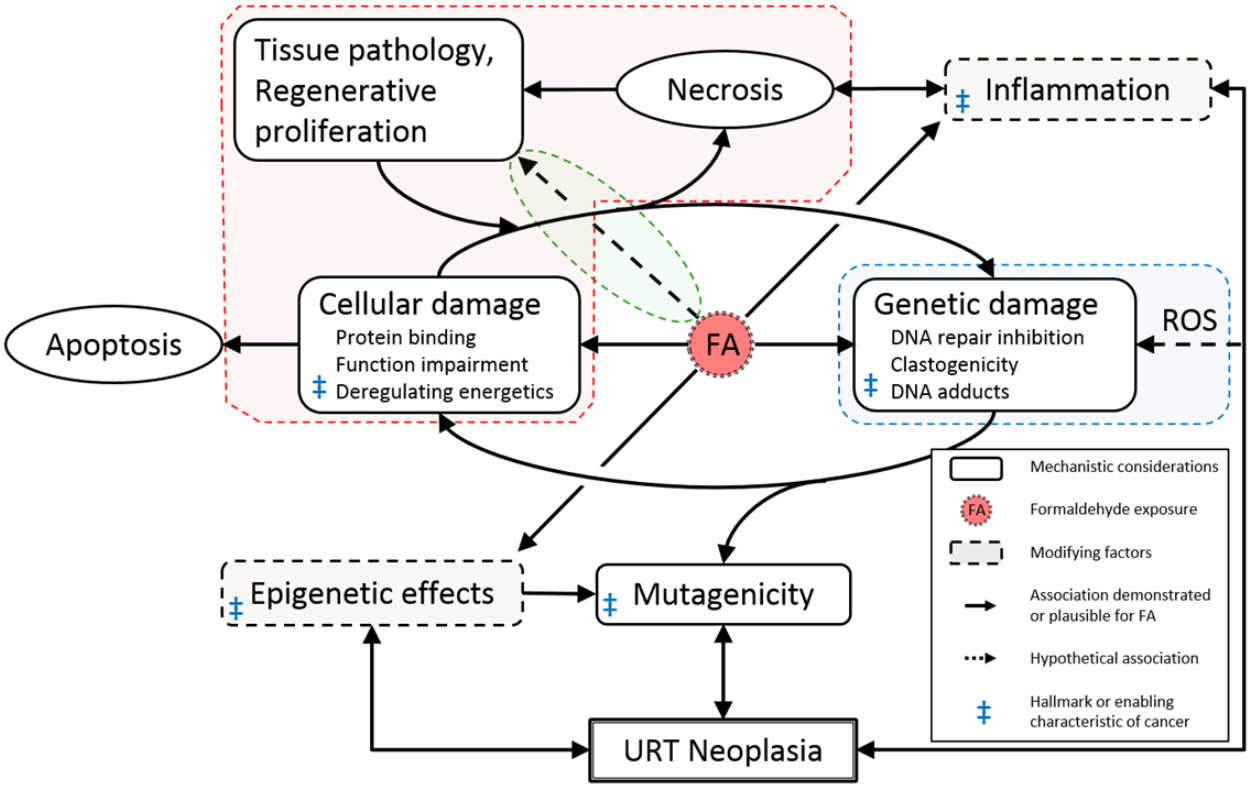


Figure 1-25. An integrated cancer mode-of-action (MOA) network for the URT.

Various effects occur in a manner dependent upon duration and magnitude of formaldehyde (FA) inhalation exposure. Primary mechanistic considerations in call-out boxes are described in the following tables and figures (blue/genetic damage, see Table 1-39; green/formaldehyde-induced proliferation without damage, see Table 1-40; red/tissue and cellular damage, see Tables 1-40 and 1-41) with evidence identified from the formaldehyde database as possibly informative of molecular mechanisms. These mechanistic considerations or modifying factors are consistent with those factors described as cancer hallmarks, enabling, or key characteristics of carcinogens (Smith et al., 2016; Hanahan and Weinberg, 2011).

Table 1-38. Concordance of temporal and dose-response relationships among formaldehyde effects induced in F344 rat nasal epithelium in vivo

F344 Rats		Time (months) →			Time (months) →		
		0–3	4–12	13–28	0–3	4–12	13–28
		Genotoxicity[a]			*Necrosis*[b]		
Exposure (mg/m³) ↓	0–2	+	ND	ND	–	–	–
	2–7	++	ND	ND	–/+	–	–
	>7	+++	ND	ND	++	+	+
		Hyperplasia and/or metaplasia[c]			*DNA synthesis*[d,e]		
Exposure (mg/m³) ↓	0–2	–	–	+	–/+	–[f]	–[f]
	2–7	–/+	+	++	+	–[f]	–[f]
	>7	+	++	+++	+++	++[f]	++[f]
		Tumorigenesis (polypoid adenoma)[g]			*Tumorigenesis (squamous cell carcinoma)*[g]		
Exposure (mg/m³) ↓	0–2	–	–	–	–	–	–
	2–7	–	–	+	–	–	–/+
	>7	–	–	++	–	+	+++

Male F344 rats were the most widely evaluated sex/strain/species/evaluated, but observations were comparable between rat sexes, where available. The presence or absence of treatment-related effects across all available studies (as determined by EPA review) in or near the nasal anterior lateral meatus (ALM, where specified, generally within Level II), were depicted as follows: "–" indicates the absence of effects; "ND" indicates no data available for the specified endpoint/dose/time combination; –/+ indicates an equivocal response, or evidence limited to the highest extreme of the exposure range indicated; +, ++, +++ indicate the presence of an exposure-related effect, with symbol number corresponding to increasing magnitude, incidence, or severity, relative to concurrent controls and other exposure level/duration entries within an effect category (see Section 1.2.4 and Appendix A.4).

[a]Includes DNA-protein and DNA-DNA crosslinks or increases in N^2-hmdG DNA adducts attributed to exogenous formaldehyde exposure.

[b]Direct evaluation necrosis was not frequently reported, and apoptosis has not been directly measured; significant exposure-related tissue destruction was inferred from pathological determination of necrosis, erosion, disarrangement, or atrophy of the nasal epithelium.

[c]Tissue reactive or adaptive responses to irritant or cytotoxic effects were determined by evaluating hyperplasia or squamous metaplasia (typically combined in reporting by study authors) of the nasal respiratory or transitional epithelium; however, the biochemical stimulus of this tissue reaction remains unclear, as such areas of hyperplasia could also include areas of dedicated preneoplastic foci.

[d]DNA label incorporation as a measure of proliferation at the individual cell level in the ALM was measured by incorporation of BrdU, [^{3}H]-thymidine or [^{14}C]-formaldehyde into DNA, and reported as an index normalizing affected (positive) cells as a fraction of the total respiratory epithelium (see detailed summary in Appendix A.5.6).

[e]DNA synthesis has been evaluated following both continuous and intermittent exposures; while effects of continuous exposure are depicted herein for purposes of drawing comparisons across similar exposure scenarios, intermittent exposure may be also informative for some human exposure scenarios.
[f]Results from a single study reporting rat nasal epithelial cell DNA label incorporation following 26, 52, or 78 weeks of exposure (Monticello et al., 1996).
[g]Both polypoid adenomas (PA) and squamous cell carcinomas (SCC) were described as likely arising from the respiratory or transitional epithelium, typically on or near the ALM. However, SCCs were typically associated with areas of hyperplasia or squamous metaplasia, whereas PAs were not.

Formaldehyde directly adducts DNA and proteins, causing dose-responsive increases in DNA-protein (DPX) or DNA-DNA (DDC) crosslinks, as well as DNA mono deoxyguanosine (hmdG) adducts (see Table 1-38, also see Appendix A.4). Evidence from humans and rodents suggests that formaldehyde exposure can lead to increasing levels of reactive oxidative species (ROS) and possibly inhibit cellular detoxification mechanisms (see Appendix A.5.6), which would be expected to further exacerbate oxidative damage to cellular constituents and DPX formation. Following these initial effects, single-strand DNA breaks could be created more frequently, and DNA repair could be inhibited, possibly leading to an accumulation of genetic damage at the chromosome (clastogenicity) and sequence level (gene mutations). While the specific nature of persistent genetic damage leading to URT cancer following formaldehyde exposure is unclear, heritable changes in genetic material are a prerequisite step for carcinogenesis following a mutagenic mode of action. The observations most relevant to genotoxic effects and sequelae to URT neoplasia are summarized in Table 1-39.

Table 1-39. Genotoxicity and mutagenicity in the upper respiratory tract

Observations from the available in vivo database *(see Appendix A.4 for details)*[a,b]	Exposure level (mg/m^3)[c]	Statistical associations[d]
Human		
Acute or short-term exposure: controlled		
• No effect or limited ↑ on MN incidence in nasal/buccal epithelial tissue	*≤1, or 17 mg/m^3-hrs*[e]	NR
Subchronic exposure: repeat environmental (pathology and medical students)		
• ↑ MN incidence in nasal and buccal epithelium, stronger association in centromere-negative MN	0.5–2 [0.07–5]	NR and −/+ assoc. w/↑ CE
Chronic exposure: repeat occupational/environmental		
• ↑ Binucleation, but not nuclear bud or MN frequency, in buccal epithelium from furniture workers	0.04–0.1 [NR]	+ assoc. w/↑ [C] No assoc. w/↑ D
• ↑ MN frequency in nasal epithelium from workers	0.1–1 [0.05–5]	NR
• ↑ MN frequency in buccal epithelium from anatomy/pathology faculty and staff, laboratory or factory workers	0.2–NR [0.05–5]	+ assoc. exposed:referent

Observations from the available in vivo database *(see Appendix A.4 for details)*[a,b]	**Exposure level (mg/m^3)[c]**	**Statistical associations[d]**
		+ association w/↑ D
Nonhuman primate		
Acute or short-term exposure: controlled		
• ↑ DPX in the nasal mucosa; larynx, trachea, and/or carina; maxillary sinuses and lower respiratory tract of rhesus monkeys	≥0.9; ≥2; 7	− assoc. w/↑ distance from POE
• ↑ Exogenous FA $^{13}CD_2$-N^2-hmdG adducts and DPXs in maxilloturbinates of cynomolgus monkeys	≥2	+ assoc. w/↑ [C]
Rodent		
Acute or short-term exposure: controlled		
• ↑ DPX in the nasal epithelium; no effect in bronchoalveolar lavage fluid or nasal olfactory mucosa of F344 rats	≥0.4; *≥18*	− assoc. w/↑ distance from POE
• ↑ Exogenous FA $^{13}CD_2$-N^2-hmdG adducts and DPXs in nasal epithelium of F344 rats	≥0.9	+ assoc. w/↑ [C], D
Subchronic exposure: controlled		
• ↑ DPX in the nasal epithelium of F344 rats	≥0.9	− assoc. w/↑ distance from POE
• No effect on MN incidence in nasal epithelium of F344 rats	*≤18*	NR

[a]Treatment-associated increase (↑), micronucleus (MN), DNA-protein crosslinks (DPX), DNA monomethyl deoxyguanosine adducts resulting from exogenously administered formaldehyde (FA $^{13}CD_2$-N^2-hmdG), single-strand DNA breaks (SSBs).

[b]The earliest duration reported by the study authors to elicit the specified effect is noted for controlled exposure studies, or the mean duration reported in epidemiological studies; multiple values are provided in cases where the study authors described only a range of exposure durations, or to represent a range of average durations from a collection of similar epidemiological or experimental reports.

[c]For experimental studies, lowest effective concentrations (LEC) are presented, while for individual epidemiological studies, mean exposures are listed, otherwise the range of mean exposures is presented to represent a collection of studies reporting similar effects, with the overall range reported in individual studies or collections in [ ]; determinations were made by EPA review considering potentially biologically relevant effects that were attributed by the study authors to formaldehyde exposure; "≥" indicates that higher exposures were evaluated that also indicated an exposure-related effect. Where no effect was reported, the highest ineffective concentrations (*HIC*), or ranges of exposure are indicated; "≤" indicates that concentrations lower than the HIC were also evaluated.

[d]Results of association, regression, correlation, or trend analysis as reported by study authors; "NR" indicates that either associations were not evaluated or that no significant associations (assoc.) were reported; positive (+), weakly positive (−/+) associations, inverse association (−); with (w/), exposure duration (D), cumulative exposure (CE), exposure concentration ([C]), apical portal of entry (POE).

[e]This study employed a complex and variable exposure protocol, with individuals experiencing 17 mg/m^3-hours of cumulative formaldehyde exposure distributed throughout a period of 40 hours over 10 workdays (2 weeks).

[f]Results presented from respiratory or transitional epithelial tissue generally described as located in "Level II" of the anterior rodent nasal passages, including the nasal lateral meatus, septum, naso- and maxilloturbinates, as described in Section 1.2.4.

In addition to directly damaging DNA, formaldehyde inhalation can cause a number of pathological cellular changes in the URT, such as inhibited mucous flow and decreased ciliary beat, rhinitis and inflammation, ciliastasis, cilia loss, and possibly sporadic epithelial proliferation at low-to-moderate exposure levels that elicit marginal increases in frank tissue toxicity as evidenced by a lack of necrosis, epithelial degeneration, or squamous metaplasia in the nasal passageways (see Section 1.2.4). Any molecular mechanisms responsible for such respiratory epithelial proliferation remain to be determined, but could include some of the cytokines and eicosanoids associated with URT inflammation and leukocyte extravasation, epigenetic activation, or suppression of cell cycle regulatory machinery through changes in gene regulation, including miRNA, loss of contact-inhibition signaling, or even direct stimulation of epithelial mitosis via adduction of growth factor-signaling mediators (see Appendix A.5.6 for the evidence available on some of these potential events). Accelerated cell cycle progression can increase the rate of random genotoxic events in proliferating cells (indirect genotoxicity), which—if improperly repaired due to insufficient delay in G1 phase, failure to arrest in S phase, or deficiency of DNA repair machinery—could lead to heritable mutations and eventually URT neoplasia (Branzei and Foiani, 2008). Tissue stem cell proliferation rate and the contribution of this random or "background" mutagenesis to human lifetime cancer risk has been proposed to be significant for a variety of tissues (Tomasetti and Vogelstein, 2015), although the relevance, magnitude, and scope are still under debate (Rozhok et al., 2015; Wild et al., 2015; Wodarz and Zauber, 2015). Experimentally, the magnitude of formaldehyde-induced DNA synthesis is dramatically increased as a function of concentration and, to a lesser extent, duration, reaches maximal levels after 1–3 months with short-term or subchronic exposure, and then appears to diminish in the only study that looked at changes after exposure longer than 13 weeks (see Appendix A.5.6). Observations from direct DNA labeling studies are summarized in Table 1-40 (scenarios involving cytotoxic exposures are described below).

Table 1-40. Direct measurements of DNA synthesis in the upper respiratory tract

Observations from the available in vivo database *(see Appendix A.5.6 for details on proliferation)*[a,b]	Exposure level (mg/m^3)[c]	Statistical associations[d]
Nonhuman primate		
Acute—subchronic exposure: controlled		
• ↑ Epithelial cell proliferation in nasal and extranasal transitional and respiratory epithelium of rhesus monkeys	7	– assoc. w/↑ D, distance from POE
Rodent[e]		
Acute exposure: controlled		
• ↑ Epithelial cell proliferation in nasal septum, lateral meatus, or turbinates of Wistar rats; in the anterior nose (not otherwise specified) in Sprague Dawley rats	≥4; ≥3	NR; NR

Observations from the available in vivo database *(see Appendix A.5.6 for details on proliferation)*[a,b]	Exposure level (mg/m^3)[c]	Statistical associations[d]
• ↑ Epithelial cell proliferation in the nasal lateral meatus, or maxilloturbinates in F344 rats	≥7	− assoc. w/↑ D + assoc. w/↑ CE[f]
• ↑ Epithelial cell proliferation in the nasal lateral meatus, or nasoturbinates in $B6C3F_1$ mice	≥15	− assoc. w/↑ D + assoc. w/↑ CE[f]
Subchronic exposure: controlled		
• ↑ Epithelial cell proliferation in nasal septum, turbinates, or lateral meatus of Wistar rats	≥4	+ assoc. w/↑ [C] and not CE
• ↑ Epithelial cell proliferation in the nasal lateral meatus, septum, and/or turbinates of F344 rats	≥3−7[g]	− assoc. w/↑ distance from POE + assoc. w/↑ [C], D
Chronic exposure: controlled		
• ↑ Epithelial cell proliferation in the nasal lateral meatus in F344 rats	≥12	− assoc. w/↑ D, distance from POE

[a]Treatment-associated increase (↑).
[b]The durations reported by the study authors to elicit the specified effect are noted for controlled exposure studies; multiple values represent different durations from several experimental reports.
[c]Lowest effective concentrations (LEC) are presented for experimental studies, as determined by EPA review considering potentially biologically relevant effects that were attributed by the study authors to formaldehyde exposure; "≥" indicates that higher exposures were evaluated which also indicated an exposure-related effect.
[d]Results of association, regression, correlation, or trend analysis as reported by study authors; "NR" indicates that either associations were not evaluated or that no significant associations (assoc.) were reported; positive (+) or inverse association (−); with (w/), exposure duration (D), cumulative exposure (CE), exposure concentration ([C]), apical portal of entry (POE).
[e]Results presented from respiratory or transitional epithelial tissue generally described as located in "Level II" of the anterior rodent nasal passages, including the nasal lateral meatus, septum, naso- and maxilloturbinates, whereas "Level I" commonly included the high-flux region and nose tip, as described in Section 1.2.4 and Appendix A.2.
[f]These associations are for "Level I" epithelial cells; only exposure concentration ([C]) was positively associated with cells in "Level II."
[g]LEC reported varied among reports from different authors and following exposures of different durations.

At higher, cytotoxic exposure levels, regenerative tissue proliferation concomitant with and resulting from cytotoxic epithelial pathology (including squamous hyperplasia, metaplasia, and dysplasia, with or without evidence of frank necrosis; discussed in Section 1.2.4) occurs in an exposure concentration- and duration-dependent manner. The relative contribution of exposure concentration and duration to this process may not be equal, particularly for events that segue from hyperplasia (exposure duration appears to be substantially more important to the development of metaplasia in laboratory animals than to the development of hyperplasia; see Section 1.2.4); however, specific data defining the relative contributions are unavailable. Metaplasia or hyperplasia is induced at moderate to high exposure levels after even short-term exposure, and extending the duration generally both increases the severity of nasal tissue pathology observed and decreases the exposure concentration necessary to elicit significant cytotoxicity (see Section 1.2.4).

Pathological indications of significant epithelial necrosis in F344 rats are primarily reported following exposure to relatively high concentrations, with similar results in Wistar or Sprague Dawley rats, although occasionally necrosis is reported at more moderate exposure levels. Under these conditions, the tissue rhinitis/inflammation, macromolecule adduction, or inhibition of cellular function is presumably severe enough, possibly in conjunction with tissue glutathione (GSH) depletion, to trigger cell death and significant regenerative pathology in the nasal respiratory or transitional epithelium. Together, these effects can increase damage from all sources to cellular constituents (e.g., membrane lipids and proteins, cytosolic proteins, DNA), and amplify genotoxicity while simultaneously decreasing the capacity for and fidelity of DNA repair. Thus, both direct and indirect effects of formaldehyde exposure at these levels can feed forward to increase insurmountable cellular toxicity. Cytotoxicity and death of more sensitive cells in the respiratory epithelial tissue compartment could select for and trigger compensatory proliferation among more resistant cells in the population, possibly including the division and differentiation of local pluripotent stem cells, all of which may replicate to replenish the damaged nasal mucosa. The magnitude of these tissue proliferative effects may also fluctuate as the result of epithelial tissue responses to chronic, continuous (i.e., metaplastic differentiation to a squamous phenotype) versus episodic (variable pathology) exposure scenarios. In this manner, formaldehyde exposure may accelerate proliferation as a field effect at the epithelial tissue level, causing genotoxicity and mutagenesis in both actively proliferating (direct and indirect genotoxicity) and more quiescent cells (direct genotoxicity only). Observations relevant to cytotoxic tissue pathology and regenerative proliferation are summarized in Table 1-41.

Table 1-41. Epithelial pathology, cytotoxicity, and regenerative proliferation in the upper respiratory tract

Observations from the available in vivo database *(see Appendix A.5.6 for details)*[a,b]	Exposure level (mg/m^3)[c]	Statistical associations[d]
Human		
Acute Exposure: Controlled[e]		
• ↑ Nasal mucosal membrane swelling; nasal and throat irritation	≥0.07; ≥0.3	NR; + assoc. w/↑ [C]
• ↓ Nasal mucociliary function, mucus flow rate; ↑ rhinitis and permeability index	≥0.3; ≥0.5	No assoc. w/D; NR
Chronic Exposure: Repeat Occupational/Residential		
• ↓ Nasal patency (airway volume)	0.01 [0.003–0.02]	− assoc. w/dust, NO_2, mold
• ↑ General symptoms of rhinitis, URT irritation, or inflammation	0.05–1 [0.01–2]	+ assoc. w/↑ [C], No assoc. w/D
• ↓ Nasal mucociliary function	0.3 [0.05–0.5]	No assoc. w/D

Observations from the available in vivo database *(see Appendix A.5.6 for details)*[a,b]	Exposure level (mg/m^3)[c]	Statistical associations[d]
• ↑ Nasal hyperplasia, keratinization, or squamous metaplasia	0.3–NR [0.02–2.5]	No assoc. w/D + assoc. w/age >50
Nonhuman Primate		
Acute Exposure: Controlled		
• ↓ Cilia content and ↑ hyperplasia or squamous metaplasia in nasal epithelium, nasopharynx, and larynx of rhesus monkeys	7	– assoc. w/↑ distance from POE
Subchronic Exposure: Controlled		
• ↑ Squamous metaplasia and hyperplasia in nasal epithelium, nasopharynx, and larynx of rhesus monkeys	7	+ severity w/↑ D – assoc. w/↑ distance from POE
• ↑ Squamous metaplasia and hyperplasia in nasal turbinates of cynomolgus monkeys	≥4	+ assoc. w/↑ [C]
Rodent[f]		
Acute Exposure: Controlled[g]		
• ↑ Nasal rhinitis, hyperplasia, or squamous metaplasia in Wistar rats	4	NR
• ↓ Microvilli content in nasal epithelial cells, ↓ nasal mucociliary function, flow rate; ↑ nasal squamous metaplasia of F344 rats	≥3; ≥7	– assoc. w/↑ [C], D; NR
• ↑ Nasal squamous metaplasia or hyperplasia in Swiss-Webster or $B6C3F_1$ mice	≥4	NR
Subchronic Exposure: Controlled		
• ↑ Nasal rhinitis, hyperplasia, or squamous metaplasia; ↓ cilia content of nasal septa epithelium in Wistar rats	≥4; 4	+ assoc. w/↑ [C] and not CE; NR
• ↑ Nasal hyperplasia or squamous metaplasia in F344 rats	≥7–12	– assoc. w/↑ distance from POE
• ↑ Nasal squamous metaplasia and seropurulent inflammation in $B6C3F_1$ mice	≥12	NR
Chronic Exposure: Controlled		
• ↑ Nasal rhinitis, hyperplasia, or squamous metaplasia in Wistar and F344 rats	≥1 and ≥3	NR and + assoc. w/↑ [C], D
• ↑ Nasal squamous metaplasia (but not rhinitis or hyperplasia) in Sprague Dawley rats	18	NR
• ↑ Nasal rhinitis, hyperplasia; nasal squamous metaplasia and dysplasia in B6C3F1 mice	≥3; ≥12	NR; NR

[a]Treatment-associated increase (↑), treatment-associated decrease (↓), hours (hrs), upper respiratory tract (URT).
[b]The earliest duration reported by the study authors to elicit the specified effect is noted for controlled exposure studies, or the mean duration reported in epidemiological studies; multiple values are provided in cases where the study authors described only a range of exposure durations, or to represent a range of average durations from a collection of similar epidemiological or experimental reports.
[c]For experimental studies, lowest effective concentrations (LEC) are presented, while for individual epidemiological studies, mean exposures are listed, otherwise the range of LECs or mean exposures are presented to represent a collection of studies reporting similar effects, with the overall range reported in individual epidemiological studies

or collections shown in brackets ([ ]); determinations were made by EPA review considering potentially biologically relevant effects that were attributed by the study authors to formaldehyde exposure; "≥" indicates that higher exposures were evaluated that also indicated an exposure-related effect.

[d]Results of association, regression, correlation, or trend analysis as reported by study authors; "NR" indicates that either associations were not evaluated or that no significant associations (assoc.) were reported; positive (+), inverse association (−); with (w/), exposure duration (D), cumulative exposure (CE), exposure concentration ([C]); apical portal of entry (POE).

[e]Due to the abundance of acute exposure human studies, only those rated as Tier I or IIA are summarized, as described in Appendix A.5.6.

[f]Results presented from respiratory or transitional epithelial tissue generally described as located in "Level II" of the anterior rodent nasal passages, including the nasal lateral meatus, septum, naso- and maxilloturbinates, as described in Section 1.2.4.

[g]Due to the abundance of acute exposure rodent studies, only those rated as Tier I or II are summarized, as described in Appendix A.5.6.

Relationships among the various events discussed above are integrated into a mechanistic network depicted in Figure 1-26, along with the modifying factors of chronic airway inflammation, oxidative stress, and epigenetic effects, which are also likely to stimulate or enhance URT tumorigenesis. Together, these primary mechanistic events and modifying factors form potential adverse outcome pathways (AOP), which are illustrated as a network of interconnected events [adverse outcome network (AON)], with some duplication of events across individual pathways for clarity (see Figure 1-27). These figures highlight various interactions among mechanistic elements for which some evidence exists in the formaldehyde database. They also facilitate the discussion and evaluation of this evidentiary support. The figures are not intended to illustrate every possible relationship among various aspects of formaldehyde toxicity and do not represent an attempt to exhaustively list all possible carcinogenic mechanisms. Furthermore, the understanding of how such signaling circuits actually operate in human carcinogenesis is still fragmentary and the current subject of intense study (Weinberg, 2014). The following section serves to evaluate the supporting evidentiary data pertaining to the events depicted in these figures.

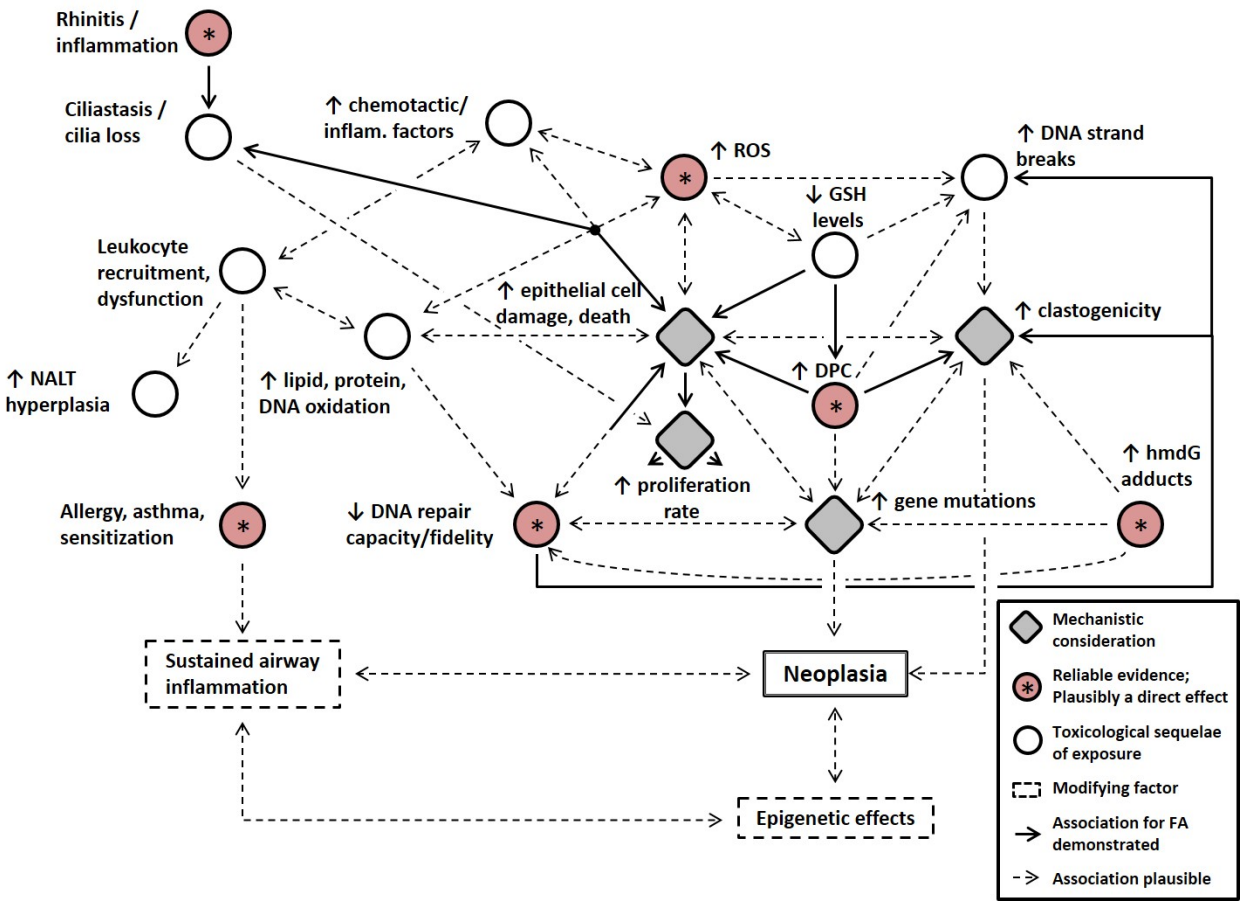


Figure 1-26. Mechanistic relationships relevant to URT carcinogenesis.

Integration of the molecular evidence available for the spectrum of formaldehyde- [FA-] related health effects pertinent to upper respiratory tract carcinogenesis summarized in the previous sections. Endpoints are depicted with varying degrees of support (with solid lines representing evidence from exposure in vivo, or consistent findings across multiple types of in vitro evidence). The identification of "reliable evidence" and related conclusions depicted in this figure are based primarily on evaluations conducted elsewhere (i.e., robust or moderate evidence described in Appendices A.4 and A.5.6). Plausible relationships are illustrated in a manner consistent with the cancer MOA schematic in Figure 1-25, including the hallmarks and enabling characteristics of cancer outlined therein.

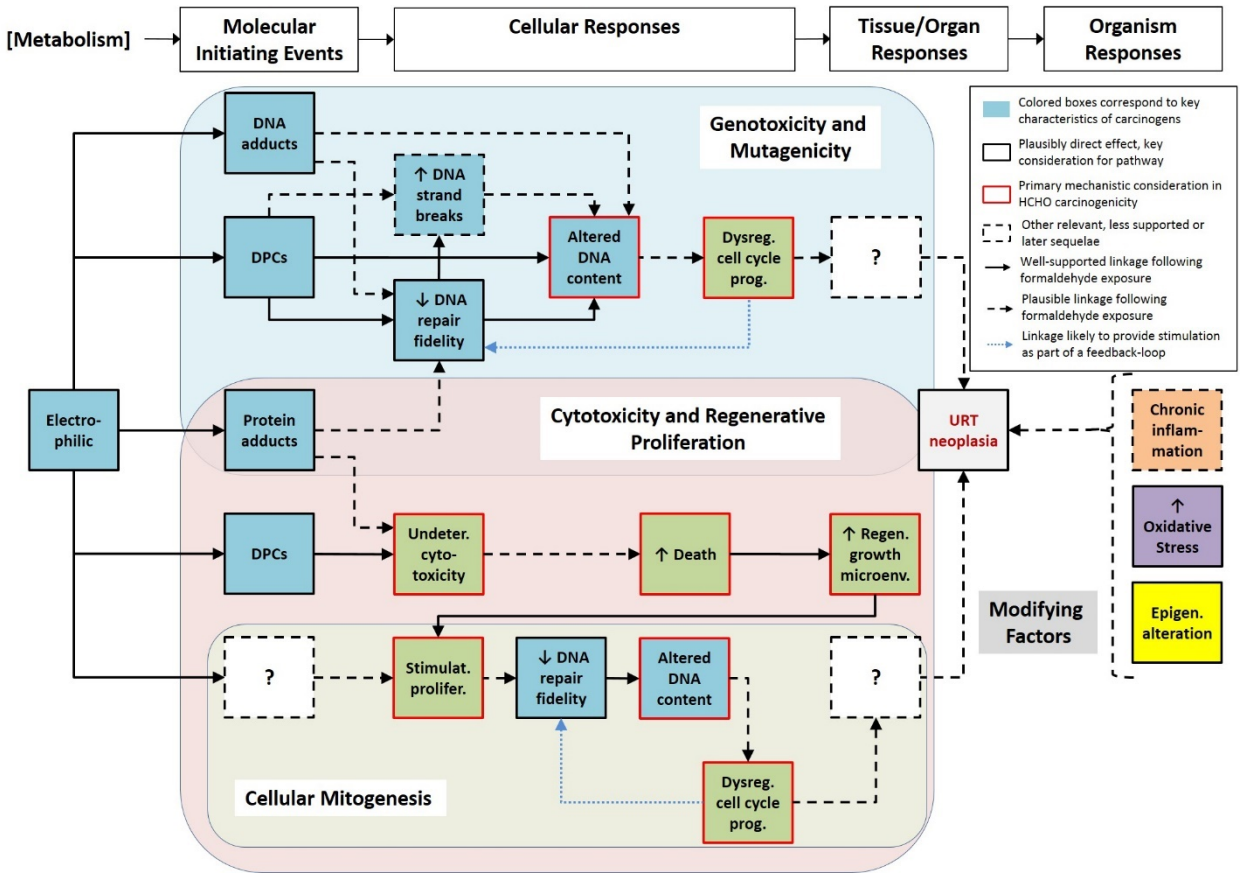


Figure 1-27. Network of adverse outcome pathways relevant to URT carcinogenesis.

Integration of the possible key events in pathways describing the role of genotoxicity and mutagenicity, cellular mitogenesis, and cytotoxicity and regenerative tissue proliferation in URT carcinogenesis following formaldehyde exposure. Endpoints are depicted with varying degrees of support (with solid lines representing evidence from exposure in vivo, or consistent findings across multiple types of in vitro evidence), with plausible relationships as hashed arrows, and possible feed-back loops illustrated as dotted reverse-facing blue lines. Boxes of varying colors represent events associated with related groups of key characteristics of carcinogens (Smith et al., 2016); electrophilicity, genotoxicity, and DNA repair elements are in blue, cell death and proliferation elements are in green, while the influence of chronic inflammation, oxidative stress, and epigenetic alterations are depicted as factors modifying the network in orange, purple, and yellow, respectively.

Evaluation of experimental support for the hypothesized mode of action

Genotoxicity

DNA-protein crosslinks (DPXs) were significantly elevated in the respiratory tracts of rhesus monkeys after 3 days of inhalation exposure, with lowest effective concentrations (LEC) increasing with anatomical distance from the apical POE, from 0.9 mg/m^3 in the nasal turbinates, to 2 mg/m^3 in the larynx, trachea, and carina (pooled samples), and 7 mg/m^3 in maxillary sinuses and lungs (Casanova et al., 1991), demonstrating direct genotoxicity as an early effect in tissues

analogous with sites of tumor formation in humans. In rats, increased DPX levels from exogenous formaldehyde were observed in the nasal lateral, medial, and posterior meatus (Casanova et al., 1994) or the entire nasal cavity of rats after ≥0.86 mg/m^3 ^{14}C-formaldehyde inhalation (Casanova et al., 1989), following single and multiple inhalation exposures over 0.25–81 days. Exogenous DPXs resulting from exposure to ^{13}C, d_2-labeled formaldehyde were reported in nasal passages from both nonhuman primates and rats. In rat nasal passages, DPX levels accumulated several-fold following 28 days of exposure to 2.5 mg/m^3 and remained largely unchanged following 7 days of recovery postexposure (different time points were not evaluated in nonhuman primate studies, Lai et al., 2016). Interestingly, while DPX levels increased by 2-fold to 30-fold over control levels from 0.9 to 18 mg/m^3 in rat nasal passages (NTP, 2010; Liteplo and Meek, 2003), the rate of DPX formation per unit of formaldehyde exposure (DPX/ppm exogenous formaldehyde) increased to a plateau at 7 mg/m^3, where it remained constant from 7 to 18 mg/m^3 (Swenberg et al., 2013; Casanova-Schmitz et al., 1984b). In both rhesus monkeys and F344 rats, DPX incidence was inversely associated with increasing anatomical distance from apical POE (Casanova and Heck, 1997; Casanova et al., 1994; Casanova et al., 1991; Casanova et al., 1989; Lam et al., 1985; Casanova-Schmitz et al., 1984b; Casanova-Schmitz and Heck, 1983). While increased DPX formation in human peripheral white blood cells (WBCs) has been positively associated with duration of exposure to concentrations ≥0.3 mg/m^3 [(Lin et al., 2013; Shaham et al., 2003; Shaham et al., 1997; Shaham et al., 1996); see Appendix A.4], DPX levels have not been evaluated in analogous human POE tissues (i.e., nasal, buccal, or nasopharyngeal epithelium).

Bulky DNA adducts, such as DPX, can block progression of the DNA polymerase complex, possibly contributing to genotoxicity or cell death in the URT (for further discussions see Appendices A.4 and A.5.6; (Wong et al., 2012; Heck and Casanova, 1999)). After a single exposure in rats, the inhibition of DNA replication due to DPX blockage was also predicted to be significant at >7 mg/m^3 (Heck and Casanova, 1999). While DNA replication was thought to be only marginally affected after a single exposure to lower concentrations (<1% at 1 mg/m^3 in rats), this effect may increase in magnitude or impact with the accumulation of DPXs and DNA adducts resulting from repeated exposure, as discussed below. Although the mechanisms regulating these effects remain undetermined, exposures ≥7 mg/m^3 are associated with increasingly severe epithelial pathology, cell death, and hyperproliferation in rat nasal passages following subchronic exposure, as well as dramatic increases in SCC formation after chronic exposure (see discussions of the specific animal evidence in Sections 1.2.4 and 1.2.5).

In addition to forming crosslinks, biochemical investigations have demonstrated that formaldehyde can react with DNA to form predominantly N^6-hydroxymethyl-deoxyadenosine (N^6-hmdA) and N^2-hydroxymethyl-deoxyguanosine (N^2-hmdG) adducts, with dA adducts more abundant than dG (Cheng et al., 2008; Zhong and Hee, 2004; Beland et al., 1984). While both DNA adducts have been detected in various tissues in vivo, likely resulting from endogenous formaldehyde reactivity, studies administering deuterium-labeled formaldehyde (^{13}C, d_2) have

detected labeled N^2-hmdG, but not N^6-hmdA, in the URT epithelium of both rodents and nonhuman primates (see Table 1 42; (Lu et al., 2012; Lu et al., 2011; Lu et al., 2010b); see Appendix A.4; (Yu et al., 2015b; Swenberg et al., 2013; Moeller et al., 2011), as well as human HeLa cells in culture (Lu et al., 2012). The inability to detect ^{13}C, d_2-N^6-hmdA was surprising, since ^{13}C, d_2-N^2-hmdG is reliably quantifiable following low levels of exposure, and increases in an exposure-dependent manner in both rodents and nonhuman primates (Yu et al., 2015b; Swenberg et al., 2013); the reason for the apparent absence of ^{13}C, d_2-N^6-hmdA adducts formed by reaction with exogenous formaldehyde remains unknown (see Appendix A.2). N^2-hmdG adducts resulting from exogenous exposure were positively associated with exposure concentration in the nasal maxilloturbinates of cynomolgus monkeys after 2 days, with an LEC of 2 mg/m^3 (Moeller et al., 2011), and also in the nasal epithelium of F344 rats after 1 to 28 days, with an LEC of 0.86 mg/m^3 (Yu et al., 2015b; Lu et al., 2011; Lu et al., 2010b). However, formaldehyde exposure up to 0.37 mg/m^3 in F344 rats failed to induce DPXs or hmDNA adducts in the nasal epithelium or in systemic tissues (Leng et al., 2019). As with DPXs, rat nasal N^2-hmdG adduct formation was also positively associated with exposure duration, with adducts accumulating to levels ≥5 times higher after 28 days of exposure to 2.5 mg/m^3 compared with single exposures; different time points were not evaluated in nonhuman primate studies (Yu et al., 2015b; Swenberg et al., 2013; Lu et al., 2010b). No studies have assessed the formation of exogenous hmDNA adducts in any tissues from humans exposed to formaldehyde.

Together with the above, acute exposure in rats and nonhuman primates appears to be sufficient to significantly increase formation of DPXs at an LEC of approximately 0.86 mg/m^3 and exogenous N^2-hmdG adducts at LECs of 0.86 and 2 mg/m^3 in analogous nasal tissues from both species. The observation that both DPXs and N^2-hmdG adducts are positively associated with exposure concentration in both nonhuman primates and rats (Lai et al., 2016; Yu et al., 2015b; Swenberg et al., 2013; Lu et al., 2011; Moeller et al., 2011; Lu et al., 2010b), and that they accumulate in rat nasal passages with repeat exposure (Lai et al., 2016; Yu et al., 2015b), is consistent with the hypothesis that DPXs may undergo spontaneous hydrolysis to form N^2-hmdG adducts (Yu et al., 2015b). While some DPXs may undergo hydrolysis to form N^2-hmdG adducts following exogenous formaldehyde exposure, other DPXs appear to be quite stable in vivo; it may be these latter DPXs that play a more important role in formaldehyde-mediated respiratory tract mutagenicity and carcinogenicity (Lai et al., 2016; NRC, 2011).

In addition to DNA adducts, strand breaks and cytogenetic endpoints have also been observed following formaldehyde exposure, and such damage can lead to heritable mutations, deletions, amplification, or chromosomal abnormalities if not successfully repaired. While DNA strand breaks have not been evaluated in apical POE tissues from rats or nonhuman primates, DNA SSB incidence was significantly increased in a concentration-dependent manner in both lung epithelial cells and PBLs from Sprague Dawley rats after 14 days of exposure to ≥6 mg/m^3, in the absence of significant protein or lipid oxidation in lung tissue (Sul et al., 2007; Im et al., 2006), corresponding with increased lung cell apoptosis observed following 28 days of exposure to

≥7 mg/m^3 (Aydin et al., 2014). Likewise, while strand breaks have not been measured in adult human URT tissues, increased SSBs have been reported in PBLs following occupational exposure to ≥0.3 mg/m^3 (Aydın et al., 2013; Lin et al., 2013; Costa et al., 2008, see Appendix A.4).

Unlike DNA stand-breaks, clastogenicity (in particular, MN formation) has been evaluated in human URT tissues. Acute, controlled exposures in healthy human volunteers yielded equivocal results; furthermore, MN incidences fell dramatically in both tissues during 21 days of postexposure monitoring (Zeller et al., 2011; Speit et al., 2007). Binucleation only, a proposed early event in MN formation, was elevated in buccal tissues from workers repeatedly exposed to low formaldehyde levels (mean location-specific concentrations of 0.04–0.11 mg/m3; (Peteffi et al., 2015). Although MN incidence was not significantly elevated in rat URT tissues after 28 days of exposure to ≤18 mg/m^3 (see Table 1-42) (Speit et al., 2011; Neuss et al., 2010), the majority of human studies have reported significant MN induction in the buccal epithelium after 5–35 years of occupational exposures to higher concentrations, averaging ≥0.2 mg/m^3 (see Table 1-42) (Costa et al., 2019; Aglan and Mansour, 2018; Ladeira et al., 2013; Ladeira et al., 2011; Viegas et al., 2010; Burgaz et al., 2002; Burgaz et al., 2001), and in the nasal epithelium of adults after an average of 7–11 years at ≥0.1 mg/m^3 (Costa et al., 2008; Ye et al., 2005; Ballarin et al., 1992). Results in students from shorter- duration classroom exposures (60–90 days) to 0.5–2 mg/m^3 have been lower in magnitude and less consistently positive, showing a stronger association between cumulative exposure and buccal versus nasal MN incidence and a stronger association with centromere-negative MN incidence, consistent with MN formation following DNA strand breakage (Ying et al., 1997; Titenko-Holland et al., 1996; Suruda et al., 1993). This hypothesized mechanism is consistent with the gene expression profile of human B-lymphoblastoid cells (Tk6) directly exposed to cytotoxic concentrations of formaldehyde in vitro, with transcript changes more akin to DNA-alkylating clastogenic agents than aneugenic spindle poisons (Kuehner et al., 2013). In buccal epithelium from human students or factory workers, MN incidence was positively correlated with exposure duration ($p < 0.01$) following exposure to 0.06–0.6 mg/m^3 for ≥1 year (Viegas et al., 2010), and positively correlated with cumulative exposure in male ($p = 0.01$) or male + female ($p = 0.06$) student populations exposed to 0.5–2 mg/m^3 for 90 days (Titenko-Holland et al., 1996; Suruda et al., 1993). Compared with the evaluations of URT tissues, cytogenetic endpoints have been more frequently evaluated in PBLs from occupational exposure cohorts (for further discussion, see Section 1.3.3 *Evidence on Mode of Action for Lymphohematopoietic Cancers* and Appendix A.4). Most of the studies conducted over the past 20 years have reported increased PBL MN incidence in formaldehyde-exposed humans, including the majority of studies reporting formaldehyde-associated increases in buccal or nasal MN incidence (Kirsch-Volders et al., 2014). Together with the above, the existing evidence consistently supports the association of MN induction in nasal and buccal tissue from human cohorts occupationally exposed to formaldehyde, in a manner temporally, biologically, and dose-responsively concordant with observations of

nasopharyngeal and sinonasal carcinogenesis across a range of exposure scenarios and concentrations.

Similar MN induction in epithelial cells of the URT has also been associated with increased human cancer risk in other populations (Ramirez and Saldanha, 2002; Lippman et al., 1990). Independent of formaldehyde exposure, a strong correlation between POE (buccal) and systemic (PBL) MN incidence has also been reported in samples collected from >6,500 healthy human subjects across 10 countries (r = 0.86; (Kirsch-Volders et al., 2014; Ceppi et al., 2010), suggesting that increases in PBL genotoxicity are relevant to human URT cancer risk, although the magnitude of MN induction in buccal cells is typically less than in PBLs (Holland et al., 2008). Elevated PBL MN and nuclear bud incidence, such as that observed in cohorts of formaldehyde-exposed workers, are predictive for lung cancer risk in smokers (Fenech et al., 2011; El-Zein et al., 2006) and are associated with increased cancer incidence in otherwise healthy individuals (Kirsch-Volders et al., 2014; Bonassi et al., 2008; Holland et al., 2008; El-Zein et al., 2006); see Section 1.3.3 *Evidence on Mode of Action for Lymphohematopoietic Cancers*). Parallel increases in buccal and PBL MN incidence have also been observed in human workers chronically exposed to wood dust, another URT carcinogen (Rekhadevi et al., 2009). Similarly, in radon-exposed miners, a 1% increase in the frequency of aberrant PBLs was associated with a 60% increase in lung cancer risk (Smerhovsky et al., 2002; Smerhovsky et al., 2001). Together, this evidence supports associations between local and peripheral clastogenicity and between tissue clastogenicity and human respiratory carcinogenesis.

The mutation profile of formaldehyde-induced rodent tumors has not been well characterized, and it is unclear which of the various genotoxic endpoints elicited by formaldehyde exposure may lead to permissive mutations in either rodent or human URT carcinogenesis. *P53* mutations were specifically evaluated in SCCs isolated from the nasal passages of F344 rats following 2 years of exposure to 18 mg/m^3 formaldehyde (Wolf et al., 1995a; Recio et al., 1992), and in hyperplastic nasal tissues following 90 days of exposure to similar concentrations (Meng et al., 2010). While not detected in hyperplastic epithelium, the *p53* mutations at codon 271 detected in five of the 11 rat URT SCCs have also been described in human URT cancers (Wolf et al., 1995a; Audrezet et al., 1993; Recio et al., 1992; Hollstein et al., 1991). At 18 mg/m^3, nasal squamous metaplasia preceding or concomitant with hyperplasia is significantly elevated early after first exposure (within 7 days; see Section 1.2.4), prior to the emergence of dysplasia at 365 days, in the nasal regions of F344 rats, which eventually harbor SCC after 330–548 days (Kamata et al., 1997; Monticello et al., 1996; Kerns et al., 1983). The absence of *p53* mutations in reactive nasal mucosa after 90 days of exposure is consistent with *p53* mutations acting as a selective or permissive factor acquired during the latter stages of formaldehyde-initiated carcinogenesis, facilitating increased genetic instability and the progression of nascent neoplasms to SCCs, which emerge months later (Hanahan and Weinberg, 2011, 2000). Perhaps consistent with this potential temporal relationship, a recent study of short-term (i.e., 8-week) exposure to high levels of formaldehyde in

two strains of *p53* deficient mice failed to observe any treatment-related increases in nasal tumors at 32 weeks post-exposure, despite pronounced metaplasia (Morgan et al., 2017). Additional study using longer-term exposures, ideally in rat models (as mice are demonstrably less sensitive), would help clarify the role of *p53* in URT carcinogenesis.

The proportion of human URT SCCs exhibiting *p53* mutations is similar to that reported in formaldehyde-elicited rat URT SCC (~45%), and codons orthologous to those with mutations in rat nasal SCC are also mutated in human URT SCC (Catalogue of Somatic Mutations in Cancer [COSMIC] build v73; filters: upper aerodigestive tract, all subtissues, carcinoma, squamous cell; accessed 10 July, 2015; http://cancer.sanger.ac.uk/cancergenome/projects/cosmic/). However, this has not been examined specifically in formaldehyde-exposed humans. The observation that formaldehyde-induced rat URT carcinomas share similar *p53* mutations with cancers in analogous human tissues suggests that rat and human URT tissues may be subjected to similar initiating or selective biological processes, which further supports the relevance of rodent URT tumors in informing human cancer risk.

Summary:

Genotoxicity in the respiratory or transitional epithelium temporally and dose-responsively precedes and anatomically coincides with sites of significant SCC and PA induction (see Section 1.2.5) in rats following chronic formaldehyde exposure as a function of increasing concentration (NTP, 2010; Liteplo and Meek, 2003). In both rats and nonhuman primates, nasal DPX and exogenous formaldehyde N_2-hmdG adducts were elevated in an exposure concentration- or duration-related manner after 1–28 days of experimental exposure to formaldehyde concentrations ≥ 0.9 mg/m^3 within the range of average occupational exposures associated with increased DPXs in human PBLs (0.5–4 mg/m^3) after various durations of exposure (see Appendix A.4) and increased MNs in human nasal (0.1–1 mg/m^3) or buccal tissue (0.2–0.5 mg/m^3) after ≥5 years (Appendix A.4). Human mortality risks from nasopharyngeal cancer were also elevated with both increasing exposure concentration and duration, with elevated risks evident at concentrations ≥1.23 mg/m^3 and after ~20 years following first exposure (see Section 1.2.5). The coherence of strong and consistent evidence for genotoxicity spans multiple evidence types from exposed humans to relevant model systems and species, in analogous POE and surrogate tissues, incorporating pertinent aspects of dose-response and temporality (i.e., preceding other mechanistic events), all of which strongly supports a role for direct DNA damage leading to mutagenicity in formaldehyde-induced URT carcinogenesis.

Cellular proliferation

Studies employing labeled nucleotides or analogs have reported increased epithelial cell proliferation in the nasal and extranasal passageways of rhesus monkeys after 7 or 42 days of exposure to 7 mg/m^3, concurrent with increased tissue hyperplasia and metaplasia in the nasal epithelium, nasopharynx, and larynx (see Section 1.2.4 and Appendix A.5.5). Acute exposure

(1–9 days) to similar concentrations also stimulated epithelial proliferation in the anterior nasal passages of F344, Wistar, and Sprague Dawley rats, while only exposures to ≥15 mg/m^3 increased proliferation in similar tissue from B6C3F$_1$ mice. This difference in exposure concentrations required to induce proliferation in nasal epithelium across rodent species may result from the increased reflex bradypnea observed in mice compared to similarly exposed rats. Respiratory minute volumes of mice acutely exposed to 15–18 mg/m^3 decrease such that they are roughly equivalent to a 7 mg/m^3 exposure in rats (see Appendix A.3) (Swenberg et al., 2013). This difference in rodent physiology between mice and rats is also consistent with the reported SCC incidence of 1–2% following chronic exposure to 18 and 7 mg/m^3, respectively (see Section 1.2.5), and with the apparent resistance of mice to formaldehyde-elicited cytotoxic nasal pathology (see Section 1.2.4).

In Wistar rats, proliferation was increased in the anterior nasal passages after 28 or 90 days of exposure with an LEC of 4 mg/m^3, a concentration not frequently evaluated in other species (see specific evaluations of proliferation in Appendix A.5.6) (Wilmer et al., 1989; Zwart et al., 1988; Wilmer et al., 1987). In F344 rats, cellular proliferation was induced to a similar extent after 90 days at ≥12 mg/m^3 (Andersen et al., 2010; Monticello et al., 1996) or 7 mg/m^3 in some studies (Casanova et al., 1994). A lesser magnitude of proliferation was also apparent following exposure to ≥3 mg/m^3 (Andersen et al., 2010; Meng et al., 2010; Monticello et al., 1996). In both strains, some evidence suggests increases in proliferation may occur at 0.8–2.5 mg/m^3 (Andersen et al., 2010; Meng et al., 2010; Casanova et al., 1994; Zwart et al., 1988) although this was inconsistent across studies (see Appendix A.5.6). While proliferation in the anterior nasal passages may appear to be stimulated to a greater extent at slightly lower exposure levels in Wistar versus F344 rats (due in part to choice of exposure concentrations evaluated), the strain sensitivity to nasal SCC induction was reversed: nasal tumors were present in only 4% of Wistar rats after 28 months of exposure to 12 mg/m^3, while 22% of F344 rats developed tumors after 24 months of exposure to the same concentration (see Section 1.2.5; (Monticello et al., 1996; Woutersen et al., 1989). This pattern also appears in PA incidence, where PAs were reported in ~1% (1 rat) of Wistar rats exposed to 11 mg/m^3 for ≤28 months (with lifetime observations), versus 6% of F344 rats exposed to 12 mg/m^3 for 24 months (Monticello et al., 1996; Woutersen et al., 1989; Feron et al., 1988). Unlike the differences seen with Wistar rats, incidence of both nasal SCCs and PAs appear to be generally similar between Sprague Dawley and F344 rats exposed to 18 mg/m^3 for 24–28 months (see Section 1.2.5), although the limited evidence in Sprague Dawley rats precludes a comparison of URT proliferation with F344 rats following repeat exposure (see Table 1-26). While limited, the available data suggest that some strain differences exist in the URT tumor response in Wistar versus F344 rats, while proliferation appears to be similarly induced in both rat strains.

Integrating across all available studies, the magnitude of proliferation induced in F344 rats was generally similar following exposure durations of 4–90 days (see Appendix A.5.6). In the single study available reporting URT epithelial proliferation in rats following chronic as well as

subchronic exposures, the proliferation response declined between 45 and 90 days, most strikingly at 7 mg/m^3, and then decreased gradually throughout 548 days of continuous exposure (Monticello et al., 1996). An inverse association between nasal epithelium DNA synthesis and exposure duration was reported between 7 and 42 days of exposure in rhesus monkeys (Monticello et al., 1989), suggesting that a proliferative peak may have been reached fairly rapidly in primates (≤7 days).

Investigations into the relative mitogenic versus cytotoxic consequences of formaldehyde exposure in vitro have revealed that while significant cytolethality was observed at >1 mM in cultured human colon carcinoma (HT-29), T lymphocyte (Jurkat E6-1) and umbilical vein endothelial cells (HUVEC) (Saito et al., 2005; Tyihák et al., 2001), lower and more physiologically relevant dose levels (0.1 mM; see Appendix A.2) induced proliferation in both HT-29 and HUVEC cells, and to a greater extent in the neoplastic HT-29 cells compared with the nonneoplastic HUVEC (Tyihák et al., 2001). However, ≥0.1 mM induced endoplasmic reticulum (ER) stress and increased the ratio of proapoptotic to antiapoptotic markers in both human lung carcinoma (A549; (Lim et al., 2013) and lymphoblast cell lines, with greater sensitivity observed in DNA repair deficient cells (Ren et al.) (see Appendix A.5.6). Increased sensitivity to formaldehyde-induced cell death has been consistently reported in eukaryotic cell lines deficient in excision, DNA crosslink, or chromosomal breakage repair (Mchale et al., 2014; Ren et al., 2013; Noda et al., 2011; Rosado et al., 2011; de Graaf et al., 2009; Ridpath et al., 2007), suggesting that unresolved genotoxicity could contribute to some of the cytotoxicity observed with increasing levels of formaldehyde exposure. Formaldehyde-stimulated cell cycle progression may be highly context dependent and only observed in circumstances where the concomitant genotoxicity and low-level toxicity (e.g., ER stress) are adequately controlled. This variable proliferation response in vitro is consistent with some in vivo observations of increased epithelial proliferation in the nasal passages of F344 rats following subchronic exposure at subcytotoxic exposure levels (~0.8–3 mg/m^3; see Section 1.2.4 and a specific proliferation analysis in Appendix A.5.6). However, nasal epithelial proliferation in the absence of cytotoxic nasal pathology was not consistently observed, and cell-density adjusted cellular proliferation indices correlate well with tumor formation following chronic exposures to ≥7 mg/m^3, concentrations that induced significant epithelial pathology in rodent nasal passages (see Section 1.2.4).

Summary:

Nasal epithelial cell proliferation was positively associated with the induction of squamous metaplasia and necrosis or epithelial erosion in F344 rats (Andersen et al., 2010) and correlated with SCC incidence as a function of both anatomical location and exposure concentration following exposures ≤19 mg/m^3 for up to 548 days (Swenberg et al., 2013; Monticello et al., 1996). The mutually permissive relationship between chemical carcinogenicity and epithelial cell proliferation has been described for several respiratory tract carcinogens and rodent models of human cancers (Monticello et al., 1993). Such a relationship can accelerate the acquisition of traits consistent with

a current understanding of the carcinogenic process (Goodson et al., 2015; Sonnenschein and Soto, 2013; Hanahan and Weinberg, 2011), as exemplified in the well-described etiology of mutagen-induced rat mammary gland tumorigenesis (Russo et al., 1990). The available data suggest that formaldehyde may elicit some mitogenicity at low-to-moderate exposures through an unknown cellular mechanism independent from the regenerative tissue proliferation associated with cytotoxicity following exposure to higher concentrations (see Figures 1-25–1-27). However, the limited evidence supporting proliferation as an effect independent from cytotoxic tissue pathology is not strong or consistent; furthermore, while the database contains several reports evaluating cellular proliferation at a molecular level (i.e., DNA nucleotide analog incorporation), it suffers from a dearth of molecular evaluations on other cellular functions, such as markers of toxicity, cell cycle regulation, or death, which prevents a more precise delineation of mitogenic effects at a cellular level from compensatory proliferation at a tissue level.

URT cytotoxicity, pathology

In humans, nasal airway function may be impaired at average exposures as low as 0.01 mg/m^3, suggesting that pathological URT changes occur even at low exposures (see Table 1-42) (Norback et al., 2000), while increasingly severe nasal histopathology (including hyperplasia, keratinization, and metaplasia) is associated with average chronic exposures ≥0.3 mg/m^3 (see Table 1-42) (Ballarin et al., 1992; Boysen et al., 1990; Holmstrom et al., 1989c; Edling et al., 1988; Odkvist et al., 1985). The incidence of distinct dysplasia, a dedicated preneoplastic lesion, was elevated in study participants with higher average chronic exposure, ranging from 0.1 to 3 mg/m^3 (see Section 1.2.4). Human nasal and throat irritation and cytotoxicity was positively associated with exposure concentrations ≥0.2 mg/m^3 in controlled acute exposure trials or after a single 8-hr work shift (see Table 1-42) (Priha et al., 2004; Kulle et al., 1987) and average exposure to 0.05–1 mg/m^3 in occupational cohort studies (Holness and Nethercott, 1989; Horvath et al., 1988). Consistent with these observations, fluctuation in ciliary beat frequency was also reported in primary human nasal cells exposed to 0.5–3 mg/m^3 following differentiation into a functional ciliated epithelium and cultured on an air-liquid interface (ALI) in vitro (Wang et al., 2014). However, unlike the positive association between human MN induction and exposure duration, or the clear relationship between rat squamous metaplasia induction and formaldehyde exposure duration (see Section 1.2.4), no significant associations were reported between exposure duration and various indications of human nasal mucosal pathology (see Table 1-42).

Similar to observations following chronic human exposure, the incidence of squamous metaplasia and hyperplasia in the nasal turbinates of cynomolgus monkeys was also positively associated with exposure concentrations ≥1 mg/m^3 (Rusch et al., 1983). Although lesion severity in rhesus monkeys was positively associated with extending exposure duration from 7 to 42 days at 7 mg/m^3 (Monticello et al., 1989), this observation is not necessarily discordant with the human data set, which generally evaluated pathology resulting from chronic durations as a function of differences in years of exposure versus days, as was evaluated in the nonhuman primates.

Nonhuman primates may be more resistant to nasal irritation and cytotoxicity than humans, as squamous metaplasia and hyperplasia were observed following 42 days exposure to 7 mg/m^3 in rhesus monkeys (Monticello et al., 1989), or 180 days of exposure to 4 mg/m^3 to cynomolgus monkeys, with 1 of 6 monkeys affected at 1 mg/m^3 (vs. 0/12 in controls), and no effects observed at 0.2 mg/m^3 (Rusch et al., 1983), although no studies have evaluated exposure durations directly analogous to chronic human exposure.

In F344 rats, nasal mucociliary function and flow rate decreased in an exposure concentration- and duration-associated manner following acute exposures to ≥3 mg/m^3 (Morgan et al., 1986a; Morgan et al., 1986c). Incidence or severity of squamous metaplasia also increased in both a duration- and concentration-dependent manner following exposures ≥3 mg/m^3 (Kerns et al., 1983); all effects were inversely associated with increasing distance from the apical POE (Casanova et al., 1994). Nasal pathology in Wistar rats was positively associated with exposure concentration, but not cumulative exposure, following subchronic exposures (Wilmer et al., 1989, 1987). This result is consistent with similar relationships reported between DNA synthesis rates and exposure concentration in the same anatomical regions (i.e., Level II) in both Wistar and F344 rats (see Table 1-42) (Wilmer et al., 1989; Zwart et al., 1988; Wilmer et al., 1987; Swenberg et al., 1986). Generally, formaldehyde exposure elicited similar pathology and ultrastructural changes in the analogous nasal passages of both nonhuman primates and rats (see Section 1.2.4). F344 rats appear to be similarly sensitive to the onset of nasal cytotoxicity induced by chronically inhaled formaldehyde compared with nonhuman primates, since a similar duration of exposure (180–365 days) induced nasal squamous metaplasia or hyperplasia in both species at ≥3 mg/m^3, while higher concentrations of ≥7–12 mg/m^3 were generally required to induce similar pathology following shorter durations (30–90 days; see Table 1-42). However, nasal damage in nonhuman primates (rhesus monkeys) became more developed, covered the URT epithelium to a greater extent, progressed to posterior nasal regions, and involved the larynx/trachea in less time (1.5 months) and at lower exposure levels (Monticello et al.) than similar changes observed in rats (Kerns et al., 1983). Likewise, nasal squamous metaplasia in cynomolgus monkeys was detected in all animals exposed to 4 mg/m^3 after 6 months (Rusch et al., 1983), while a comparable prevalence of analogous pathology in F344 rats required exposure to 18 mg/m^3 and ≥18 months to develop (see Section 1.2.4).

Other rodent species appear to be less sensitive to formaldehyde-induced nasal dysplasia, SCC and PA (in order of decreasing sensitivity): F334 and Sprague Dawley rats > Wistar rats > B6C3F1 mice > hamsters (see Section 1.2.5). Necrosis, inflammation, hyperplasia, or squamous metaplasia were observed in the anterior nasal passages of F344 rats, Wistar rats, and B6C3F$_1$ mice after short-term high-concentration exposures, as well as in the posterior nasal cavity of F344 rats after 6 months, and in the larynx/trachea after 18 months of exposure to 18 mg/m^3, although tumors of the larynx or trachea have not been associated with formaldehyde exposure in rodents (see Section 1.2.4). Conditions that induced nasal dysplasia in rats and mice consistently resulted

in SCC formation after an additional 6–12 months of exposure, whereas neither dysplasia nor SCCs were observed in hamsters (see Section 1.2.5). While formaldehyde-associated benign PAs and malignant SCCs may share similar tissue level origins (i.e., the transitional or respiratory but not olfactory epithelium), this reflects a neoplastic fate arising from morphologically different epithelial populations and does not imply that PAs are precursor lesions to SCC. In the rodent nasal cavity, SCCs are thought to arise directly from hyperplastic or dysplastic tissue (i.e., atypical squamous metaplasia) and do not necessarily progress through a benign tumor intermediate (McConnell et al., 1986).

Summary:

Progressive tissue cytotoxicity and induction of proliferative pathological lesions in the URT respiratory or transitional epithelium temporally and dose-responsively precede and anatomically coincide with sites of significant SCC and PA induction (see Section 1.2.4) in rats following chronic formaldehyde exposure as a function of increasing concentration (NTP, 2010; Liteplo and Meek, 2003). Similar lesions were also observed in the URT of nonhuman primates exposed up to 180 days, which appeared to progress farther along the primate respiratory tract. In humans, some indications of URT cellular toxicity have been reported at very low concentrations, with hyperplasia, keratinization, and metaplasia observed following chronic exposures ≥0.3 mg/m^3, which are concentrations approximately 10-fold lower than those eliciting similar effects in experimental animal models. Together, strong and consistent evidence exists associating URT epithelial pathology-driven tissue proliferation with SCC induction in rodent experimental models. Along with limited information from both nonhuman primates and occupationally exposed humans, these observations support a significant role for regenerative tissue proliferation in URT carcinogenesis associated with formaldehyde exposures high enough to induce cytotoxic URT pathology.

Summary of evidence supporting the primary mechanistic considerations:

In F344 rats chronically exposed to formaldehyde, there is a clear temporal, dose-responsive, and biological relationship in the appearance of exposure-related genotoxicity, sustained epithelial damage, cellular proliferation, and eventual SCC or PA development, consistent with similar relationships evident in analogous URT tissues from both the nonhuman primate and human databases. Furthermore, the chronic formaldehyde exposure concentrations reported to elicit nasal cytotoxic pathology appear to be higher in the rats and nonhuman primates evaluated experimentally (≥3 mg/m^3), compared with the results from human epidemiological cohorts (≥0.3 mg/m^3; see Table 1-42), whereas formaldehyde-associated genotoxicity has been induced in analogous POE tissues from rats, nonhuman primates, and humans exposed to similar formaldehyde concentrations (see Table 1-42). Together, genotoxicity, cellular proliferation, and cytotoxicity-induced tissue regenerative proliferation exhibit multiple layers of coherence as a function of species and anatomy, temporality, concentration, and duration of exposure. When

integrated, this evidence forms a biologically relevant MOA for formaldehyde exposure-induced URT carcinogenesis (U.S. EPA, 2005a).

Other factors modifying the mode of action

Oxidative stress, immune disease, and dysfunction

Increased rhinitis, nasal irritation, URT inflammation, and some indications of increased oxidative stress were observed in human cohorts after environmental or occupational exposures at the lower end of the range of average formaldehyde exposures associated with nasal hyperplasia and metaplasia. Rhinitis has been observed following subchronic or longer exposure in F344 rats and B6C3F1 mice, as well as chronically exposed human workers, and some observations suggest that oxidative stress may in part evolve as an effect secondary to the activation of inflammatory leukocytes in the human respiratory tract (see Section 1.2.3 and Appendix A.5.6). The prevalence of allergic conditions and asthma symptoms are increased in both children and adults exposed to formaldehyde, suggesting that immune dysfunction occurs to some extent in respiratory tract tissues following formaldehyde exposure (see Section 1.2.3 Immune-mediated Conditions). These observations may imply a decreased functional activity of immune effector cells. Whether these effects are due to immunosuppression, inappropriate polarization, or exposure-related cytotoxicity, such immune dysfunction could promote a chronic inflammatory environment and permit cancer progression (Jia et al., 2014; Coussens et al., 2013a, b; Balkwill et al., 2012; Mantovani et al., 2008).

In experimental rodent studies, depletion of nonprotein sulfhydryls (NP-SH, primarily GSH) increased DPX formation in the nasal mucosa of F344 rats following formaldehyde exposure to >1 mg/m^3 (Casanova and Heck, 1987), while GSH coadministration attenuated increases in DPX formation in systemic tissues from formalin-exposed BALB/c mice [Ye et al. (2013a); see also Appendix A.4 and A.5.6]. Although alterations in cellular GSH content may affect DPX formation and the mutagenic potential of formaldehyde exposure, it is unclear whether formaldehyde exposure itself will reduce URT glutathione levels in rodents. For example, even though glutathione reductase activity was decreased in the rat URT following short-term exposure to ≥4 mg/m^3, total non-NP-SH content actually increased (Cassee et al., 1996). A few other rodent studies have reported increased oxidative stress from the lower respiratory tract (LRT) following short-term exposures; however, data on oxidative stress endpoints from evaluation of URT tissues is limited, and it remains unclear whether LRT responses indicate analogous responses in URT passages (see Appendix A.5.6). In vitro, cellular GSH concentration was inversely correlated with formaldehyde cytotoxicity in human oral fibroblast cells and rat hepatocytes (Nilsson et al., 1998; Ku and Billings, 1984). In conditions where GSH was sufficiently decreased, formaldehyde inhibited mitochondrial respiration and led to increased lipid peroxidation and ROS production (IARC 88; (Teng et al., 2001), which could trigger NF-κB activation (Zhang et al., 2013a) and thus initiate an inflammatory signaling cascade. While formaldehyde may directly deplete cellular GSH pools to some extent, the resulting impact on cellular cytotoxicity can be amplified by other sources of oxidative stress (Saito

et al., 2005). Taken together, formaldehyde exposure may exacerbate oxidative stress primarily resulting from inflammation, cytotoxicity, or sulfhydryl depletion, which could further augment DPX-mediated genotoxicity as well as increasing ROS-mediated genetic instability and cell death. This could result in an amplification of both direct and indirect mutagenicity in the nasal epithelium.

Tumor immunosurveillance may play an important role specifically in limiting human nasopharyngeal carcinoma development; for example, patients with acquired immune deficiency syndrome (AIDS) are at significantly higher risk of developing both nonkeratinizing (commonly associated with Epstein-Barr virus [EBV] infection) as well as keratinizing nasopharyngeal carcinoma (Shebl et al.). In vitro, formaldehyde attenuates the perforin secretion and cell lytic activity of cultured mouse and human natural killer (NK) cells at subcytotoxic concentrations (Kim et al., 2013a; Li et al., 2013b), which would limit NK-mediated destruction of infected epithelial cells and prolong URT infection, possibly inhibiting any tumor-suppressive function of these cytotoxic lymphocytes. Consistent with this theory, 2 weeks of formaldehyde exposure attenuated both NK cell numbers and activity in the lungs of both naïve and tumor-bearing mice. This attenuation was associated with enhanced malignancy, growth, and neutrophil involvement of lung metastases formed by injected syngeneic melanoma cells (Kim et al., 2013a). Additional evidence for other formaldehyde-induced immune dysfunction comes from allergic sensitization studies and reports of exacerbated immune-mediated airway hyperresponsiveness presensitized rodents (see Section 1.2.3). Further, evidence exists to suggest the possibility that formaldehyde exposure may alter immune cell phenotypes, maturation and survival at a systemic level (see relevant mechanistic discussions in Sections 1.2.3 and 1.3.3); however, few studies have examined such evidence specifically within respiratory tissues, and those testing endpoints that might otherwise be most informative to this possibility (Zhao et al., 2020a) had methodological limitations that prevent clear interpretation. Together, however, the available data suggest that formaldehyde exposure may induce immune suppression or dysfunction in both experimental animals and humans, which could reduce the effectiveness of local immunosurveillance in suppressing tumor progression and metastasis, thus enabling URT carcinogenesis (Hanahan and Weinberg, 2011, 2000).

In summary, nasal infection and allergic symptoms are exacerbated in humans following exposure to fairly low formaldehyde levels, concomitant with or preceding epithelial tissue distress, inflammation, and preneoplastic lesion formation. Chronic inflammation is highly relevant to and positively associated with human risk of respiratory tract cancers; however, the specific mechanistic relationships between formaldehyde-induced inflammation, immune dysfunction, infection, allergy, oxidative damage, and URT cancer remain unclear.

DNA repair inhibition

The primary effects of formaldehyde interactions with DNA are N^2-hmdG adducts, DPXs and DDCs, and strand breaks, and repair of such formaldehyde-mediated genotoxicity appears to be crucial to cell survival. Consistent with this hypothesis, DNA repair genes are rapidly induced in rat

nasal mucosa following acute or subchronic exposure in vivo (Rager et al., 2014; Andersen et al., 2008; Hester et al., 2005) and human B-lymphoblastoid cells in vitro (Kuehner et al.).

The primary mechanism for repair of N^2-hmdG adducts is unclear. While nucleotide or base excision repair (NER/BER) may be responsible, the removal of small DNA adducts species may also result from nonspecific cellular processes (Brooks and Zakhari, 2014; Lindahl, 1993). The existence of two phases in the elimination of formaldehyde N^2-hmdG adducts from the rat nasal mucosa in vivo also supports a role for multiple removal mechanisms (Swenberg et al., 2013). DPXs are unlikely candidates for direct removal via excision repair in mammalian cells, although a fraction of smaller crosslink products (likely DDCs) may be removed via NER activity or proteolysis (see Appendices A.4 and 5.6 for detailed discussions). DPXs are more likely repaired via activity of the BRCA/Fanconi anemia family (FANC) proteins, components of the homologous recombination repair pathway, which regulate DPX repair following chronic or lower formaldehyde concentrations in mammalian cells and can attenuate the formation of DSBs and some chromosomal abnormalities (see Appendix A.4) (Ren et al., 2013; Rosado et al., 2011; Nakano et al., 2009). If unresolved, DPXs could lead to SSBs, DSBs, various cytogenetic abnormalities, and genomic instability (Kumari et al., 2015; Brooks and Zakhari, 2014; Kirsch-Volders et al., 2014; Ren et al., 2013; Langevin et al., 2011; Noda et al., 2011; Nakano et al., 2009; Ridpath et al., 2007). Additionally, DNA repair pathways are differentially engaged as a function of damage location in relation to DNA replication machinery, supporting a role for the context of DNA damage in determining the manner of its resolution (de Graaf et al., 2009).

In cultured human fibroblasts, exogenous formaldehyde directly interfered with DNA-binding damage sensor complex recruitment to DNA adducts and inhibited the repair of DNA lesions induced by either ultraviolet light or cisplatin adduction (Luch et al., 2014), consistent with similar observations in other human tissues and cells (see Appendix A.4 for a detailed discussion). This interaction also inhibited the migration and function of BER, and consequently inhibited the repair of oxidative DNA lesions. These results suggest that formaldehyde may inhibit excision repair by directly interfering with the DNA damage detection apparatus, which could delay the recognition and repair of DNA damage induced by both formaldehyde as well as other agents. However, any direct impact on the BRCA/FANC-mediated DNA repair pathway, which is likely to be responsible for removing formaldehyde-induced DPXs following chronic exposure, remains to be elucidated.

Members of the X-ray repair cross-complementing gene (XRCC) family serve as scaffolding proteins for the repair of single- and double-strand DNA breaks, including those caused by oxidative or UV-induced DNA damage (Kirsch-Volders et al., 2014). Despite several correlations between XRCC polymorphisms and increased sensitivity to formaldehyde-induced genotoxicity in human tissues and cells, the role for XRCC family proteins in regulating formaldehyde mutagenicity remains unclear (see Appendix A.4 for a detailed discussion). The molecular mechanisms by which formaldehyde causes MN are also unknown, but incomplete repair of DNA-protein or DNA-DNA

crosslinks, and the consequent stress from stalled replication forks, could result in DNA strand breaks and possibly centromere-negative MN formation (Brooks and Zakhari, 2014; Kirsch-Volders et al., 2014; Nakano et al., 2009). Taken together, the available data suggest that formaldehyde exposure may inhibit the detection and repair of lesions resulting directly from formaldehyde-DNA interactions, as well as genotoxicity resulting from other sources, and may thereby accelerate tissue carcinogenesis by exacerbating both direct and indirect mutagenesis. However, the available data are insufficient to determine any independent contribution of such interference in DNA repair to URT carcinogenesis.

Epigenetics and toxicogenomics

Changes in message RNA (mRNA) transcript levels from pathways relevant to URT carcinogenesis (e.g., cell cycle, proliferation signaling, apoptosis, and DNA repair) have been reported in URT tissues following formaldehyde exposure, possibly mediated by microRNA (miRNA) regulation, changes in DNA/histone modifying marks including methylation, acetylation and formylation, or by responses to cellular toxicity and tissue distress (see Appendix A.5.6 for a detailed discussion). After repeated exposure, mRNA levels for genes involved in growth signaling pathways increased in a concentration- or duration-related manner in F344 rats (Rager et al., 2014; Andersen et al., 2010), and some of these pathway perturbations were also reported in nonhuman primates (Rager et al., 2013).

In nasal tissues from acutely exposed nonhuman primates, significant induction of miR-125b and suppression of miR-29a were observed (Rager et al., 2013; Swenberg et al., 2013). Expressions of several candidate mRNA targets of miR-125b were also decreased in this study, consistent with miR-125b induction, including two that were also reported to be affected in subchronically exposed rats (Andersen et al., 2010) (see Appendix A.5.6). In analogous rat nasal tissues, expression of several members from the growth-suppressing miRNA family let-7 decreased following subchronic exposure (Rager et al., 2014), consistent with observations from exposed A549 lung carcinoma cells (Rager et al., 2011). Decreased expression of let-7 family members was found in nasopharyngeal carcinomas compared with healthy tissue (Li et al., 2011), and this effect has been reported to promote proliferative and oncogenic cellular signaling pathways in respiratory tract cancers (Jakopovic et al., 2013). Despite the numerous significant changes in miRNA expression levels reported following formaldehyde exposure, miR-203 was the only target reported to be similarly affected (decreased) in analogous nasal tissue from both rats and nonhuman primates (Rager et al., 2014; Rager et al., 2013) (see Appendix A.5.6). Overall, changes in expression of these miRNAs are generally consistent with observations in human lung, prostate, breast, and bone marrow cancers (Garzon et al., 2009; Ma and Weinberg, 2008; Fabbri et al., 2007). The abundance of highly significant changes in specific targets within individual arrays or experiments, but limited concordance across expression array data sets or species, is not unusual; however, it greatly complicates interpretation and integration of various data streams (Weinberg, 2014).

DNA methylation and histone modification can promote carcinogenesis through steric regulation of enhancer/promoter binding and transcription factor-DNA association, thereby affecting gene transcription (Vaissière et al., 2008). DNA methylation was globally decreased in human bronchial epithelial cells exposed to formaldehyde in vitro for up to 24 weeks, which may have been mediated by the down-regulation of de novo methyltransferase genes (Liu et al.). Formaldehyde may affect gene transcription via posttranslational modification (PTM) of histone proteins, in part by directly adducting unmodified lysine residues in histones to form N^6-formyllysine, thus preventing acetylation of this residue (Edrissi et al., 2013a; Lu et al., 2008). Such irreversible adduction could interfere with transcriptional activation, nucleosome organization (Wisniewski et al., 2008), and DNA lesion repair activity (Luch et al., 2014). Levels of these formylated lysine adducts increase in a concentration-dependent manner in the URT of rats exposed to ≥0.9 mg/m^3 (Edrissi et al., 2013b), levels at which increased DPXs are also observed (see Table 1-39, and Appendix A.4). In addition, exogenous formaldehyde can induce histone phosphorylation through activation of MAP kinase signaling in vitro (Yoshida and Ibuki, 2014). In A549 cells, as histone serine phosphorylation increased, lysine acetylation levels correspondingly decreased, providing an additional (indirect) mechanism by which exogenous formaldehyde attenuates histone acetylation and potentially modulates gene transcription. c-Jun N-terminal protein kinase (JNK) was the primary regulator of this histone phosphorylation, which led to elevated nuclear c-Fos and c-Jun protein expression (Shi et al., 2014; Yoshida and Ibuki, 2014). Together, c-Fos and c-Jun comprise the transcription factor AP-1, which can play an early role in human respiratory tract carcinogenesis (Karamouzis et al., 2007). Likewise, increased histone phosphorylation may be an important mechanism specifically in human nasopharyngeal carcinogenesis (Li et al., 2013a), suggesting that these epigenetic effects may play a causal role in human URT cancer formation.

The existing evidence illustrates myriad time- and concentration-dependent effects following formaldehyde exposure, indicating the potential for both direct and indirect impacts on transcriptional activity, in addition to inhibiting protein translation via miRNA dysregulation. What is lacking, however, are conceptual paradigms and computational strategies for integrating systems and cancer biology data streams (Weinberg, 2014). While provocative, in the absence of direct hypothesis evaluation and more explicit phenotypic anchoring, the causal contribution of epigenetic effects to URT carcinogenesis cannot be evaluated independently from the primary mechanistic considerations outlined above.

Mode of action evidence integration and summary of analysis

Prolonged inflammation or irritation to the nasal mucosal surface has been associated with squamous metaplasia of the respiratory or transitional epithelium following exposure to infectious agents such as fungi or bacteria, but such exposures did not result in neoplasia (Brown et al., 1991; Monticello et al., 1990b). Likewise, chemical URT irritants such as dimethylamine, glutaraldehyde, ethylacrylate, hydrogen chloride, and chlorine gas cause rhinitis, inflammation, and cytotoxicity

leading to squamous metaplasia or hyperplasia, but do not induce rat nasal tumors following chronic exposure (NRC, 2014b; Mcgregor et al., 2006; Wolf et al., 1995b; Buckley et al., 1985; Sellakumar et al., 1985; Albert et al., 1982). However, a number of genotoxic chemicals that also induce pathological changes in the rat nasal epithelium similar to formaldehyde (e.g., acetaldehyde, acrolein, 4-[N-methyl-N-nitrosamino]-1-[3-pyridyl]-1-butanone [NNK] and 1,2-epoxybutane) also induce nasal tumors including SCCs and PA-like lesions (NTP, 2011; U.S. EPA, 2003; Monticello et al., 1993; Monticello et al., 1990b; NTP, 1988; Woutersen et al., 1986). The comparison between formaldehyde and glutaraldehyde is particularly informative, as similar rat nasal cytotoxic pathology (e.g., squamous metaplasia, hyperplasia, inflammation) is elicited by exposure to both aldehydes (Hester et al., 2005), and yet glutaraldehyde exposure does not induce rat nasal tumors even after 24 months of exposure, while such tumors are induced following ≥12 months of formaldehyde exposure (Mcgregor et al., 2006). It has been proposed that glutaraldehyde exposure causes more epithelial cell death in the nasal mucosa compared with formaldehyde, possibly resulting in part from the greater inability of cells to repair or otherwise resolve any glutaraldehyde-DNA adducts (Mcgregor et al., 2006; Hester et al., 2005). The observation that a more effectively cytotoxic but less effectively mutagenic agent, glutaraldehyde, induces similar cytotoxicity-induced regenerative URT pathology to formaldehyde, yet appears unable to elicit rat URT tumors, suggests that cytotoxicity-induced regenerative proliferation alone is insufficient to induce URT carcinogenesis resulting from formaldehyde exposure.

The underlying balance between formaldehyde-associated cytotoxicity and genotoxicity may not only be responsible for the induction of these rare URT tumors in rats, but may also be key to the difference in phenotype between formaldehyde-induced nasal squamous metaplasia and that normally encountered in the aging rat. Gamma-glutamyl transpeptidase activity, present in normal and metaplastic epithelium in unexposed animals, is absent in the frequently atypical squamous metaplasia associated with formaldehyde exposure (Dinsdale et al., 1993; Brown et al., 1991). Such atypical squamous metaplasia (i.e., dysplasia) has been noted as a possible precursor to SCC in the rat URT (Monticello et al., 1990b). Together with the above, several lines of evidence converge to support the conclusion that while inflammation, squamous metaplasia, or hyperplasia alone are clearly not sufficient to induce nasal cancer in rats (Monticello et al., 1993), the amplified cellular proliferation occurring in regenerating tissues may be a mechanism by which genotoxicity-induced DNA mutation rates are augmented, facilitating neoplastic transformation. The marked increase in formaldehyde-initiated clones observed in vitro following growth stimulation by 12-O-tetradecanoylphorbol-13-acetate (TPA) in two-stage transformation studies (Boreiko and Ragan, 1983; Ragan and Boreiko, 1981) is also consistent with this conceptual model.

Strong and consistent evidence for formaldehyde-induced direct genotoxicity and mutagenicity comes from studies in mammalian cell lines, controlled inhalation studies in rodents and nonhuman primates, and occupationally exposed humans, wherein mutagenicity anatomically coincides with and temporally precedes URT tumorigenesis. Strong and consistent evidence

associates URT tissue pathology of increasing severity and regenerative proliferation with squamous cell carcinoma (SCC) formation in experimental rodent studies at moderate-to-high exposure levels, consistent with some measurements of cytotoxicity reported in analogous nasal or buccal tissues from formaldehyde-exposed humans (see Table 1-43). Experimental evidence also links polypoid adenoma (PA) formation to formaldehyde exposure in several rat strains that also develop SCCs, and limited evidence associates increased PA incidence across a range of exposure concentrations in F344 rats. Limited evidence from a subset of experimental rodent studies also supports nasal epithelial cell proliferation in the absence of significant epithelial tissue pathology following acute, discontinuous, or moderate concentration exposure scenarios; however, while even intermittent proliferative stimuli could promote the growth of both nascent and malignant clones, the specific role for formaldehyde-induced cellular proliferation as an effect independent from either concomitant genotoxicity or tissue pathology remains undetermined. Evidence supporting the URT cancer MOA depends not only on temporality, duration, and concentration of exposure, but also anatomical location within the URT (i.e., incidence or severity of all primary mechanistic considerations decreases following an anterior-to-posterior gradient within the URT). While significant evidence supports some association between formaldehyde exposure and immune disease or dysfunction, including chronic inflammation and increased oxidative stress, the existing database is not sufficient to evaluate the independent contribution of these effects to URT carcinogenesis. Likewise, while formaldehyde appears to inhibit various cellular DNA repair pathways, the independent contribution of this effect to URT carcinogenesis remains to be determined.

There is sufficient evidence to conclude that formaldehyde induces URT carcinogenicity via at least two primary mechanistic considerations: genotoxicity-associated mutagenicity and cytotoxicity-induced regenerative proliferation. By means of its fundamentally mutagenic activity, formaldehyde damages DNA and increases the mutational burden of the URT mucosa when this damage is not adequately repaired, while mucosal cytotoxicity creates a tissue microenvironment driving continuous proliferation, facilitating the accumulation of mutations arising from both direct and indirect genotoxicity, thereby increasing the rate at which initiated clones are formed as well as stimulating the expansion of existing neoplastic colonies (see Table 1-43). The involvement of both genotoxicity- and cytotoxicity-induced proliferation in the URT MOA is internally consistent with the available formaldehyde evidence, and is also externally consistent with the described activities of other reported URT toxins and carcinogens.

Table 1-42. Summary considerations for upper respiratory tract (URT) carcinogenesis

Hypothesized mechanistic event	Experimental support for mechanistic event	Human relevance	Weight-of-evidence conclusion and biological plausibility
Direct genotoxicity and mutagenicity (see Table 1-39)	• ↑ MN incidence in URT mucosa from human students and workers following subchronic-to-chronic exposure • ↑ DPX and/or hmdG adducts in URT tissues of rhesus or cynomolgus monkeys, following acute exposure • ↑ DPX or hmdG adducts and accumulation in URT tissues of F344 rats following acute to subchronic exposure • No effect on MN incidence URT tissues of F344 rats follow subchronic exposure	Yes. Markers of direct genotoxicity correspond anatomically and temporally with subsequent URT neoplasia in experimental animal models, are consistent with increased MN induction following exposure in humans, and are presumed relevant to human carcinogenesis.	Strong and consistent evidence for formaldehyde-induced direct genotoxicity and mutagenicity exists from both experimental animal models and human molecular epidemiology to support a significant role for mutagenicity in URT carcinogenesis.
Cytotoxicity-induced regenerative proliferation (see Tables 1-40 and 1-41)	• ↓ Nasal mucociliary function, ↑ nasal hyperplasia, keratinization and/or squamous metaplasia, URT rhinitis, irritation, and inflammation in humans following acute to chronic exposure • ↓ Nasal cilia content, ↑ hyperplasia and squamous metaplasia in URT tissues from monkeys following acute to subchronic exposure • Associated with ↑ URT cell proliferation in rhesus monkeys • ↓ Nasal mucociliary function, ↑ nasal rhinitis, hyperplasia and squamous metaplasia and/or dysplasia in various rat strains and B6C3F1 mice following acute to chronic exposure • Associated with ↑ URT cell proliferation rats and mice	Yes. Increasing incidence or severity of URT dysfunction or pathology is positively associated with formaldehyde exposure in humans, nonhuman primates, and rats. A continuum of similar epithelial pathology is observed across affected species at POE tissues, and therefore the resulting increased cellular turnover observed in experimental models is presumed relevant to human carcinogenesis.	Strong and consistent evidence exists which associates the nasal epithelial pathology-driven proliferation with SCC abundance following formaldehyde exposure in rodent experimental models to support a significant role for regenerative proliferation in URT carcinogenesis.
Cellular mitogenesis in the absence of cytotoxic tissue pathology (see Table 1-41)	• Clear evidence of ↑ URT cell proliferation under conditions also resulting in tissue pathology in rhesus monkeys • Exposure to subcytotoxic concentrations not evaluated • Clear evidence of ↑ URT cell proliferation under conditions	Yes. Cellular proliferation may be increased at lower exposures and/or following shorter durations of exposure than that eliciting tissue pathology, which suggests that mitogenesis may be directly stimulated by	Limited and inconsistent evidence associates cellular proliferation with formaldehyde exposures below those eliciting cytotoxic pathology in the rat nasal epithelium, which precludes a determination as to the

Hypothesized mechanistic event	Experimental support for mechanistic event	Human relevance	Weight-of-evidence conclusion and biological plausibility
	also resulting in tissue pathology in Wistar and F344 rats (≥4 mg/m^3) • Suggestive evidence of ↑ URT cell proliferation under conditions not clearly causing tissue pathology (<4 mg/m^3; *see Appendix A.5.6)*	formaldehyde exposure. Proliferation is expected to accelerate and enhance carcinogenesis in both humans and model systems, and is therefore presumed relevant to human carcinogenesis.	importance of this phenomenon in URT carcinogenesis.
Oxidative stress, immune disease and dysfunction in the URT (see Appendix A.5.6)	• ↑ LRT infection frequency, inflammation, allergic outcomes in children; ↑ leukocyte activation, allergy symptoms, chronic URT inflammation and ↓ infection resistance in adult workers following subchronic-chronic exposure • ↑ LRT oxidative stress, markers of inflammation and leukocyte recruitment in rats and mice; ↑ airway wall thickening or remodeling in mice and rats following OVA sensitization • ↑ Malignancy and neutrophil involvement of lung metastases, ↓ lung NK cell numbers and activity in C57BL/6 mice	Yes. Nasal infection, markers of persistent inflammation and/or immune dysfunction are positively associated with a range of formaldehyde exposure in both humans and rodents. Oxidative stress and chronic inflammatory diseases, including immunosuppression, are presumed relevant to human carcinogenesis. The relevance of other immune system dysfunctions to human carcinogenesis, such as allergy, is less clear.	While significant evidence exists supporting oxidative stress, chronic inflammation and various immune dysfunctions following formaldehyde exposure in humans and experimental animal models *(see Appendix A.5.6)*, the evidence supporting associations between these effects and URT carcinogenesis is insufficient to evaluate the contribution of these effects independently in either humans or experimental animal models.

Mode of action conclusions for URT cancers

Support for the hypothesized mode of action in experimental animal models

Strong, consistent evidence from rodent and nonhuman primate models supports the role for both direct (i.e., potentially DPX or hmDNA adduct-associated) mutagenicity, as well as indirect genotoxicity, mutagenicity, and regenerative proliferation resulting from respiratory tissue pathology, in rodent URT carcinogenesis. DNA labeling studies in rodent nasal epithelium suggest that cell division may also accelerate in response to marginally cytotoxic tissue concentrations resulting from short-term, lower level, or discontinuous exposure scenarios, although this evidence was neither strong nor consistent across similar studies and model systems. Observations of mutagenicity, cytotoxic epithelial pathology, and proliferation correspond histologically, anatomically, temporally, and dose-responsively with subsequent SCC and PA formation, consistent with contribution of both mutagenesis and regenerative proliferation to rodent URT carcinogenesis following formaldehyde exposure.

Relevance and applicability of the hypothesized mode of action to human cancer

Mutagenicity is presumed to be a relevant component of URT carcinogenesis in humans, supported by strong evidence of direct genotoxicity in both rodent and nonhuman primate experimental models and consistent observations of direct genotoxicity and mutagenicity from human epidemiological studies. Increased nasal epithelial cell proliferation (in rats and nonhuman primates) coincides anatomically with dysplastic lesions found in tissues from similar species, as well as with progressive, proliferative lesions in the nasal/buccal epithelium and nasopharynx of chronically exposed humans. This cross-species concordance, combined with the observation that cellular proliferation may be induced at lower exposures or following shorter durations of exposure than those eliciting tissue metaplasia, suggests that cellular proliferation in the presence of marginal tissue toxicity may also be potentially relevant to human URT carcinogenesis, as this episodic exposure scenario may be more frequently encountered in human populations than the continuous, chronic high-level exposures traditionally employed in rodent cancer bioassays. Increasing incidence or severity of nasal dysfunction and progressive pathology is associated with escalating formaldehyde exposure concentration or duration in humans, nonhuman primates, and rats. While POE tissue sensitivity to formaldehyde toxicity may quantitatively differ in humans versus rats and other rodents, qualitatively similar nasal dysfunction and pathology consistent with preneoplastic stages of cancer progression are observed across analogous tissues from all affected species, and therefore conclusions derived from these model systems are presumed relevant to human URT carcinogenesis. Given this presumed relevance, the potential for an increased susceptibility of specific human populations to developing URT cancers can be informed by both the human data and relevant mechanistic evidence from experimental model systems (see Section 1.4.1).

In general, URT findings in animals are found to be relevant to the URT cancer types and locations observed in humans despite significant differences in the occurrence of the individual cancer types. Firstly, site concordance is not required (U.S. EPA, 2005a). Secondly, the lack of a clear site-specific correspondence may be attributed to large interspecies differences in anatomy and airflow which in turn dictates formaldehyde distribution.

Regarding human NPC, the observed formaldehyde exposure-induced nasal tumors and mechanistic changes in animals are considered directly applicable to interpreting changes in the human nasopharynx. The nasopharynx is part of the nasal cavity and a recognized target of inhaled nasal toxicants across species (Chamanza and Wright, 2015).

Similarly, the URT MOA is considered relevant and applicable to the interpretation of human SNC, although some uncertainties remain. Across species, the sinuses are positioned close to the nasal cavity and encounter inspired air (Reznik, 1990). Analyses of sinonasal cancer cases indicate that most sinonasal cancers are squamous cell carcinomas (the primary tumor type in animals) and the upper nasal cavity is generally the primary site of tumor occurrence, in more than 40% of cases(the maxillary sinus is the next most common site), although it is often difficult to

pinpoint the exact anatomical location from which the cancers developed (Dutta et al., 2015; Llorente et al., 2014; Turner and Reh, 2012). While these similarities support the relevance of the animal data to human SNC, it is necessary to consider the anatomy of the rodent and human URT given the importance of the distribution of inhaled formaldehyde and, as compared to the nasopharynx and other parts of the nasal cavity, a reduced flow of inspired air reaches sinonasal regions and the sinuses specifically (via narrow channels from the nasal cavity) (Kumar et al., 2016; Xiong et al., 2008). Although tumors in the sinonasal regions of exposed rodents or monkeys were not observed, this may be partially explained by differences in anatomy. Specifically, while humans have four paranasal sinuses, rodents and monkeys only have one, and the sinus in rodents is much smaller, thus presenting a smaller target for potential cancer development and a reduced capacity for detection as compared to in humans. Additional uncertainties in drawing interpretations across species include differences in airflow and tissue/cellular composition, which cannot be easily evaluated. Taken together, while there is some uncertainty in the applicability of the MOA to SNC, the mechanistic evidence (as well as the evidence on nasal cancers in animals) is interpreted as applicable to and supportive of human SNC.

The hypopharynx and oropharynx, and to a greater extent the larynx, are more distal from the POE than the nasopharynx and sinonasal tissues. Oronasal breathing in humans, as compared to nasal-only breathing in rodents, may suggest a greater relevance of tissue sites close to the oral cavity for human exposure; thus, mechanistic changes in rostral parts of the URT (i.e., the nasal cavity) in animals may be more relevant to human oropharyngeal cancer. In general, however, based on the known reactivity and distribution of inhaled formaldehyde, a greater level of uncertainty in the applicability of the animal nasal findings is inferred for these human cancer types, most notably laryngeal cancer, as compared to NPC or SNC.

Utility of mechanistic data for informing hazard quantification decisions

Since strong and consistent evidence supports the contribution of both direct genotoxicity and mutagenicity as well as cytotoxicity-induced regenerative proliferation as primary mechanistic considerations relevant to the pathogenesis of formaldehyde-associated URT cancer in rodents, mechanistic data relevant to these endpoints may be useful for informing quantification of nasal cancers in experimental animals following chronic formaldehyde exposure. In particular, quantitative evaluation of these mechanisms may inform a biological response basis for guiding dose-response extrapolations of rodent SCCs, as described in Section 2.2.1.

Integrated Summary of Evidence for Upper Respiratory Tract Cancers

Table 1-43 summarizes the evidence integration judgments and supporting rationale for the individual URT cancers.

Epidemiological findings provide *robust* evidence for nasopharyngeal cancers (NPCs), based on groups with occupational exposure. Consistent increases in NPC risk were reported by numerous *high* and *medium* confidence studies involving occupational exposure to formaldehyde

among diverse populations in different geographic locations and exposure settings that accounted for expected temporal relationships for cancer induction and progression, with several reporting a large magnitude of relative risk (RR ≥3). A dose-response gradient was reported for various measures of exposure, including cumulative exposure, duration of exposure, and peak exposure. *Robust* evidence for nasal cancers is provided from studies in experimental animals (rats and mice). In animals, the incidence of lesions, as well as the tumor invasiveness and latency, was reproducibly shown to worsen with increasing formaldehyde exposure level. The distribution of tumors was dependent on duration of exposure as well as formaldehyde concentration. Mechanistic changes associated with the development of cancer in the nasal cavity were consistently observed in humans and experimental systems, including genotoxicity, epithelial damage and proliferation, and eventual cancer development in relevant URT tissues. The mechanistic changes and URT lesions exhibited a temporal and dose-response relationship coherent with carcinogenesis and supportive of a mutagenic MOA (see *Evidence on MOA for upper respiratory tract cancers)*. The observed formaldehyde exposure-induced nasal tumors and mechanistic changes in animals are considered directly relevant to changes in the human nasopharynx (the nasopharynx is part of the nasal cavity and a recognized target of inhaled nasal toxicants). Thus, based on *robust* human evidence, *robust* animal evidence, and mechanistic evidence supporting a mutagenic MOA for NPC, the **evidence demonstrates** that formaldehyde inhalation causes nasopharyngeal cancer in humans, given appropriate exposure circumstances. This conclusion is primarily based on studies of groups exposed to occupational formaldehyde levels and coherent findings in animals, with tumors in rodents generally only observed at formaldehyde concentrations above 6 mg/m^3.

Epidemiological findings also provide *robust* evidence for sinonasal cancer (SNC), based on groups with occupational exposure. The *robust* judgment for SNC is supported by a smaller set of epidemiological studies than for NPC, although a large, pooled analysis of 12 casecontrol studies included a large number of cases and greater detail on formaldehyde exposures, which increased confidence. This study observed an increasing trend in risk for adenocarcinoma with higher cumulative exposure among men and women in analyses that controlled for key confounders including exposure to wood dust. The studies were conducted in different geographic locations and exposure settings that accounted for expected temporal relationships for cancer induction and progression. Rodent nasal cancers and related mechanistic changes in the nasal cavity are considered relevant to human SNC (see discussion in *Evidence on MOA for upper respiratory tract cancers*), although some uncertainty in their applicability to SNC, as compared to NPC remains, and thus judgments of both *robust* and *moderate* animal evidence were considered. Ultimately, given this uncertainty in applicability, while the animal and mechanistic evidence cited for NPC is judged as informative and supportive for interpreting SNC, including providing sufficient support for a mutagenic MOA for this cancer type, the animal evidence overall is interpreted as *moderate* rather than *robust*. Based on *robust* human evidence, *moderate* animal evidence, and mechanistic evidence supporting a mutagenic MOA for SNC, the **evidence demonstrates** that formaldehyde inhalation

causes sinonasal cancer in humans, given appropriate exposure circumstances. This conclusion is primarily based on studies of groups exposed to occupational formaldehyde levels.

For oropharyngeal/hypopharyngeal cancers, the human evidence is *slight*, based on data from highly exposed workers, and s*light* animal evidence is provided from relevant observations of preneoplastic lesions and mechanistic changes. Taken together, the **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation might cause oropharyngeal/hypopharyngeal cancers given appropriate exposure circumstances.

The human and animal evidence is *indeterminate* for laryngeal cancers and, overall, the **evidence** is **inadequate** to determine whether formaldehyde inhalation may cause this cancer.

Table 1-43. Evidence integration summary for effects of formaldehyde inhalation on URT cancers

Evidence	Evidence judgment	Hazard determination
Nasopharyngeal cancer (NPC)		
Human evidence	*Robust*, based on: *Human health effect studies:* •Consistent increases in risk across numerous *high*, *medium* and *low* confidence studies •Very strong associations (eight studies reported at least a threefold increase in risk for some exposure categories, three of the eight were of *high* or *medium* confidence, direction of potential bias toward the null) •Evidence of exposure-response relationships across multiple measures of increased exposure • A temporal relationship consistent with causality (i.e., allowing for cancer induction, latency and mortality) *Biological Plausibility:* Although not as strong as the animal database of mechanistic studies, mechanistic evidence from human studies indicates a clear biological relationship with genotoxicity, epithelial damage and proliferation, and eventual cancer development in relevant URT tissues	The **evidence demonstrates** that formaldehyde inhalation causes nasopharyngeal cancer in humans, given appropriate exposure circumstances[a] Primarily based on studies of groups of workers exposed to occupational formaldehyde levels, coherent findings in animals (with tumors in rodents generally only at formaldehyde levels above 6 mg/m^3), and a well-supported MOA for nasal tumor development *Potential Susceptibilities*: There is very little evidence to evaluate the potential risk to sensitive populations and/or lifestages. However, several animal studies suggest that prior damage to the nasal epithelium might increase the development of cancer in these damaged regions.
Animal evidence	*Robust* , based on: *Animal health effect studies:* • Tumors of the respiratory tract (predominantly nasal squamous cell carcinomas, SCCs, but including other epithelial and nonepithelial tumors) were consistently observed in mice and in several strains of rats in numerous *high* and *medium* confidence studies, but not in hamsters, generally at formaldehyde levels above 6 mg/m^3. • The lesions progressed to more posterior locations with increasing duration and concentration of formaldehyde exposure • The development of these lesions, particularly the SCCs, depended on the duration of observation and, based on an increasing incidence and severity of lesions in animals exposed for longer periods of time, the formaldehyde exposure duration. Most notably, the lesion incidence, as well as the tumor invasiveness and latency, was reproducibly shown to worsen with increasing formaldehyde exposure level. *Biological Plausibility:* Mechanistic changes consistent with cancer development in nasal tissues were observed across species, including rats, mice, and monkeys. In F344 rats chronically exposed to formaldehyde, a clear	

	temporal, dose-responsive, and biological relationship was observed in the appearance of genotoxicity, sustained epithelial damage, cellular proliferation, and eventual tumor development.	
Other Inferences	• *Relevance of the animal evidence to human NPC*: The types of findings were consistent and coherent across species (including humans). Although site concordance is not essential (U.S. EPA, 2005a), considering the anatomy of the rodent and human URT and the importance of the distribution of inhaled formaldehyde, the observed formaldehyde exposure-induced nasal tumors and mechanistic changes in animals are considered directly relevant to changes in the human nasopharynx. • *MOA*: Together, genotoxicity, cellular proliferation, and cytotoxicity-induced regenerative proliferation exhibit multiple layers of coherence as a function of species, anatomy, temporality, concentration, and duration of exposure, and when integrated, form a biologically relevant MOA for formaldehyde-induced URT carcinogenesis (U.S. EPA, 2005a). While the chronic formaldehyde exposure concentrations reported to elicit nasal cytotoxic pathology appear to be higher in the rats and nonhuman primates evaluated experimentally (≥4 mg/m^3), compared with the results from human epidemiological cohorts (≥0.3 mg/m^3), formaldehyde-associated genotoxicity has been induced in analogous POE tissues from rats, nonhuman primates and humans exposed similarly (≤0.9 mg/m^3).	
Sinonasal cancer (SNC)		
Human evidence	*Robust*, based primarily on: *Human health effect studies:* • Consistent increases in risk across a set of *medium* and *low* confidence studies; four (2 *medium* and *2 low* confidence) studies reporting at least a threefold increase in risk, primarily for adenocarcinoma, including the largest study, a pooled analysis of 12 case-control studies, demonstrating a clear exposure-response relationship. • Increased risk of lower magnitude reported by two other medium confidence studies. • Null results in 3 insensitive low confidence studies. *Biological Plausibility:* The human mechanistic evidence cited for NPC is informative and supportive for interpreting the biological plausibility of SNC (see discussion in MOA analysis).	The **evidence demonstrates** that formaldehyde inhalation causes sinonasal cancer in humans, given appropriate exposure circumstances[a] Primarily based on studies of groups of workers exposed to occupational formaldehyde levels. Although less certain than the support provided for NPCs, animal and MOA evidence provide support for the human evidence. *Potential Susceptibilities*: There is very little evidence to evaluate the potential risk to sensitive populations and/or lifestages. However, several animal studies suggest that prior damage to the nasal epithelium might increase the development of cancer in these damaged regions.
Animal evidence	*Moderate*, based on: *Animal health effect studies:* (Same evidence base as for NPC above; see "*Other inferences, relevance of the animal evidence to human SNC*" for justification) • Note: tumors were not reported in the maxillary sinus of exposed animals *Biological Plausibility:* (Same mechanistic evidence base as for NPC above) • Although infrequently examined, studies that measured noncancer lesions in the maxillary sinus did not detect treatment-related respiratory tract pathology, although cell proliferation was observed (see Section 1.2.4). • Although also poorly studied, some mechanistic changes consistent with the MOA for nasal cancers, including increased DPX in the monkey maxillary sinus, have been observed.	

Other Inferences	• *Relevance of the animal evidence to human SNC*: The types of findings were consistent and coherent across species (including humans). The strong animal and mechanistic evidence for nasal cancers across species is interpreted to provide *moderate* evidence supportive of sinonasal cancer (a judgment of *moderate* rather than *robust* reflects some uncertainty in interpreting the nasal cavity findings in animals as fully applicable to human sinonasal cancer specifically; see discussion in MOA analysis). • *MOA*: Similar to the inference above, although there is uncertainty in the application of the identified MOA to SNC, the evidence overall is interpreted to provide reasonable support for the mutagenic MOA asapplicable to SNC.	
Oropharyngeal/ Hypopharyngeal cancer (OHPC)		
Human evidence	*Slight*, based on: *Human health effect studies:* •Increased risks in two of three *medium confidence* studies that evaluated multiple metrics of exposure and reported three- to fivefold increases in those highly exposed, including one which demonstrated clear exposure-response relationships across several metrics •However, little evidence of increases in risk (near the null) across one *medium* and two *low* confidence results *Biological Plausibility:* Although cells from exposed humans in tissues closely apposed to the oropharynx and, more indirectly, the hypopharynx (e.g., buccal cells) demonstrate mechanistic changes consistent with the development of cancer, including genotoxicity, these data were not interpreted as sufficient to further strengthen the human evidence judgment beyond *slight*.	The **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation might cause oropharyngeal /hypopharyngeal cancer, given appropriate exposure circumstances[b]
Animal evidence	*Slight*, based on: *Animal health effect studies:* • While most findings in animals were localized to the nasal cavity, some data suggest that changes in more caudal (e.g., in the trachea) regions, including evidence of dysplasia (a dedicated pre-neoplastic lesion) in one study, can occur with very high formaldehyde exposures and/or different breathing patterns (e.g., oronasal breathing in monkeys). • Changes in the more caudal URT tissues most relevant to OHPC were generally less direct indicators of cancer development, were less severe, or occurred only at very high exposure levels. *Biological Plausibility:* Mechanistic changes within caudal portions of the rodent and monkey URT have been observed, and oronasal breathing in humans (contrasting nasal-only breathing in rodents) infers an increased potential relevance of mechanistic changes in rostral (anterior) regions of the rodent to human OHPC. However, this was not interpreted as sufficient to further strengthen the evidence judgment beyond *slight*.	
Other inferences	• *Relevance of the animal evidence to human OHPC*: While cancer site concordance is not required for hazard determination (U.S. EPA, 2005a), given the known reactivity and distribution of inhaled formaldehyde, a lesser level of confidence in the applicability of the animal nasal findings is inferred for OHPC as compared to NPC or SNC. • *MOA*: While aspects of the MOA for nasal cancers, including NPC and SNC, may be operant for OHPC, the evidence overall is not interpreted to provide reasonable support for a MOA that is relevant to OHPC.	
Laryngeal cancer		
Human	*Indeterminate*, based on:	There is **inadequate evidence**

	Human health effect studies: • Suggestive associations reported in two *medium* confidence studies • Inconsistent evidence on exposure-response relationships • The moderate survival rate for laryngeal cancer may indicate that mortality data are not as good a proxy for incidence. *Biological Plausibility:* Human mechanistic data specifically related to this cancer type are lacking.	to determine whether formaldehyde inhalation may be capable of causing laryngeal cancer in humans
Animal	*Indeterminate*, based on: *Animal health effect studies:* • No studies observed tumors in the rodent or monkey larynx, nor were preneoplastic lesions such as dysplasia detected. *Biological Plausibility:* The evidence for mechanistic changes specifically within the larynx included findings in rodents and monkeys consistent with the MOA for nasal cancers, specifically noncancer lesions (e.g., tissue damage, hyperplasia, and squamous metaplasia) and genotoxicity (i.e., increased DPX). Although these mechanistic changes alone could support a judgment of *slight*, in the absence of experimental confirmation (or a biological understanding) that these mechanistic changes are likely to lead to cancer or preneoplastic lesions at sublethal formaldehyde concentrations, the animal evidence was judged as *indeterminate*.	
Other inferences	• *Relevance of the animal evidence to human laryngeal cancer*: The mechanistic changes observed in similar regions of the rodent and monkey URT are considered relevant to the interpretation of laryngeal cancer. • MOA: No potential MOA was identified for this cancer type.	

[a]The "appropriate exposure circumstances" are more fully evaluated and defined through dose-response analysis in Section 2.
[b]Given the uncertainty in this judgment and the available evidence, this assessment does not attempt to define what might be the "appropriate exposure circumstances" for developing this outcome.

1.3. SYNTHESIS OF EVIDENCE FOR NONRESPIRATORY EFFECTS

This section synthesizes research on nervous system effects (see Section 1.3.1), developmental and reproductive toxicity (see Section 1.3.2), and cancer effects beyond the respiratory tract (see Section 1.3.3), specifically in the lymphohematopoietic (LHP) system. Very little information has been reported concerning cancer associations at other nonrespiratory sites (e.g., brain; see Appendix A.5.9 for details). Evidence relevant to assessing carcinogenicity is synthesized for LHP cancer subtypes in Section 1.3.3 (i.e., myeloid leukemia, lymphatic leukemia, multiple myeloma, and Hodgkin lymphoma; note: non-Hodgkin lymphoma was not systematically evaluated: see Appendix A.5.9).

1.3.1. Nervous System Effects

Numerous studies suggest that formaldehyde inhalation might result in noncancer nervous system effects; however, the evidence across studies is generally weak and the database is incomplete. Few studies in humans are available; formaldehyde exposure was reported to be associated with neurobehavioral deficiencies as indicated by poorer performance in tests of short-term memory and psychomotor responses, and with the motor neuron disease, amyotrophic

lateral sclerosis (ALS). Observations in rodents include altered performance in tests of locomotion and anxiety, and in learning and memory tests. In many of these animal neurobehavioral studies, a confounding factor was introduced when test animals were exposed to the known neurotoxicant, methanol, in formalin solutions. Experimental animal studies without methanol coexposure suggest that repeated formaldehyde exposure may lead to amplified behavioral responses to certain challenges (e.g., pharmacological), possibly through persistent modifications to neural pathways. Similarly, studies from one laboratory suggest that developmental exposure to formaldehyde at concentrations well above those causing adverse effects on the respiratory system (see Sections 1.2.1−1.2.4) results in long-lasting changes in brain structure. To date, none of these potential nervous system changes are supported by an experimentally verified mechanistic hypothesis outlining how formaldehyde might elicit neurotoxicity without systemic distribution. Overall, a definitive association between formaldehyde inhalation and neurotoxicity could not be concluded. Most of the available experiments had significant study design deficiencies and corroboration across the database was incomplete; thus, overall, the **evidence suggests**, but is not sufficient to infer, the potential for formaldehyde inhalation to cause nervous system effects in humans (i.e., based on *slight* evidence from human or animal health effect studies). Additional research is needed to draw a more certain evidence integration judgment.

Literature Search and Screening Strategy

Studies in humans or experimental animals examining the potential nervous system effects of formaldehyde exposure were retrieved in a comprehensive systematic literature search of PubMed, Web of Science, and ToxNet through September 2016 (see Appendix A.5.7), and a systematic evidence map updating the literature through 2021 (see Appendix F). Human (observational epidemiology or controlled exposure) studies of neurobehavioral tests or specific neurological diseases were included. Studies of symptoms that may be associated with nervous system effects (e.g., headache, fatigue) were not included due to the highly subjective nature of these endpoints as compared to the other available data (these measures were primarily based on self-administered questionnaires that varied in type and specificity), and because many of the commonly reported symptoms are not necessarily specific to effects on the nervous system. In vivo inhalation animal exposure studies were included, but in vitro studies and studies of other exposure routes (e.g., oral, injection), including a multitude of studies using formaldehyde exposure (typically hind paw or forepaw injections) as a model to study nociceptive (pain) behaviors in rodents, were not included. These experiments are considered unlikely to reproduce the distribution of formaldehyde and its metabolites following inhalation exposures (i.e., inhaled formaldehyde has negligible distribution beyond the POE [see Appendix A.2], whereas other exposure routes may allow for substantial distribution to nervous system tissues). In addition, most of the oral and injection exposure experiments are confounded by methanol in the aqueous formaldehyde formulations, reducing the ability of these experiments to attribute any observed effects to formaldehyde. Unlike formaldehyde, methanol, a known neurotoxicant, is transported in

the blood to nervous system tissues. In vitro studies possess the same limitations (i.e., direct formaldehyde interaction with cells from nervous system tissues and methanol confounding). Finally, studies examining nervous system effects (e.g., memory loss; neurodegeneration) associated with increases in endogenous formaldehyde levels in the brain were identified by the literature search but not deemed PECO-relevant. These studies were not included in this evidence synthesis because formaldehyde inhalation does not appear to cause appreciable changes in formaldehyde levels in nonrespiratory tissues such as the brain and no hypothesis currently exists to explain how inhaled formaldehyde would affect endogenous formaldehyde levels in the CNS (see Appendix A.2). However, similar to other health effects (see Section 1.3.3), studies suggesting that CNS effects can result from reduced function of enzymes responsible for clearing formaldehyde from relevant tissues (e.g., downregulated ALDH2 in (Ai L, 2019; Tan et al., 2018), highlight an area of interest to future studies on potential susceptibility to inhaled formaldehyde exposure.

The bibliographic databases, search terms, and specific strategies used to search them are provided in Appendix A.5.7, as are the specific PECO criteria. Appendix A.5.7 includes a literature flow diagram that summarizes the results of the sorting process using these criteria and indicates the number of studies that were selected for consideration in the assessment through 2016 (see Appendix F for the identification of newer studies through 2021). These studies in animals and humans were evaluated to interpret the quality and relevance of the study results for use in interpreting the potential for formaldehyde exposure to cause neurotoxicity (see Appendix A.5.7).

Methodological Issues Considered in Evaluation of Studies

A key consideration for interpreting nervous system effects following formaldehyde inhalation involves possible coexposure to methanol when aqueous formaldehyde solutions are used as the test article. Findings in experimental studies describing the effects of formalin but not controlling for methanol, and studies failing to indicate the formaldehyde source, are identified throughout this section and automatically characterized as *low* confidence (at best); these studies contribute very little weight to the evidence integration conclusions pertaining to the potential for formaldehyde exposure to induce nervous system effects. Evaluation of the exposure protocol, including consideration of the potential impact of irritant or odorant effects on behavioral measures, was emphasized during study evaluations, contributing to the identification of some studies as not informative for characterizing hazard. The database of studies evaluating the potential for formaldehyde inhalation exposure to cause nervous system effects included very few studies interpreted with *medium* or *high* confidence. Overall, studies were primarily of *low* confidence and the majority of identified studies were interpreted as *not informative* for at least one of the outcomes examined.

Nervous System Effects in Human Studies

The identified studies describing results of neurobehavioral tests, as well as the occurrence or mortality from neurological disease are described in this section. These studies are summarized

in Tables 1-44 and 1-45. The tables are organized by study design (observational, acute controlled exposure), confidence in study results, and publication year.

While several observational epidemiology and controlled exposure studies report nervous system impairment in humans following exposure to formaldehyde, there are notable limitations in the available data and the results from some of the studies are potentially confounded by coexposures. Specifically, data from both observational and experimental studies showed an association between formaldehyde exposure and impaired performance in neurobehavioral tests of memory, dexterity, and psychomotor function (Lang et al., 2008; Kilburn and Warshaw, 1992; Bach et al., 1990; Kilburn et al., 1989; Kilburn et al., 1987). In prospective studies from one research group, Weisskopf et al. (2009) and Roberts et al. (2015) both noted an association between formaldehyde exposure and death from the fatal motor neuron disease, ALS, in different study populations in the United States; a separate case-control study from another research group in Sweden also identified an association among individuals younger than 65 years of age, but not in the overall analysis using national registry data (Peters et al., 2017). A national registry-based case-control study in Denmark by the same research group in the United States also observed an association (Seals et al., 2017), but a subsequent analysis using the same cases examining joint effects by multiple health and chemical risk factors observed an inverse association in both men and women, although only the latter reached statistical significance (Bellavia et al., 2021). Two other studies failed to identify an association (Pinkerton et al., 2013; Fang et al., 2009). All of the studies were limited by uncertainty in individual exposure assignments, except for the study by Pinkerton et al. (2013), which evaluated a cohort of garment workers with known formaldehyde exposure and detailed information on employment history. The cohort studies were limited by a very low number of exposed cases.

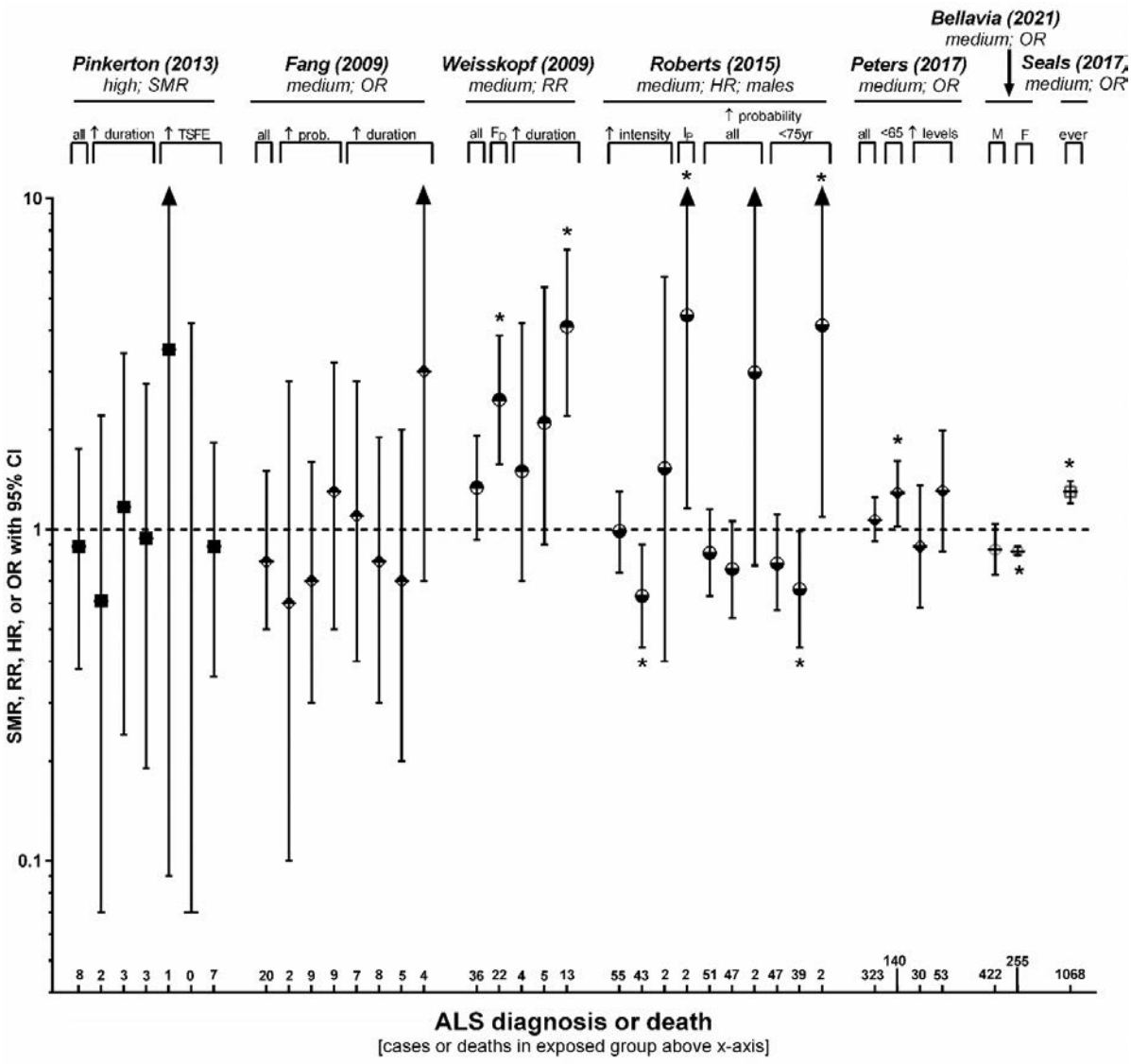


Figure 1-28. Human studies of *medium* or *high* confidence examining the potential for formaldehyde exposure to cause ALS.

Seven epidemiological studies of *medium* or *high* confidence were identified, all of which examined potential associations with amyotrophic lateral sclerosis (ALS) [notes: a *medium* confidence, acute controlled exposure study of neurobehavior, Lang et al. (2008), is not presented; results from Roberts et al. (2015) are only presented for males; all results in females were null]. Estimates of risk (i.e., odds ratios [ORs], standardized mortality ratios [SMRs], relative risks [RRs], or hazard ratios [HRs]), 95% confidence intervals (CIs), and number of exposed cases or deaths are presented for different comparisons within the studies, including full cohort (e.g., ever/never exposed) comparisons (unlabeled) and comparisons across multiple groups by: increasing duration, probability (prob.), time since first exposure (TFSE) [note: null results comparing date of first exposure in Pinkerton et al. (2013) are not shown], or age-restricted (e.g., younger than 65 years: ≤65). Different shapes reflect different research groups. Other abbreviations: F_D = full cohort comparison excluding persons not providing duration information; I_P = maximum intensity in persons with a high probability of exposure compared to controls; M = males; F = females; all = overall (full cohort comparisons).

Neurobehavioral tests

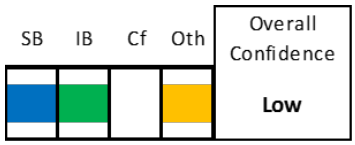
A series of epidemiology studies examined neurobehavior in histology technicians using standardized test batteries designed to assess higher brain functions (Kilburn and Warshaw, 1992; Kilburn et al., 1989; Kilburn et al., 1987) (see Table 1–44). It is important to note that the majority of formaldehyde exposure in this occupation is from formalin (containing methanol), which introduced bias due to confounding of unknown magnitude and thus reduced the reliability of the results for interpreting the effects of formaldehyde exposure. All of these studies were ultimately considered to be of *low* confidence during study evaluation. Decreased performance in multiple tests of memory and tests of dexterity, balance, coordination, motor control, and reaction time was observed with increased daily hours of formaldehyde exposure (Kilburn et al., 1989; Kilburn et al., 1987). Although these workers were also exposed to solvents that can affect behavior (e.g., xylene), hours of daily exposure to solvents was only correlated with decreased performance in a single memory test (Kilburn et al., 1989; Kilburn et al., 1987). The effects of formaldehyde exposure on neurobehavior were not verified when a comparable test battery was performed in a slightly larger (350 versus 305 technicians), but possibly overlapping, study (Kilburn and Warshaw, 1992). In addition, a smaller group (n = 19) tested yearly over a 4-year period did not experience worsening effects with continued work exposure, but this analysis did not specifically address formaldehyde exposure (Kilburn and Warshaw, 1992). These latter results suggest a lack of worsening effects with cumulative exposure, but they did not incorporate a consideration of the relative magnitude of exposure (e.g., hours of daily exposure to formaldehyde).

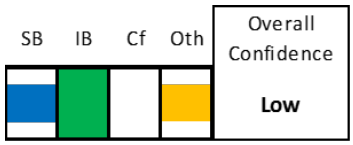
Three acute, controlled exposure studies evaluated performance in standardized neurobehavioral tests (see Table 1–44). Two of these studies included multiple tests assessing concentration, short-term memory, and motor control (Bach et al., 1990; Andersen and Molhave, 1983), while the third focused on decision reaction time (Lang et al., 2008). Although Bach et al. (1990) reported decreased performance in multiple neurobehavioral tests following controlled exposures at ≥0.480 mg/m^3, particularly in workers with previous chronic formaldehyde exposure, the exposure groups were not well matched for a number of variables relevant to test performance, most of the responses were not concentration dependent, and distractibility due to possible irritation cannot be ruled out (irritation measurements were subjective). In contrast to these results, Andersen and Molhave (1983) indicated that they found no effects of exposure on performance in cognitive tests, but the supporting data were not provided. Increased decision reaction times in response to visual, auditory, or combined visual/auditory stimuli were observed with exposure to 0.369 mg/m^3 formaldehyde by Lang et al. (2008); the motor component of the reaction times was unaffected by exposure. These increases were not observed at higher exposure levels and did not exhibit the same dose-response pattern as effects on irritation; thus, additional experiments are needed to better explain the findings.

Taken together, the epidemiological and human-controlled exposure studies provide mixed results suggesting that formaldehyde exposure might be associated with deficits in performance in

neurobehavioral tests related to memory, coordination, and motor control. However, the reliability of these results is unclear and additional experiments are needed to clarify the potential contributions of variables that are known to affect these measures, but which were poorly controlled in these studies, including coexposures to neurotoxicants, irritation, and differences in population characteristics such as age or education.

Table 1-44. Summary of alterations in neurobehavioral tests in relation to formaldehyde exposure in observational epidemiology and controlled exposure studies

Reference and study design	Exposure measures	Results
Observational epidemiology studies		
Reference: Kilburn et al. (1989); Kilburn et al. (1987) (United States) Survey, *n* = 305 female histology technicians attending histology conference in Boston (167 of 658 in 1982, 25.4% or Anaheim (218 of 704, 31%, in 1983. Age 23–78 years, mean 40 years. Work duration, mean 17 years. Seventy-nine female referent laboratory technicians in Los Angeles (participation rate not reported). **Outcome:** Neurobehavioral battery (10 tests) administered in 1 hour by trained personnel. **Analysis:** Multiple regression, formaldehyde (hours) controlling for age, education, smoking, home solvent exposure and number of cover-slipped slides. **Evaluation:**[a]  Potential selection bias (could be influenced by perceived exposure and effects), limited detail presented in results.	Self-reported estimated formaldehyde exposure (average 4.3 hr/d) and xylenes (average 112 cover-slipped slides). Most recent exposures were at least several days prior. Hr formaldehyde/day correlated with number of slides/day, $p < 0.05$. Source of formaldehyde is most likely formalin (containing methanol).	Statistically significant association ($p < 0.05$) between hr/d formaldehyde exposure: Recall memory (stories): One of two tests Visual memory (diagram): One of three tests Associative memory (digit span): One of two tests Dexterity (pegboard): One of one test Balance (sharpened Romberg): One of one test Perceptual motor speed (trail making): One of two tests Age associated with performance decrements in nine tests; solvent exposure (# of slides cover-slipped) associated with one test ($p < 0.05$) No association with formaldehyde observed for choice reaction time, peripheral nerve function, or spatial relation tests.
Reference: Kilburn and Warshaw (1992) (United States) Prospective study; histology technicians attending histology conferences between 1982 and 1987; 19 histology technicians tested yearly across 4 years (46–50 years old); 299 technicians tested 2–3 times across 4 years (44–47.9 years old); 350 histology technicians tested once (38–40.4 years old); sex not reported.	Duration of formaldehyde exposure up to 37 years. Self-rated exposure scales. Source of formaldehyde is most likely formalin (containing methanol).	For single test analysis (*n* = 250), formaldehyde exposure was not associated with age-related change in performance in tests encompassing memory, cognition, pattern recognition, dexterity, decision-making, motor speed, or balance (beta and SE not provided; reported as not statistically significant). No decline seen in smaller group (*n* = 19) tested across 4 years.

Reference and study design	Exposure measures	Results
Outcome: 2−3 h neurobehavioral battery; testers blinded to exposure status. **Analysis:** Multiple regression, adjusting for age. Other variables considered were sex, years of employment, smoking, and nonoccupational exposures. **Evaluation:**[a]  Potential selection bias, limited detail presented in results. Longitudinal analysis limited by sample size and did not specifically address formaldehyde exposure.		
Acute, controlled exposure studies		
Reference: Lang et al. (2008) (Germany) *N* = 21 (of 26 volunteers selected based on screening; five left study), 10 women, 11 men (results were combined), age 19–39 years, healthy nonsmokers. Exposure order randomly assigned; double blinded. Ten 4-hour exposures, one per day, over 10 days. **Outcome**: Reaction times (Vienna Test System) to visual and acoustic stimuli measured before and after exposures. **Evaluation**: *Medium* confidence. Tested immediately after exposure.	Four hours in groups of four. Formaldehyde levels[a]: Clean air, 0.185, 0.369, and 0.615 mg/m^3; additional 0.369 and 0.615 mg/m^3 with peaks up to 1.23 mg/m^3. Additional 0.0, 0.369, and 0.615 mg/m^3 with ethyl acetate introduced as a "mask" for formaldehyde. (Analytical concentrations achieved were measured, but not reported.) Formaldehyde generated from paraformaldehyde; ethyl acetate at 12–16 ppm (irritant threshold of EA reported at 20 ppm, identified from scientific literature).	↑ in decision reaction time upon visual stimulus at 0.3 and 0.3+ethyle acetate (data presented graphically, $p < 0.05$). ↑ in decision reaction time upon acoustic or audio-visual stimulus at 0.3 ppm only (data presented graphically, $p < 0.05$; comparison group for contrast not stated). The motor speed component of the decision reaction time was unaffected by exposure.
Andersen and Molhave (1983) (Denmark) *N* = 16 healthy students, age 30–33, 68.8% male, 31.2% smokers, groups of four over 4 days. Exposure order determined by Latin square design, blinding not indicated. **Outcome**: Numerical addition: tested 3×/d (once in clean air; twice during exposure); multiplication: tested 1×/d during exposure; card punching: tested 2×/d (once in clean air; once during exposure). **Evaluation**: *Low* confidence. Tested during exposure; results not reported.	Five hours; 0.3, 0.5, 1.0, and 2.0 mg/m^3 (analytical concentrations achieved were not reported: indicated as within 20% of target concentrations). Formaldehyde generation via thermal depolymerization of paraformaldehyde, dynamic chamber.	The study authors reported no change in performance in addition (speed and accuracy), multiplication, or transfer of numbers to punch cards, but data were not provided.
Reference: Bach et al. (1990) (Denmark) 32 with occupational exposure to formaldehyde (>5yr); age 18−64 years;	Formaldehyde concentrations 0, 0.15, 0.4, and 1.2 mg/m^3 [analytical concentrations achieved: 0.04, 0.21, 0.48, and 1.10 mg/m^3].	Occupational group showed significantly ↓ performance on the digit symbol test ($p < 0.025$ for pooled exposure groups, 0, 0.15, and 0.4 compared to 1.2

Reference and study design	Exposure measures	Results
selected from 108 workers (recruitment and selection not described). Referent group (n = 29 from 546 selected randomly from a population registry); attempted frequency matching by average age, education, and smoking prevalence but workers had higher smoking prevalence and lower education (detailed demographic data not reported). Formaldehyde-exposed excluded from referent group. Exposure order by balanced Latin square design; double blinded—Furfuryl mercaptan (coffee aroma) used to mask odor. **Outcome:** Four performance tests twice during exposure. **Evaluation:** *Low* confidence. Education and smoking imbalance in workers and referents; tested during acute exposure.	5.5 hr (0.5 hr pre-exposure in chamber and gradual increase in formaldehyde). Formaldehyde vapor generation not reported; however, assumed to be from depolymerization of paraformaldehyde based on protocols used in the same exposure chamber as reported by a coauthor (Andersen and Molhave, 1983).	mg/m^3); controls showed an inverse relationship; digit span (p < 0.025) for total digit sum in one of the six test components—lowest scores in 0.4 mg/m^3 group, and graphic continuous line test (p < 0.05 only for the 0.4 mg/m^3 group); effects were not dose-related. Addition test: Dose-related performance decrements (↓ # of additions and ↑ reaction time). Data were presented graphically. Matching was not completely successful; due to last-minute substitutions, the exposed workers, particularly the 1.2 mg/m^3 group, had a lower education and different proportion of smokers; the 1.2 mg/m^3 group had a lower average age and fewer smokers overall. Exposure groups were not comparable.

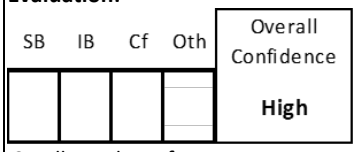
[a]Evaluation of sources of bias or study limitations (see details in Appendix A.5.7). SB = selection bias; IB = information bias; Cf = confounding; Oth = other feature of design or analysis. Extent of column shading reflects degree of limitation. Direction of anticipated bias indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact would be likely to be away from the null (i.e., spurious or inflated effect estimate).
Results from *low* confidence studies are shaded; these findings are considered less reliable.
[b]Formaldehyde levels in the study converted to mg/m^3 from ppm.

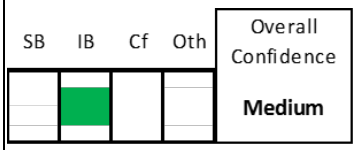
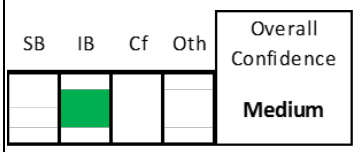
Nervous system disease

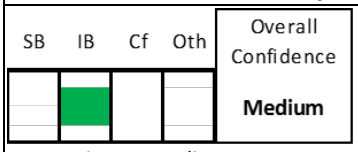
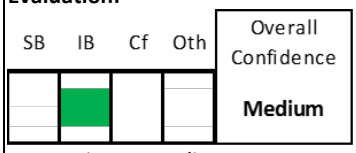
In a large and well-designed, prospective study of risk factors associated with amyotrophic lateral sclerosis (ALS) mortality, years of self-reported exposure to formaldehyde was associated with a 2.5–fold (95% CI 1.58, 3.86) increased mortality risk when examined across individuals reporting duration data (this information was available for 22 of the 36 cases reporting formaldehyde exposure) (Weisskopf et al., 2009) (see Table 1–45). The overall risk was no longer significantly elevated when individuals who reported exposure but did not report duration were included in the analysis (all 36 cases; RR = 1.34; 95% CI 0.93,1.92). Risk increased with increasing duration of formaldehyde exposure, with a fourfold risk seen with >10 years of exposure (13 cases). In total, Weisskopf et al. (2009) followed 987,229 people and identified 1,156 ALS deaths (1,120 of these cases reported that they were not exposed to formaldehyde), but formaldehyde intensity was not assessed, and the duration of exposure was self-reported. A second study from the same research group also identified some evidence of an association between formaldehyde exposure and ALS death in a national study (Roberts et al., 2015). An odds ratio (OR) of 4.43 was observed among individuals with a high probability, high intensity exposure, based on only two cases of ALS; no cases were observed among individuals with high probability, medium intensity exposure. Formaldehyde exposure assignments were made by industrial hygienists using a job-exposure

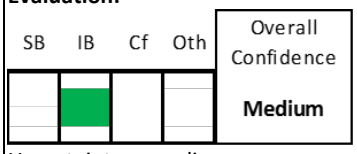
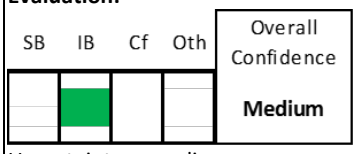
matrix with estimates of intensity and probability of exposure for the most recent job held by participants, although duration was not assessed. More recently, two registry-based studies in Sweden and Denmark observed associations of similar magnitude between ALS diagnosis and occupational formaldehyde exposure analyzing all incident ALS cases occuring over a 20- to almost 30-year period. Both studies used a job-exposure matrix developed for the Nordic Occupational Cancer Study (NOCCA) with exposure data specific to each country. The Swedish study observed no association in the entire analytic group of blue-collar workers and farmers, however an odds ratio of 1.28 (95% CI 1.02, 1.61) was observed when the analysis was restricted to persons younger than 65 years of age (Peters et al., 2017). In Denmark, occupational exposure to formaldehyde was associated with ALS incidence in the entire cohort (RR 1.3, 95% CI 1.2, 1.4) and associations of the same magnitude were observed across all exposure quartiles in comparison to nonexposed (Seals et al., 2017). Hence neither study observed an (exposure-response trend. Also, the potential effect of confounding by smoking on the formaldehyde—ALS association (Wang et al., 2011; Armon, 2009) was not addressed. Paradoxically, the direction of the association was reversed when investigators used a machine learning method to select joint predictors and interaction terms and then included these health and chemical risk factors for ALS in the model (Bellavia et al., 2021). An OR of similar magnitude but less precise than that reported by Peters et al. (2017) (OR = 1.3; 95% CI 0.5, 3.2) was observed for participants with a high probability of exposure in a small case-control study, although no association with exposure duration was observed (Fang et al., 2009). Although the longitudinal design of the prospective studies makes it unlikely that the association between formaldehyde exposure and ALS death is attributable to some types of bias, a study with detailed evaluations of formaldehyde exposure (probability, frequency) and duration of exposure in the exposed populations failed to confirm an association (Pinkerton et al., 2013). Exposure in the cohort of garment workers (Pinkerton et al., 2013), in particular, was more certain, based on monitoring data in the 1980s, year of hire, and years of employment. However, all of the studies, except Peters et al. (2017) and Seals et al. (2017) were limited by small numbers of exposed cases, which leads to decreased sensitivity to detect an association that might exist, or decreased stability in effect estimates. Overall, evidence is emerging that formaldehyde exposure may pose a hazard for ALS, but there is a large degree of uncertainty due to the mixed nature of the findings. As risk factors for increased risk of ALS are complex and poorly defined, it remains possible that the findings of Weisskopf et al. (2009), and the less robust but supportive findings by Roberts et al. (2015), Peters et al. (2017) and Seals et al. (2017), identify a true risk of formaldehyde exposure. However, additional research designed to address the identified limitations would help to clarify these study results.

Table 1-45. Summary of human studies of nervous system disease risk in relation to formaldehyde exposure

Reference and study design	Exposure measures	Results
Observational epidemiology studies		
Reference: Pinkerton et al. (2013) (United States) Prospective cohort, 11,098 garment workers (82% women) exposed to formaldehyde-treated fabric for ≥3 mo. (late 1950s to early 1980s). **Outcome:** Vital status through 2008, underlying cause of death, ICD-10 G12.2, ICD-9 335.2, ICD-8 348.0 and ICD-7 356.1. **Analysis:** Life-table analysis based on U.S. population, excluded missing birth date (*n* = 55), deaths (*n* = 8), lost to follow-up prior to date file begin date (*n* = 13); SMRs and 95% CI, adjusted for age, calendar time, sex, race; no information on smoking. **Evaluation:**[a]  Small number of cases.	Monitoring in 1980s, geometric mean 0.15 ppm (GSD 1.9 ppm), constant levels across departments and facilities, year of first exposure (42% before 1963), time since first exposure (median 39.4 years) and exposure duration (median 3.3 years); no other exposures associated with ALS.	**Amytrophic lateral sclerosis mortality** *N* = 11,022, 414,313 person-years at risk; eight ALS deaths; mortality for COPD and lung cancer in cohort was similar or greater than national rates (Meyers et al., 2013) indicating that possible confounding by smoking would be in direction away from the null, not a concern for these null results. All eight deaths were recorded due to ALS in death certificates. Deaths / SMR (95% CI): Overall: 8 / 0.89 (0.38, 1.75) Yr of 1st exposure Before 1963: 5 / 0.84 (0.27, 1.96) 1963–70: 3 / 1.29 (0.27, 3.78) ≥1973: 0 / 0.00 (0.00, 4.92) Duration <3 yr: 2 / 0.61 (0.07, 2.21) 3–9 yr: 3 / 1.17 (0.24, 3.41) 10+ yr: 3 / 0.94 (0.19, 2.75) TSFE[a] <10 yr: 1 / 3.50 (0.09, 19.52) 10–19 yr: 0 / 0.00 (0.00, 4.19) 20+ yr: 7 / 0.89 (0.36, 1.83) [a]TSFE: time since first exposure
Reference: Bellavia et al. (2021) (Denmark) Population-based case-control Cancer cases, 1982-2009, from Seals et al. (2017) with complete data for several health factors and environmental risk factors previously linked with ALS (N = 1086). Controls, 100 per case matched on being alive on index date for case diagnosis, same birth year and sex (N = 111,507). Excluded individuals with less than 5 years work experience. **Outcome:** see Seals et al. (2017) **Analysis:** Selected joint predictors and interactions using boosted regression trees and Logic regression, which were included in a logistic regression model adjusting for age, SES, and geography. Model used a 3-year lag. Evaluated diabetes, obesity, physical/ stress trauma, CVD (1977-2009) and lead, diesel exhaust and solvents. **Evaluation:**[a]	see Seals et al. (2017) Formaldehyde exposure metric was ever/never exposed. Anticipate exposure misclassification and large variation in prevalence and intensity of exposure across individuals. In men, correlations between formaldehyde, diesel exhaust and solvents were 0.22 and 0.41, respectively (Phi coefficients)	**Amytrophic lateral sclerosis** Ever formaldehyde Exposed / Controls N (%) / Cases N (%) / OR (95% CI) Men: 43,760 (0.64) / 422 (0.63) / 0.87 (0.73, 1.04) Women: 28.100 (0.65) / 255 (0.61) / 0.86 (0.84,0.89) Logistic regression mutually adjusting for age, SES, and geography, diesel exhaust (male), solvents, trauma, CVD, diesel*CVD (male), solvents*trauma (male), diesel*trauma (male), and diesel*solvents (male), lead (female), lead*solvents (female) and trauma*formaldehyde (female).

Reference and study design	Exposure measures	Results
 Uncertainty regarding exposure assessment; adequacy of 3-year lag is unknown		
Reference: Seals et al. (2017) (Denmark) Population-based case-control study, Registry-based case identification using the Danish National Patient Register, 1982-2009 (3650 incident cases). Controls obtained from Central Person Registry (All Denmark residents since 1968), 4 per case matched on sex, age, and no ALS diagnosis in Hospital Register as of date of diagnosis for matched case (index date). **Outcome:** Cases identified from Danish National Patient Register, discharge diagnosis ICD-8 348.0 or ICD-10 G12.2. Case definition was 1st diagnoses on or after 1/1/1982–12/31/2009. **Analysis:** Conditional logistic regression adjusted for age, sex, index date, SES, marital status and residence. No information on smoking status. **Evaluation:**[a]  Uncertainty regarding exposure assessment; adequacy of 3-year lag is unknown	Occupational histories obtained from Danish Pension Fund databases. Used NOCCA (Nordic Occupational Cancer Study)- Danish JEM for periods 1960-74, 1975-84, and 1985 and after. Inputs year and industry code and outputs prevalence of exposure for each job along with expected exposure level (ppm) in exposed. The JEM has not been validated to estimate levels. Cumulative expected exposure calculated (prevalence multiplied by expected level) summed over jobs and time (3- and 5-year lags). Exposure misclassification expected due to variation of tasks within industries.	**Amytrophic lateral sclerosis** Exposure — Controls N (%) — Cases N (%) — RR (95% CI) None — 10,934 (75) — 2582 (71) — 1.0 (ref) Ever — 3666 (25) — 1068 (29) — 1.3 (1.2, 1.4) Quartiles (mg/m^3) <0.016 — 935 (6.4) — 262 (7.2) — 1.3 (1.1, 1.5) 0.016-0.1 — 976 (6.7) — 272 (7.5) — 1.2 (1.1, 1.4) 0.1- 0.34 — 873 (6.0) — 268 (7.3) — 1.4 (1.2, 1.6) >0.34 — 882 (6.0) — 266 (7.3) — 1.3 (1.1, 1.5)
Reference: Peters et al. (2017) (Sweden) Nested case-control study, 5,020 patients diagnosed with ALS between 1991 and 2010 and 25,100 Swedish controls (5 per ALS case) matched by birth year and sex, alive on case's date of diagnosis; source population born 1901−1970 and included in the 1990 Swedish Population and Household Census (includes persons living in Sweden for ≥1 year). **Outcome:** Cases identified from National Patient Register (primary or secondary diagnosis) through 2010 (ICD-9 335C; ICD-10 G12.2). **Analysis:** Conditional logistic regression with adjustment for education and other 11 exposures examined; restricted to individuals with at least one occupation registered in any of the censuses, occupations listed in censuses 10 years before diagnosis, and either blue collar workers or farmers (2,647 cases, 13,378 controls). **Evaluation:**[a]	Individual occupational histories obtained from 1970, 1980, and 1990 censuses; Swedish version of Nordic Occupational Cancer Study JEM (industrial hygienist estimates of prevalence and level of specific exposures at specific calendar times). Dose-response: exposure metric calculated: prevalence multiplied by annual mean level of exposure in a specific occupation at the time of a census, averaged over all three censuses, dichotomized at mean level in controls.	**Amytrophic lateral sclerosis** Cases — Control — OR (95% Ci) Restricted analytic sample (2,647 cases) All — 323 — 1,579 — 1.07 (0.92–1.25) Exposure metric (mg/m^3) Not exposed — 659 — 3,341 — 1.0 (Reference) ≤0.013 — 30 — 185 — 0.89 (0.58–1.36) ≥0.013 — 53 — 210 — 1.31 (0.86–1.99) Restricted to individuals <65 years old at diagnosis (1,014 cases) All — 140 — 576 — 1.28 (1.02–1.61)

Reference and study design	Exposure measures	Results
 Uncertainty regarding exposure assessment.		
Reference: Roberts et al. (2015) (United States) Prospective cohort, 1,469,235 occupational workers (46% women); National Longitudinal Mortality Study (NLMS) restricted to age 25+ at initial survey. Participants provided follow-up from survey until 2011 or death. **Outcome:** NLMS records matched to the National Death Index (1979–2011) with underlying cause of death as ALS: ICD-10 G12.2 or ICD-9 335.2. **Analysis:** HRs estimated for each exposure level using survival analyses with age as the time variable, separate models for men and women, adjusted for education, race/ethnicity, and income. **Evaluation:**[a]  Uncertainty regarding exposure assessment, including the influence of duration, particularly in light of the use of a one-time survey at enrollment; very small number of exposed cases (*n* = 2 in jobs with high probability and intensity of formaldehyde exposure). Note: same laboratory, data handling, and analysis methods as Weisskopf et al. (2009).	Exposure matrix by industrial hygienists at the National Cancer Institute (see Wang et al., 2009) was constructed based on participant survey at enrollment regarding their last or most recent job; no information or adjustments for other potential exposures.	**Amytrophic lateral sclerosis mortality** *N* = 757 total ALS deaths (472 deaths in men, with 100 exposed cases and 12,930,240 total person-years in men). Duration not evaluated. No information on mortality from smoking-related disease or smoking in the general cohort. Deaths matched to ALS in death certificates. No increased risk of ALS in women (data not shown): authors attribute this to occupation role. *ALS deaths in men* Deaths — HR (95% CI) Intensity Unexposed: 372 — 1.0 (Reference) Low: 55 — 0.99 (0.74, 1.30) Medium: 43 — 0.63 (0.44, 0.90) High: 2 — 1.53 (0.4, 5.80) Intensity, restricted to probability = high Unexposed: 372 — 1.0 (Referent) Low: 0 — - Medium: 0 — - High: 2 — 4.43 (1.16, 16.85) Probability Unexposed: 372 — 1.0 (Reference) Low: 51 — 0.85 (0.63, 1.15) Medium: 47 — 0.76 (0.54, 1.06) High: 2 — 2.98 (0.78, 11.30) Probability, follow-up to age 75 only Unexposed: 332 — 1.0 (Reference) Low: 41 — 0.79 (0.57, 1.11) Medium: 40 — 0.66 (0.44, 0.99) High: 2 — 4.13 (1.09, 15.69) Probability, aged 50–75 at enrollment Unexposed: 197 — 1.0 (Reference) Low: 31 — 1.00 (0.67, 1.49) Medium: 27 — 0.75 (0.47, 1.19) High: 2 — 4.76 (1.16, 19.49) Probability analyses excluding the first 5 years of follow-up or restricted to men aged 35–75 at enrollment, or to those employed at enrollment, are not shown (results were similar to the overall probability analysis).
Reference: Fang et al. (2009) (United States) Case-control study, 111 cases and 256 controls; sequential ALS cases recruited, 1993−1996, from two major referral centers; cases and controls lived in New England at least 50% of year, mentally competent, English speakers; 71%	Occupational history by structured questionnaire; industry, occupation, frequency, and duration; jobs held before ALS diagnosis or 2 years before	**Amytrophic lateral sclerosis** Association of ALS risk with occupational formaldehyde exposure (109 cases, 253 controls) Controls — Cases — OR (95% CI) Never[a]: 204 — 89 — Ref.

Reference and study design	Exposure measures	Results
of eligible cases participated; controls by random telephone screening, frequency matched on sex, age (three groups), and region, 76% of eligible (256 of 270 completed questionnaires). **Outcome:** Diagnoses by board-certified specialists in motor neuron disease using World Federation of Neurology El Escorial criteria (Brooks, 1994). **Analysis:** Unconditional logistic regression models; tested linear trend with lifetime exposure days, probability, and weighted exposure duration (four categories); adjusted for age, sex, area of residence, smoking (ever/never), and education. **Evaluation:** [a]  Uncertainty regarding exposure assessment; small number of exposed cases.	interview (controls); formaldehyde-exposed occupations identified a priori by industrial hygienist; calculated life-time hours of exposure to formaldehyde weighted by probability of exposure in specific jobs.	Ever 49 20 0.8 (0.5, 1.5) Exposure Probability[b] 0–1 7 2 0.6 (0.1, 2.8) 1 27 9 0.7 (0.3, 1.6) 2 15 9 1.3 (0.5, 3.2) *Trend p-value* 0.50 Weighted exposure duration (hr)[c] ≤10,000 14 7 1.1 (0.4, 2.8) 10,001–40,000 19 8 0.8 (0.3, 1.9) >40,000 16 5 0.7 (0.2, 2.0) *Trend p-value* 0.45 >60,000[d] 4 4 3.0 (0.7, 12.9) [a]Referent was group with no previous. occupational exposure to formaldehyde [b]Highest probability ever experienced. [c]Weights were 0.5, 1, and 2 for probabilities 0–1, 1, and 2. [d]Additional analysis.
Reference: Weisskopf et al. (2009) (United States) Prospective cohort, 987,229 men and women. American Cancer Society Cancer Prevention Study II. No major illness at baseline in 1982. Follow-up from 1989 through 2004. **Outcome:** Cause of death obtained for >98% of known deaths; underlying or contributing cause. ICD-9 (1989–1998) code 335.3; ICD-10 (1999–2004) code G12.2 (ALS represents >98% of these categories). **Analysis:** Cox proportional hazards modeling, adjusted for age, sex, smoking, military service, education, alcohol, occupation (farmer, lab technician, machine assembler, programmer), vitamin E use, and the other chemical (and X-rays) exposures assessed at baseline. **Evaluation:**[a]  Uncertainty regarding exposure assessment.	Self-report (at baseline, 1982) of current or past regular exposure to formaldehyde (and duration); data on 10 other types of chemicals and X-ray exposure also collected. Source(s) of formaldehyde exposure were not defined; likely to be occupational settings.	**Amytrophic lateral sclerosis mortality** 1,156 ALS deaths; mortality rate 11.3 and 6.7 per 100,000 person-years in men and women, respectively. N cases exposed / RR / (95% CI) Full cohort 36 1.34 (0.93, 1.92) With duration[a] 22 2.47 (1.58, 3.86) <4 years 4 1.5 (0.7, 4.2) 4–10 5 2.1 (0.9, 5.4) >10 13 4.1 (2.2, 7) CIs estimated from graph RR between other exposures and ALS ranged from 0.68 to 1.44. [a]"With duration" indicates the subset of the full cohort after excluding individuals not providing duration information.

[a]Evaluation of sources of bias or study limitations (see details in Appendix A.5.7). SB = selection bias; IB = information bias; Cf = confounding; Oth = other feature of design or analysis. Extent of column shading reflects degree of limitation. Direction of anticipated bias indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact would be likely to be away from the null (i.e., spurious or inflated effect estimate).
Results from *low* confidence studies are shaded; these findings are considered less reliable.

Abbreviations: ALS = amyotrophic lateral sclerosis; COPD = chronic obstructive pulmonary disease; GSD = geometric standard deviation; CI = confidence interval; SMR = standardized mortality ratio.

Nervous System Effects in Animal Studies

Numerous experimental animal studies report findings of neurobehavioral and structural alterations following formaldehyde inhalation. This section discusses these studies according to the type of evaluation(s) performed, specifically by studies of neuropathology (see Table 1-46), studies examining potential sensitization of the nervous system (see Table 1-47), tests of general motor-related behaviors (see Table 1-48), and tests of learning and memory (see Table 1-49). The evidence tables are organized by study confidence and the first author's last name.

As discussed below, much of the available data are difficult to interpret due to potential coexposures (e.g., methanol), possible mischaracterization of irritation-related behaviors as central nervous system- (CNS)-mediated effects, unreported or inadequate study design methods, and unclear dose-response relationships. The neurobehavioral effects reported following formaldehyde inhalation include changes in assays testing motor function, anxiety, habituation, learning and memory, and chemical sensitization in adult animals (LICM, 2008; Malek et al., 2004; Sorg et al., 2004; Malek et al., 2003a, b, c; Usanmaz et al., 2002; Sorg et al., 2001b; Pitten et al., 2000; Sorg and Hochstatter, 1999; Sorg et al., 1998; Boja et al., 1985). Nociception was unaffected in one study (Sorg et al., 1998). Several studies also indicate neuropathology or behavioral effects following developmental formaldehyde exposure (Sarsilmaz et al., 2007; Aslan et al., 2006; Songur et al., 2003; Sheveleva, 1971); no corresponding information in human studies is available for children.

In addition to these studies evaluating specific effects on the nervous system, one subchronic study (Woutersen et al., 1987) and three chronic studies (Appelman et al., 1988; Tobe et al., 1985; Kerns et al., 1983) designed to assess the general toxicity or carcinogenicity of formaldehyde reported general behavioral effects (e.g., uncoordinated locomotion) following exposure to high levels of formaldehyde (>12 mg/m^3). In these studies, no overt changes in absolute brain weight, brain histopathology, or performance in simple tests of nervous system function were observed (data not shown). These general toxicity and carcinogenicity studies were not specifically designed to assess nervous system function and did not report many of the relevant procedural details or, in most cases, the specific quantitative results. Thus, a confidence rating was not assigned to these experiments and they are not discussed further. Aside from these cursory examinations and one subchronic experiment with brief, 10-minute, daily formaldehyde exposures (Pitten et al., 2000), the remaining animal studies of the potential for nervous system effects due to formaldehyde inhalation relied on exposures of acute or short-term duration; extrapolation of these effects to long-term exposure scenarios is difficult. Figure 1–29 presents all of the *medium* or *low* confidence experimental animal studies identified (no *high* confidence studies were identified), whereas the data from the *medium* confidence animal studies are summarized in greater detail in Figure 1–30.

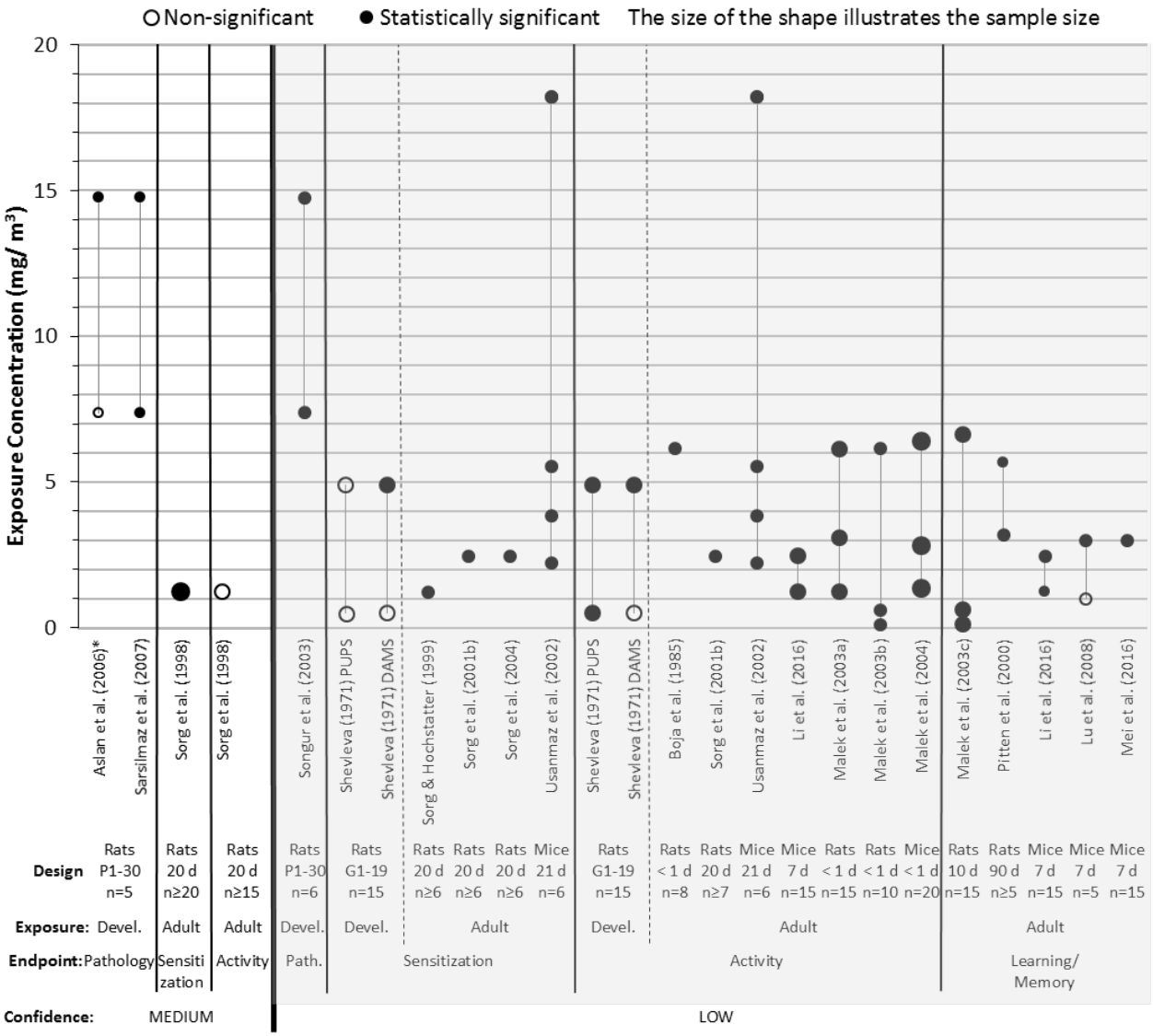


Figure 1-29. Nervous system effects in animal studies.

As no *high* confidence experimental animal studies were identified, the available studies are organized by *medium* and *low* confidence study evaluation interpretations (see Appendix A.5.7), then by endpoint, then by timing of exposure (i.e., developmental [devel.] or adult). Filled symbols indicate statistically significant effects, and the size of the points reflecting the sample size for that formaldehyde exposure group (larger size = larger *n*). The *low* confidence experiments are shown on a gray background, as the identified study limitations substantially reduce confidence in the reliability of the results; these *low* confidence experiments contribute very little to the weight of evidence for nervous system effects. Note: "Activity" refers to motor-related behaviors (e.g., open field activity). *The studies by Aslan et al. (2006) and Sarsilmaz et al. (2007) report data from the same cohort of exposed rats.

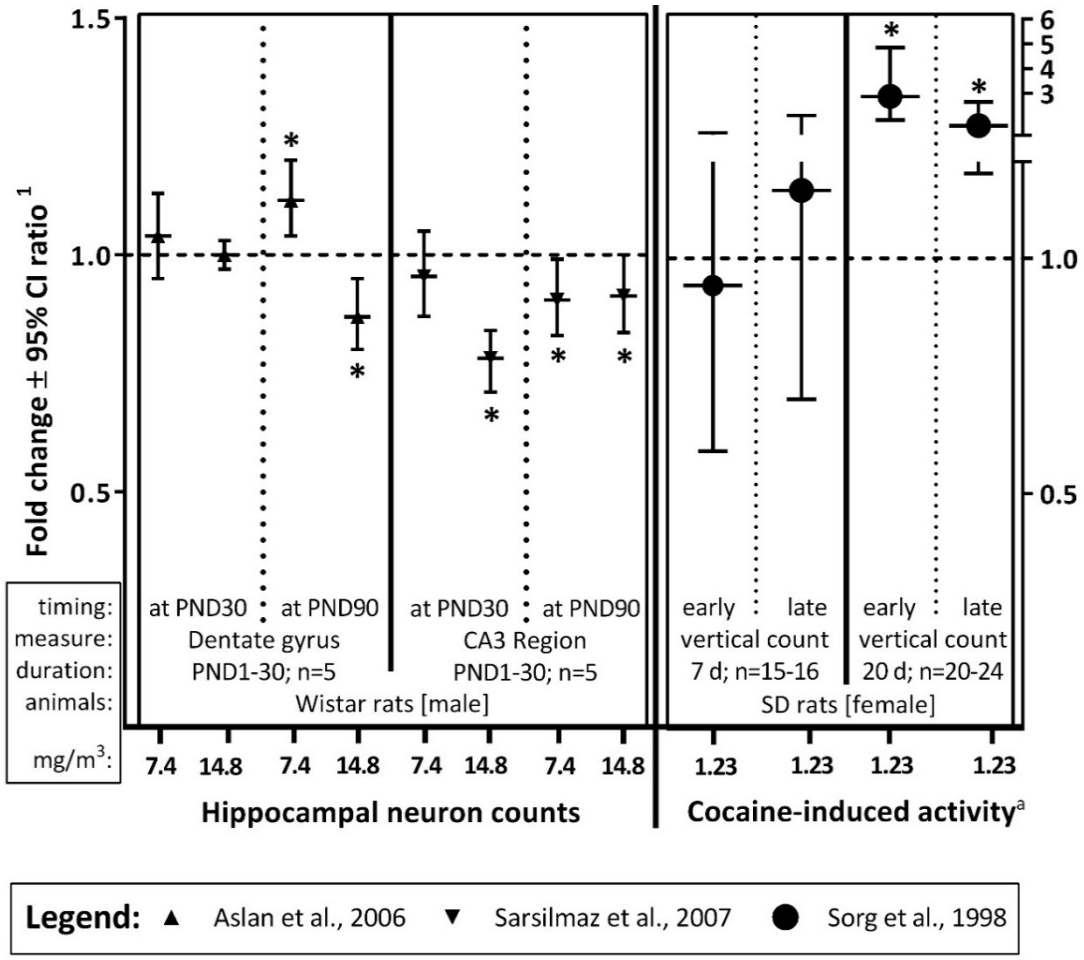


Figure 1-30. *Medium* confidence animal studies of nervous system effects.

The evidence for nervous system effects reported in *medium* or *high* confidence experimental animal studies is arrayed (note: no *high* confidence studies were identified). Two studies examined developmental neuropathology using stereological methods after postnatal exposure to 7.4–14.8 mg/m^3 formaldehyde in a single cohort of rats (Sarsilmaz et al., 2007; Aslan et al., 2006), while a third study evaluated sensitization-type responses in adult rats at 1.23 mg/m^3 (Sorg et al., 1998). [1]Results are displayed as fold change from control animals (control responses at 1 are illustrated as a dashed line), with variability in both the controls and treatment groups represented by the quotient (ratio) of the 95% CI, as calculated based on the method described by E.C. Fieller (Cox and Ruhl, 1966), which assumes Gaussian distributions. [a]Changes in vertical activity induced by stimulation with cocaine exposure following formaldehyde inhalation for 7 or 20 days and several days ("early") or several weeks ("late") of nonexposure are shown; the authors did not observe any changes in cocaine-induced horizontal activity (not shown). *$p < 0.05$, as reported by study authors. Note: all results were estimated from data presented graphically using Grab It!™, Datatrend Software.

Neuropathology

Several studies examined the effects of formaldehyde inhalation on brain neuropathology. Evidence of changes in brain structure and neuron number following developmental exposure to ≥7.38 mg/m^3 formaldehyde has been described in three publications from one laboratory

(Sarsilmaz et al., 2007; Aslan et al., 2006; Songur et al., 2003) (see Table 1–46). Two of these studies (Sarsilmaz et al., 2007; Aslan et al., 2006) were evaluations of the same cohort of animals. No overt changes in CNS pathology have been reported following subchronic or chronic formaldehyde exposures in adult rats at concentrations ranging from 0.369 to 18.5 mg/m^3 (Pitten et al., 2000; Appelman et al., 1988; Tobe et al., 1985; Kerns et al., 1983), although the methods employed in the adult animal studies were far less sensitive than those used by Sarsilmaz et al. (2007) and Aslan et al. (2006).

Neuropathological alterations were evident in male rats following exposure to 7.38 or 14.8 mg/m^3 formaldehyde from postnatal day (PND) 1 to PND 30. Specifically, in the cornu ammonis (CA) region of the hippocampus, a 4% (at 7.38 mg/m^3) or 22% (at 14.8 mg/m^3; statistically significant) decrease in the number of neurons in the pyramidal cell layer was observed at PND 30, and statistically significant, 8–9%, decreases were still observable at both concentrations at PND 90 (Sarsilmaz et al., 2007). Although the morphology of the cell nuclei determined by cresyl violet staining was indicated as normal in all regions of the hippocampus at PNDs 30 and 90 in Sarsilmaz et al. (2007) and Aslan et al. (2006), these decreased cell counts were consistent with separate observations of robust increases (59–322%) in the number of pyknotic (i.e., dying) CA neurons at PNDs 30 and 60 in Songur et al. (2003). A decrease in cell number is considered an adverse effect and a specific indicator of toxicity. The decreased magnitude of neuronal loss at PND 90 as compared to PND 30 (Sarsilmaz et al., 2007), along with a separate observation that pyknotic CA neuron counts were no longer elevated at PND90 (Songur et al., 2003), suggest some measure of recovery or adaptation 60 days after exposures were terminated. Notably, hippocampal cell number exhibits a natural decrease between PNDs 30 and 90, as demonstrated by Sarsilmaz et al. (2007) and Aslan et al. (2006).

Changes in the hippocampal dentate gyrus (DG) cell number and in volumetric measures were less clear. A significant increase in DG volume was observed at ≥7.36 mg/m^3 formaldehyde at PND 30, without any accompanying changes in cell number (Aslan et al., 2006). The authors attributed this finding to possible formaldehyde-triggered inflammation during postnatal growth of the DG, which continues until ~PND 28; however, this hypothesis was not evaluated by immunostaining. At PND 90, although DG cell number was decreased at 14.8 mg/m^3, DG volume and cell number were elevated at 7.36 mg/m^3. In contrast to decreases in cell number, an increase in cell number is not necessarily adverse. Although CA cell counts were decreased, the volume of the pyramidal cell layer on PND 30 was increased at 7.38 mg/m^3 but decreased at 14.8 mg/m^3; neither exposure group was significantly different from controls on PND 90. Changes in brain hemisphere volume [decreased at PND 30 and increased at PND 90; (Sarsilmaz et al., 2007)] suggest formaldehyde-induced structural changes or inflammation in nonhippocampal regions, or altered ventricular parameters, as the changes were not consistent with volume changes in the DG or CA regions. Volume changes can provide nonspecific measures of neural health. Although these changes are sometimes associated with regional atrophy and degeneration, they are also sensitive

to variations such as changes in neuron size or changes in the size or number of nonneuronal cells. Thus, decreased cell number is a more specific indicator of toxicity.

Exposure from PND 1 to PND 30 covers a sensitive window of hippocampal development, as a large percentage of hippocampal neurons, particularly in the DG, are generated or mature (e.g., establish permanent connections) during the early postnatal period. In addition, the stereological methods used by Aslan et al. (2006) and Sarsilmaz et al. (2007) are extremely sensitive and unbiased by design (e.g., sampling is random and systematic). These methods were not applied in any other studies, highlighting a key uncertainty in the database. The specific exposure window or methods employed could explain the general lack of overt neuropathological effects in rats exposed as adults. Importantly, these developmental studies did not appear to evaluate possible effects on nursing dams (i.e., dam health and behavior), who appear to have been exposed along with the pups from PND 1 to PND 14. It is plausible that the high-level exposures could lead to nutritional changes that influence measures of structural brain development. Pup health, which was affected at PND 30 (i.e., decreased body weight) but not PND 90 in the study by Songur et al. (2003), was not reported in the other two studies. However, CA neuron loss was still evident at PND 90 when no body-weight differences were evident (Songur et al., 2003). An additional significant limitation of these studies is that the sample size is very small considering that the analyses were performed on a pup basis rather than a litter basis, as would be preferred. Specifically, although 5–6 pups/group were analyzed, because litter effects may influence these measures, the data are better evaluated as representing only $N = 3$ litters (the authors indicate two pups were assessed from each of the three litters). Litter data were not available to determine whether such analyses would result in a greater or lesser magnitude of response, further complicating interpretation.

Complete recovery of the observed neuropathology following developmental exposure was not observed. Partial recovery was apparent, but examinations did not continue long enough to detect whether or when the observed pathology completely resolves. This supports the possibility that formaldehyde may cause long-lasting or permanent neuroanatomical changes in the brain following early-life exposure, which would substantiate characterizing it as a nervous system hazard according to Agency guidelines (U.S. EPA, 1998). However, these stereological data reflect a single cohort of exposed animals, and the study deficiencies described above limit the ability to attribute the results to formaldehyde exposure alone. In addition, the limited data supporting these effects were derived from studies only testing high-level formaldehyde exposure (i.e., well above levels demonstrated to affect the respiratory system; see Sections 1.2.1–1.2.4), introducing additional uncertainties. Thus, the potential for developmental neuropathology remains a significant concern, and this represents an area in need of further research.

Table 1-46. Developmental neuropathology in experimental animal studies

Reference and study design	Results (percentage change from control) and exposure levels
Medium confidence	
Reference: Aslan et al. (2006) Rat (Wistar); *N* = 3 litters (5 male pups) 0, 7.38, or 14.8 mg/m^3[a]PND 1–PND 30 Test article: paraformaldehyde **Main limitations**: Small sample size; potential for litter effects; note: same cohort as Sarsilmaz et al. (2007).[b]	**(Importantly, all data were analyzed on a pup basis rather than on a litter basis.)** **0 7.38 14.8 0 7.38 14.8** *Total DG cell number assessed by stereology:* at PND 30: 0 3 0% at PND 90: 0 10* −12%* Note: DG cell morphology was normal at PND 30 and PND 90. *Volume of the DG assessed by stereology:* at PND 30: 0 9* 8%* at PND 90: 0 13* −1%
Reference: Sarsilmaz et al. (2007) Rat (Wistar); *N* = 3 litters (5 male pups[b]) 0, 7.38, or 14.8 mg/m^3[a] PND 1–PND 30 Test article: paraformaldehyde **Main limitations**: Small sample size; potential for litter effects; note: same cohort as Aslan et al. (2006)[b].	**(Importantly, all data were analyzed on a pup basis rather than on a litter basis.)** **0 7.38 14.8 0 7.38 14.8** *Total CA cell number assessed by stereology:* at PND 30: 0 −4[c] −22%* at PND 90: 0 −9* −8%* Note: CA cell morphology was normal at PND 30 and PND 90 *CA volume assessed by stereology:* at PND 30: 0 15* −28%* at PND 90: 0 −7 10% *Hemisphere volume assessed by stereology:* at PND 30: 0 −3* −7%* at PND 90: 0 24* 5%*
Low confidence	
Reference: Songur et al. (2003) Rat (Wistar); *N* = 3 litters (6 male pups) 0, 7.38, or 14.8 mg/m^3[a] PND 1–PND 30 Test article: paraformaldehyde **Main limitations**: Small sample size; potential for sampling bias and litter effects.	**(Importantly, all data were analyzed on a pup basis rather than on a litter basis.)** **at PND 30 at PND 60 at PND 90** **0 7.38 14.8 0 7.38 14.8 0 7.38 14.8** *CA1 pyknotic neurons:* 0 59* 74%* 0 5 54% 0 20 −6% *CA2 pyknotic neurons:* 0 322* 336%* 0 65* 72% 0 18 9% *CA3 pyknotic neurons:* 0 273* 291%* 0 128 60%* 0 60 −19% *Body weight:* 0 −12* −21%* 0 −4 −9%* 0 −2 −5%

Results from *low* confidence studies are shaded; these findings are considered less reliable.
Abbreviations: DG = dentate gyrus; PND = postnatal day; CA = cornu ammonis.
*$p < 0.05$ versus control exposure; formaldehyde levels are underlined.
[a]Formaldehyde levels in the study (converted to mg/m^3 from ppm) were interpreted from the methods to represent the achieved mean analytical levels, although the range of measured concentrations was not reported.
[b]Sex and cohort information provided to EPA by personal communication (Kaplan, 2014, 2012).
[c]Indicated as −19% by study authors in text but estimated by EPA at −4% from data displayed graphically.

Neural sensitization

Research suggests that formaldehyde exposure might induce sensitization-like properties in neuronal networks (Sorg et al., 2004; Usanmaz et al., 2002; Sorg et al., 2001b; Sorg and Hochstatter, 1999; Sorg et al., 1998; Sheveleva, 1971) (see Table 1-47). Behavioral sensitization in animals can be initiated by drugs affecting the mesolimbic dopamine system (e.g., cocaine, morphine). Although the mechanisms are not fully understood, repeated, low-level exposures to certain chemicals and other stimuli have been hypothesized to cause a persistent modification to brain signaling, possibly

due to altered dopamine levels in limbic circuits (Bell et al., 1999; Bell et al., 1992; Antelman et al., 1980). Subsequent re-exposure to the conditioned chemical or stimulus, or challenge with other sensitizing agents, may result in amplified neural responses. These responses can be manifest as, for example, increased impulsivity, motor activity, or CNS excitability.

Possible sensitization manifest as amplified cocaine-induced locomotor activity and conditioned fear responses, as well as disrupted sleep patterns, has been reported by one group of researchers following repeated exposure to formaldehyde at 1.23–2.46 mg/m^3 (Sorg et al., 2004; Sorg et al., 2001b; Sorg and Hochstatter, 1999; Sorg et al., 1998). In the study interpreted with the highest confidence (*medium* confidence), although cross-sensitization to cocaine was not observed in female rats exposed to formaldehyde for 7 days, 4 weeks of exposure led to increased cocaine-induced vertical activity (with no difference in horizontal activity) when tested at 2–4 days (early withdrawal) and 4–6 weeks (late withdrawal) after cessation of exposure (Sorg et al., 1998). Sleep-wakefulness patterns, which are regulated in part by dopaminergic signaling (Dzirasa et al., 2006), were disrupted in male rats (females were not tested) after a 1–week withdrawal from formaldehyde inhalation (Sorg et al., 2001b); however, these results were limited by incomplete reporting (see Table 1-47). The study authors hypothesized that formaldehyde exposure may be causing a persistent stress response in the animals.

Several weeks following exposure to ≥1.23 mg/m^3 formaldehyde for 20 days, rats previously trained in a fear conditioning paradigm (a neutral odor was paired with footshock) tended to spend more time immobilized ("freezing") in the presence of the odor than did air-exposed controls, although these differences were not statistically significant (Sorg and Hochstatter, 1999). The authors concluded that the formaldehyde-treated rats had more difficulty than controls in extinguishing the fear response to the conditioned odor; however, as these changes were noted in response to odor cues, it is unclear whether formaldehyde preconditioning may have altered the sensitivity of the respiratory tract to odor. Overt damage of the nasal mucosa is not expected at these formaldehyde levels, and airway irritation at these levels is expected to be resolved two weeks after exposure (see Section 1.2.1), making causation by physical irritation unlikely. As these data could be related to observations suggesting increased anxiety following exposure (as discussed in the next subsection), the results identify the need to systematically test whether formaldehyde inhalation preconditioning influences responses related to limbic system function using olfactory-independent stimuli, and to compare any findings with responses caused by other stressors (e.g., restraint stress; chemicals with strong irritant odors, but no CNS action).

Equivocal evidence of increased CNS excitability following formaldehyde exposure has been reported in a few studies. Proconvulsant activity following acute formaldehyde exposures in mice was observed at 2.21–7.87 mg/m^3 (Usanmaz et al., 2002), but not at higher exposure levels or when formaldehyde was administered for longer durations (2–3 weeks). A critical component of sensitization was not included in this study, namely, a period of latency between the stimulus and challenge. These data are difficult to interpret because of an inability to distinguish between a

"wet-dog shake" due to an irritating odor and that due to a proconvulsive movement. Changes in pentylenetetrazole-induced seizures reported by Usanmaz et al. (2002) were also not easily interpreted, as no discernible pattern could be identified (e.g., seizure incidence was decreased at 18.2 mg/m^3 and seizure intensity was increased at 2.21 mg/m^3). In a developmental study, exposed pregnant dams displayed a significant reduction (12%) in the threshold of neuromuscular excitability at 4.92 mg/m^3, whereas neuromuscular excitability was unchanged in rat offspring exposed in utero (Sheveleva, 1971). However, the details of the study methods, including latency between exposure and testing in dams, were not provided. It is unclear whether reflex bradypnea-related responses would affect these types of measures (e.g., via transient tissue hypoxia). No other developmental studies examining these types of effects have been identified. Overall, the data indicate the potential for an effect, but the evidence is insufficient to conclude that formaldehyde exposure causes neural excitation or acts as a proconvulsant.

In some studies, it is unclear how the observed sensitization-type responses can be fully separated from potential confounders, such as responses due to irritation (the levels used are likely to elicit some irritant aversion responses) or sensitivity to the formaldehyde odor. Odor detection and irritation responses in rodents and humans differ. In general, odor detection of formaldehyde occurs at slightly lower concentrations than irritation-related responses, with human thresholds reported at 0.068–0.135 mg/m^3 (Berglund et al., 2012; Berglund and Nordin, 1992). An alternative explanation for some of the observed effects is that formaldehyde exposure, and the irritation associated with exposure, is uncontrollable or inescapable, which has the potential to modify stress and brain reward responses (Sorg et al., 1996). This is in contrast to situations of controllable stress expected to be encountered by formaldehyde-exposed humans. Additionally, explanations for sex-dependent differences in potential sensitization responses have yet to be explored. Overall, the human relevance of, and the formaldehyde-independent contributions to, the observed sensitization responses in rodents require additional research, including studies clarifying human sensitization-type responses to chemical irritants and well-controlled animal studies designed to mimic the human condition.

Table 1-47. Neural sensitization in experimental animal studies

Reference and study design	Results[a] and exposure levels
Medium Confidence	
Reference: Sorg et al. (1998) Rat (Sprague-Dawley); *N* = 15–16 (7d) or 20–24 (20d) females 0 or 1.23 mg/m^{3b} [Actual[c]: 0 or 0.779–1.76] 7 or 20 days (5 days/week) Test article: Paraformaldehyde **Main limitations**: Blinding NR; description of methods incomplete.	*Cocaine-induced vertical activity following 20-day exposures:* Early withdrawal[d] / Late withdrawal **0** / **1.23** / **0** / **1.23** Saline-induced activity (counts): 333 / 333 / 231 / 231 Cocaine-induced activity (counts): 1,233 / 3,467* / 1,983 / 3,372* Percentage change in activity by cocaine: 370% / 1,040%* / 858% / 1,460%* *No changes in cocaine-induced activity were noted after 7 days of exposure and no changes in horizontal activity were noted after 20 days of exposure.* *No changes in nociception (hot plate test) were noted after 7 or 20 days of exposure.*
Low confidence	
Reference: Sheveleva (1971) Rat (Strain NR); *N* = 15/sex 0, 0.492, or 4.92 mg/m^{3e} [Actual: 0, 1.24, 3.09, or 6.20] GD 1–GD 19 Test article: Not reported **Main limitations**: Test article and endpoint evaluation methods NR.	**0** / **0.492** / **4.92** *Neuromuscular excitability in dams:* 0 / −7 / −19%* *No changes in offspring neuromuscular excitability.*
Reference: Sorg and Hochstatter (1999) Rat (Sprague-Dawley); *N* = 4–8 females 0 or 1.23 mg/m^{3b} [Actual: not reported] 20 days (5 days/week) Test article: Paraformaldehyde **Main limitations**: Unclear impact of altered olfactory detection or cocaine injection; note: formalin use as an aversive odor was deemed irrelevant.	**0** / **1.23** *Cocaine (10 mg/kg)-induced horizontal activity (as percentage change in induced activity):* Cocaine-induced activity 2–4 days after air or formaldehyde, as compared to cocaine-induced activity prior to exposure: 198 / 407%* *Fear-conditioned responses to odor (as percentage change from nonshocked)[f]:* Freezing in the context used for shock training: 433* / 476%* Freezing with the conditioned odor 2 days later: 45 / 127%* Freezing with the conditioned odor 12 days later: 54 / 181%* *$p < 0.05$, as compared to no shock condition in the same exposure group (*t*-test). [Notes: Statistically significant differences in direct comparisons of the control and HCHO pre-exposed groups were not observed for any fear conditioning tests (*N* = 4).]
Reference: Sorg et al. (2001b) Rat (Sprague-Dawley); *N* = 6/sex 0 or 2.46 mg/m^{3b} [Actual: not reported] 20 days (5 days/week) Test article: Paraformaldehyde **Main limitations**: Description of methods incomplete; no preformaldehyde exposure comparisons.	*Sleep patterns, as assessed by EEG/EMG in Males 7 days after exposure:* [Dark: 1–12h/Light: 13–24h phase[g]]: 1–6h / 7–12h / 13–18h / 19–24h **0** / **2.46** / **0** / **2.46** / **0** / **2.46** / **0** / **2.46** Number of waking episodes: 0 / −30% / 0 / −25% / 0 / −16% / 0 / −18% Number of NREMS episodes: 0 / −25% / 0 / −21% / 0 / −10% / 0 / −18% Duration of waking episodes: 0 / 37% / 0 / 59% / 0 / 9% / 0 / 12% *Significant treatment effects noted for each measure above by 2–way ANOVA. *No changes in REMS episodes or duration of NREMS episodes were noted.* [Note: a 15–min challenge with 37% formalin odor abolished all differences.]

<table>
<tr><th>Reference and study design</th><th>Results[a] and exposure levels</th></tr>
<tr><td>Reference: Sorg et al. (2004)
Rat (Sprague Dawley); N = 7–8/sex
0 or 2.46 mg/m[3b]
[Actual: 0 or 2.66]
20 days (5 days/week)
Test article: Paraformaldehyde
Main limitations: Unclear influence of changes in olfactory detection.</td><td>Freezing responses to a conditioned stimulus (CS, odor)[h] in males:
<table><tr><th></th><th colspan="2">Day 1</th><th colspan="2">Day 2</th><th colspan="2">Day 3</th><th colspan="2">Day 4</th><th colspan="2">Day 5</th><th colspan="2">Renewal[i]</th></tr><tr><th></th><th>0</th><th>2.46</th><th>0</th><th>2.46</th><th>0</th><th>2.46</th><th>0</th><th>2.46</th><th>0</th><th>2.46</th><th>0</th><th>2.46</th></tr><tr><td>Unpaired:</td><td>0</td><td>64%*</td><td>0</td><td>19%</td><td>0</td><td>7%</td><td>0</td><td>76%*</td><td>0</td><td>0%</td><td>0</td><td>86%</td></tr><tr><td>Paired:</td><td>0</td><td>26%</td><td>0</td><td>12%</td><td>0</td><td>5%</td><td>0</td><td>22%</td><td>0</td><td>50%*</td><td>0</td><td>47%</td></tr></table>No changes observed in response to the context alone (footshock or novel).
No change in female conditioned fear behaviors (to context or CS).</td></tr>
<tr><td>Reference: Usanmaz et al. (2002)
Mouse (Balb/C); N = 6 Sex NR
0, 2.21, 3.94, 7.87, 11.9, or 18.2 mg/m[3j]: 3 hours
0 or 3.94 mg/m[3]: 2 weeks
0 or 2.46 mg/m[3]: 3 weeks
Test article: Paraformaldehyde
Main limitations: Tested immediately after exposure; blinding NR.</td><td>CNS excitability after a 3-hour exposure:
<table><tr><th></th><th>0</th><th>2.21</th><th>3.94</th><th>7.87</th><th>11.9</th><th>18.2</th></tr><tr><td>Percentage incidence of wet-dog shake[k]:</td><td>0</td><td>63*</td><td>67*</td><td>60*</td><td>25</td><td>17%</td></tr><tr><td>Percentage incidence of seizures[l]:</td><td>91</td><td>82</td><td>ND</td><td>60</td><td>ND</td><td>33%*</td></tr><tr><td>Seizure intensity (median vales):</td><td>4</td><td>6*</td><td>ND</td><td>4</td><td>ND</td><td>1</td></tr><tr><td>Seizure threshold (seconds to onset):</td><td>74</td><td>83</td><td>ND</td><td>104</td><td>ND</td><td>110%</td></tr></table>No significant effects on seizure mortality.
No significant effects on CNS excitability after 2–3 weeks of exposure.</td></tr>
</table>

Results from *low* confidence studies are shaded; these findings are considered less reliable.

Abbreviations: GD = gestational day; NREMS = nonrapid eye movement sleep; CS = conditioned stimulus; ND = not determined; NR= not reported; EEG/EMG= electroencephalogram/electromyelogram; CNS = central nervous system.

*$p < 0.05$ vs. control exposure unless otherwise indicated; formaldehyde levels are underlined.

[a]Data presented as percentage change from control, unless otherwise indicated.

[b]Formaldehyde levels in the study converted to mg/m^3 from ppm.

[c]Actual mean analytical concentrations achieved.

[d]2–4 days after discontinuing exposure, rats were given cocaine and evaluated for 2 hr (early withdrawal); an additional cocaine challenge and locomotor assessment were conducted 4–6 wk later (late withdrawal).

[e]Formaldehyde levels in the study (converted to mg/m^3 from mg/L) represented the achieved analytical levels.

[f]Context = in the context the shock was delivered, rats receiving shock training vs. those not shocked were compared at 1 day after training; conditioned odor = comparison as in "context" 2 or 12 days after training except in a novel context and with the odor used for shock training (orange oil) present. Values and statistical analyses are compared against nonshocked rats within the same treatment group.

[g]Data were recorded for 6-hour periods beginning at dark phase for 24 hours; percentage change from air controls for each period is presented; air and formaldehyde groups were significantly different by two-way ANOVAs.

[h]Several weeks after treatment an orange oil odor (CS) was either Paired (with CS presentation) or Unpaired (separately and randomly from CS presentation) with footshocks, then testing performed over subsequent days

[i]CS presented in a second, completely novel context.

[j]Formaldehyde levels in the study (converted to mg/m^3 from ppm) were interpreted from the methods to represent the achieved mean analytical levels, although the range of measured concentrations was not reported.

[k]Wet-dog shake, a possible pro-convulsive sign, is a shuddering motion in rodents that can be induced pharmacologically with agents that affect glutamatergic and/or serotonergic signaling.

[l]Seizures were induced by injection of pentylenetetrazole.

Tests of general motor-related behaviors

This section encompasses a range of behavioral tests examining general locomotion (without pharmacological manipulation) as the output. These tests span a range of test environments and testing conditions, and the observed responses often involve contributions from multiple specific behavioral processes (e.g., motor function, anxiety, arousal, olfaction, acclimation

to the test environment, etc.) that can be difficult to disentangle. Motor-related tests designed to examine learning and memory processes are discussed separately in the next section.

Animal studies that included protocols of sufficient duration to specifically assess changes in motor function (Sorg et al., 2001b; Sorg et al., 1998) either did not observe effects of formaldehyde inhalation alone (Sorg et al., 1998) or were complicated by irritant effects when tested during exposure (Sorg et al., 2001b). However, open field activity testing following formaldehyde exposure revealed decreased ambulatory activity in rats and mice, as well as elevated anxiety and reduced habituation to the test environment in nearly all available studies (Malek et al., 2004, 2003a, b; Usanmaz et al., 2002; Boja et al., 1985; Sheveleva, 1971) (see Table 1-48). Open field testing is a commonplace test that can be standardized and reproducible (Broadhurst, 1969), but which often involves a somewhat arbitrary interpretation of different behavioral features. The short testing duration used in open field tests (typically 3–5 minutes) is not of sufficient length to accurately assess motor function, and the results are also affected by the initial anxiety of the animals to the novel test environment. Thus, with these tests (which vary by laboratory), it can be difficult to separate changes in motor function and interpretation of olfactory and visual cues from changes due to exploration of a novel environment and anxiety due to open spaces and bright light (e.g., increased anxiety correlates with decreased ambulation in these tests). A second test (typically 24 hours later) measures the level of habituation or learned familiarity to the test environment. Due primarily to prominent exposure-quality issues (Malek et al., 2004, 2003a, b; Sheveleva, 1971) or significant study design concerns (Usanmaz et al., 2002; Boja et al., 1985; Sheveleva, 1971), all of the data suggesting effects of exposure on motor-related behaviors are derived from *low* confidence studies (see Appendix A5.7), limiting their interpretability.

Consistent decreases in open field locomotor activity in male mice and rats of both sexes were observed at formaldehyde concentrations as low as 0.123 mg/m^3 (with rats exhibiting enhanced sensitivity) when assessed shortly after a single, acute formaldehyde exposure (Malek et al., 2004, 2003a, b) or after exposure for 1 week (Li et al., 2016); however, these studies employed formalin exposures. From the current studies it remains unclear whether these changes persist more than a few hours after exposure, noting that motor activity testing (not open field tests) did not reveal changes several weeks after exposure (Sorg et al., 1998). A portion of this immediate response in male mice may be due to increased anxiety, as decreases in crossed inner squares occurred at notably lower levels than decreases in crossed peripheral squares (anxious animals tend to spend less time in the open and bright areas at the center of the field), suggesting an elevated stress response after acute exposure (Malek et al., 2004); however, this increased anxiety was not confirmed in a second, short-term study (Li et al., 2016), which actually reported evidence of a decrease in anxiety in both open field and elevated plus maze tests at 1.23 mg/m^3. Although, no changes were observed at 2.46 mg/m^3 and changes in plus maze activity were not observed in rats that were similarly exposed (Sorg et al., 1998). Perhaps relatedly, short-term exposure of mice to ≥1 mg/m^3 resulted in dose-dependent increases in immobility time in the forced swim test (Li et al.,

2016), a stress-related test of "behavioral despair" (Porsolt et al., 1977). When habituation to the open field was tested 24 hours after exposure, formaldehyde-treated rats and mice did not demonstrate the same degree of habituation as control animals (Malek et al., 2004, 2003a). In male rodents, the degree of habituation was reduced compared to controls. In contrast, formaldehyde-treated female rats demonstrated robust increases (50–150%) in activity at all formaldehyde exposure levels (≥1.23 mg/m^3), suggesting not only reduced habituation, but also delayed hyperactivity in these animals. These mixed results suggest a general effect on behavior across a range of tests of general motor-related behaviors, but the specifics of this effect(s) remain difficult to interpret and require clarification in studies with better-controlled formaldehyde exposures.

A serious concern that changes may be due to irritation and related phenomena (e.g., reflex bradypnea; distractibility) is raised for three of the studies which evaluated behaviors during or immediately after exposure to formaldehyde at concentrations expected to cause irritation (Usanmaz et al., 2002; Boja et al., 1985). Decreased activity from 0 to 24 hours after exposure to 6.15 mg/m^3 formaldehyde was reported using a minimally informative protocol developed for observations of rat pups (Boja et al., 1985), with activity defined as the percentage of time "active" (i.e., not sleeping or immobile). Consistent with the pattern of alterations to habituation reported by Malek et al. (2004, 2003a), after several days of daily exposure and activity testing, vertical activity measured during exposure to 2.46 mg/m^3 formaldehyde was depressed in male rats (on exposure days 12–20) and increased in female rats (on exposure days 5 and 20), as compared to controls (Sorg et al., 2001b). Usanmaz et al. (2002) noted unexplainable formaldehyde sensitivity (gastrointestinal impairment and decreased weight gain), causing them to discontinue the study, at exposures as low as 2.5 mg/m^3 for 3 weeks, which would be expected to confound their findings of decreased activity. Owing primarily to the timing of the behavioral tests, none of the observed changes in activity can be clearly attributed to formaldehyde-induced effects on the nervous system.

Reduced spontaneous mobility at PND 30 was observed in pups exposed in utero to 0.492 or 4.92 mg/m^3 (Sheveleva, 1971). In contrast, concentration-related increases in mobility were observed in these pups at PND 60 (an increased level of spontaneous mobility was also observed in dams at 4.92 mg/m^3), with the female pups exhibiting enhanced sensitivity. Increases in activity which persist into adulthood following developmental exposure are of concern. However, the methodology was insufficiently described and the significance of these formaldehyde-induced, bidirectional changes in the activity of young animals, which were dependent either on the delay between exposure and testing or the postnatal age at testing, is unclear.

Overall, the data from basic tests of motor-related behaviors suggest an effect in formaldehyde-exposed rodents. This response may be short lived, and, at least in open field tests, rats seem to be more sensitive to changes following formaldehyde exposure than mice (which would be consistent with the known toxicokinetic differences across species; see Appendix A.2) and females seem to exhibit a different pattern of responses than their male counterparts. Somewhat

differing results across some of the studies, particularly in tests other than open field activity (i.e., elevated plus maze and forced swim test), together present a complicated picture of these potential effect(s). More importantly, however, no studies using methanol-free formaldehyde and other appropriate methodology were available to clarify and confirm the findings of behavioral changes from this set of *low* confidence studies.

Table 1-48.Tests of motor-related behaviors in experimental animal studies

Reference and study design	Results[a] and exposure levels
Medium confidence (activity); *low* confidence (elevated plus maze)	
Reference: Sorg et al. (1998) Rat (Sprague-Dawley); *N* = 15–24 females 0 or 1.23 mg/m^{3}[b] [Actual[c]: 0 or 0.779–1.76] 7 or 20 days (5 days/week) Test article: Paraformaldehyde **Main limitations**: Description of methods incomplete; activity could be affected, and plus maze data are likely affected, by prior manipulations; total plus maze activity NR; blinding NR.	*No change in horizontal or vertical activity were noted following saline injections 2–4 days or 4–6 weeks after discontinuing formaldehyde exposures.* Note: activities were measured over a 2–hour period after allowing the rats to acclimate to the test environment. *No statistically significant changes in elevated plus maze performance were noted.* Note: percentage open arm entries and percentage time spent in open arms were decreased 24 and 39%, respectively after 7 days [p = 0.06 for percentage time]; percentage time in open arms was increased 21% after 20 days, but this did not approach statistical significance.
Low confidence	
Reference: Boja et al. (1985) Rat (Sprague Dawley); *N* = 8 males 0 or 6.15[b] mg/m^{3}[c] [Actual[d]: not reported] 1–2 days (switching paradigm) Test article: Paraformaldehyde **Main limitations**: Tested immediately after exposure; uncommon protocol.	*Percentage time "active" versus "inactive"[e] during exposure relative to air controls:* Day 1 HCHO (Day 1 exposed): at 30 min. −34%*; at 60 min. −66%*; at 120 min. −77%* Day 2 HCHO (Day 1 and 2 exposed): at 30 min. −76%*; at 60 min. −70%*; at 120 min. 24% Day 2 HCHO (only Day 2 exposed): at 30 min. −58%; at 60 min. −80%; at 120 min. 122% 24h post HCHO (only Day 1 exposed): at 30 min. −30%; at 60 min. −80%; at 120 min. 72%[f] Boja et al. (1985)
Reference: Li et al. (2016) Mouse (Kunming: outbred Swiss albino); *N* = 15 males 0, 1.23, or 2.46 mg/m^{3}[c] [Actual: levels confirmed] 7 days (2 hours/day) Test article: Formalin **Main limitations**: Formalin; blinding NR for tests other than forced swim; possible influence of multiple behavioral tests in the same animals.	*Open Field Activity (2-hr postexposure):* Total Distance: 0 −3.15 −18.7* Total Crossings: 0 −4.02 −20.9* Percentage Center Time: 0 39.0* −11.5 *Forced Swim (after plus maze):* Immobility Time: 0 42.3 87.6* *Elevated Plus Maze (after open field):* Total Distance: 0 0.70 −3.00 Number of Entries: 0 −14.5 −12.1 Percentage Open Arm Time: 0 20.9* −4.33 Note: Statistically significant differences in body-weight gain were observed at 2.46 mg/m^{3} (−3.7%, as compared to + 1.82% in controls).

Reference and study design	Results[a] and exposure levels
Reference: Malek et al. (2003a) Rat (LEW.1K); *N* = 15/sex 0, 1.23, 3.08, or 6.15 mg/m^{3c} [Actual: 0, 1.24, 3.09, or 6.20] 2 hours Test article: Formalin **Main limitation**: Formalin. [Note: an excessive level of variability was noted for this study, possibly due to an erroneous indication of data as Mean ± SE in this study, in contrast to Mean ± SD in the other studies by Malek et al.(2004, 2003b, c).]	Males / Females **0 / 0** — **1.23 / 1.23** — **3.08 / 3.08** — **6.15 / 6.15** *Open field activity and behaviors at 2 hours postexposure:* Locomotion: 0 / 0 — −63* / −72* — −22* / −30* — −41%* / −36%* Grooming: 0 / 0 — −47 / 4 — −23* / −17* — −34%* / −62%* Air sniffing: 0 / 0 — 103* / 1 — 118* / −23* — 104%* / 22%* Floor sniffing: 0 / 0 — 105* / −2 — 51* / 56 — 84% / 79% Wall climbing: 0 / 0 — −22* / −8 — −22* / −14 — −26%* / 16% Rearing: 0 / 0 — 28 / 58* — 32 / 74* — 2% / 42% Note: No changes in defecation. *Habituation to the open field at 26 hours postexposure (Trial 2/Trial 1[h]):* Locomotion: −80 / −78 — −44 / 140* — −35* / 42* — −21%* / 38%* Air sniffing: 161 / 78 — −31* / 48* — −13* / 174* — 12%* / 43% Climbing: 95 / 73 — −10* / 118 — −14* / 105 — 38%* / 46% Rearing: −14 / 34 — 6* / 3 — 9* / 6* — 24%* / −8% Note: No consistent changes in grooming, floor sniffing, or defecation.
Reference: Malek et al. (2003b) Rat (LEW.1K); *N* = 10/sex 0, 0.123, 0.615 or 6.15 mg/m^{3c} [Actual: 0, 0.160, 0.590, or 6.37] 2 hours Test article: Formalin **Main limitation**: Formalin.	Males / Females **0 / 0** — **0.123 / 0.123** — **0.615 / 0.615** — **6.15 / 6.15** *Open field activity and behaviors at 2 hours postexposure:* locomotion: 0 / 0 — −17* / −5 — −48* / −19* — −65%* / −39%* Air sniffing: 0 / 0 — 8* / 21* — −22* / 14* — −55%* / −11%* Floor sniffing: 0 / 0 — −23* / −5 — −39* / −23* — −64%* / −27%* Wall climbing: 0 / 0 — 21* / 54* — −55* / −4 — −72%* / −34%* Rearing: 0 / 0 — −57* / 44* — −75* / −35* — −59%* / −24% Note: No consistent changes in grooming or defecation.
Reference: Malek et al. (2004) Mouse (AB); *N* = 20 Males 0, 1.35, 2.83 or 6.40 mg/m^{3c} [Actual: 0, 1.37, 2.84, or 6.64] 2 hours Test article: Formalin **Main limitation**: Formalin.	*Open field activity and behaviors at 2 hours postexposure:* / *Habituation to the open field at 26 hours postexposure:* 2 hr (Percentage control) / 26 hr (Trial 2/Trial 1[h]) **0 / 0** — **1.35 / 1.35** — **2.83 / 2.83** — **6.40 / 6.40** Crossed inner squares: 0 / −70 — −26* / −62 — −38* / −57 — −53%* / −40% Crossed outer squares: 0 / −24 — 5 / −25 — −12 / −10 — −49%* / 41% Total crossed squares: 0 / −41 — −7 / −36 — −22* / −24 — −51%* / 15% Air sniffing: 0 / −29 — 11 / −38 — −16* / −23 — −58%* / 52% Floor sniffing: 0 / 3 — 26* / −40* — 2 / −38* — 9% / −23%* Grooming: 0 / 5 — −11 / 96* — −11 / 45* — −18% / 82%* Rearing: 0 / 3 — −22* / −11* — -37* / 8* — -44%* / 21%* Note: No consistent changes in wall climbing or defecation.
Reference: Sheveleva (1971) Rat (Strain NR); *N* = 15/sex 0, 0.492, or 4.92 mg/m^{3i} [Actual: 0, 1.24, 3.09, or 6.20] GD 1–GD 19 Test article: Not reported **Main limitations**: Test article and endpoint evaluation details NR.	Males / Females **0 / 0** — **0.492 / 0.492** — **4.92 / 4.92** *Spontaneous mobility in offspring and dams:* at PND 30: 0 / 0 — −48* / −36* — −2% / −44%* at PND 60: 0 / 0 — 16 / 42 — 32% / 291%* in dams: NA / 0 — NA / −46 — NA / 89%*

<table>
<tr><th>Reference and study design</th><th>Results[a] and exposure levels</th></tr>
<tr><td>Reference: Sorg et al. (2001b)
Rat (Sprague-Dawley); N = 7–8/sex
0 or 2.46 mg/m^3[c]
[Actual: not reported]
20 days (5 days/week)
Test article: Paraformaldehyde
Main limitations: Activity tested during exposure; description of methods incomplete.</td><td>Total vertical activity during formaldehyde exposure:
Males: ↓ at exposure days 12–20 (−25 to −55%*)
Females: ↑ at exposure days 5 (133%*) and 20 (98%*)</td></tr>
<tr><td>Reference: Usanmaz et al. (2002)
Mouse (Balb/C); N = 6 (sex NR)
0, 2.21, 3.94, 5.54, 7.87, 11.9, or 18.2 mg/m^3[j]: 3 hours
0 or 2.46 mg/m^3: 1 or 3 weeks
0, 2.46, or 3.94 mg/m^3: 2 weeks
Test article: Paraformaldehyde
Main limitations: Tested immediately after exposure; blinding NR.</td><td>
<table>
<tr><th></th><th>0</th><th>2.21</th><th>3.94</th><th>5.54</th><th>7.87</th><th>11.9</th><th>18.2</th></tr>
<tr><td colspan="8">Open field activity immediately after a 3-hour exposure:</td></tr>
<tr><td>Horizontal activity:</td><td>0</td><td>−10</td><td>−16</td><td>−28</td><td>−35*</td><td>−69*</td><td>−91%*</td></tr>
<tr><td>Vertical activity:</td><td>0</td><td>−26*</td><td>−43*</td><td>−48*</td><td>−48*</td><td>−83*</td><td>−88%*</td></tr>
</table>

Open field activity[k] and body-weight gain after 1- to 3-week exposures:
<table>
<tr><th></th><th colspan="2">1 week</th><th colspan="3">2 weeks</th><th colspan="2">3 weeks</th></tr>
<tr><th></th><th>0</th><th>2.46</th><th>0</th><th>2.46</th><th>3.94</th><th>0</th><th>2.46</th></tr>
<tr><td>Horizontal activity:</td><td>0</td><td>−28%*</td><td>0</td><td>−3</td><td>−40%*</td><td>0</td><td>−23%</td></tr>
<tr><td>Vertical activity:</td><td>0</td><td>−37%*</td><td>0</td><td>−1</td><td>−44%*</td><td>0</td><td>−32%*</td></tr>
<tr><td>Body-weight gain:</td><td>0</td><td>33%</td><td>0</td><td>0</td><td>−150%*</td><td>0</td><td>−280%*</td></tr>
</table>
</td></tr>
</table>

Results from *low* confidence studies are shaded; these findings are considered less reliable.
Abbreviations: HCHO = formaldehyde; SE = standard error; SD = standard deviation; GD = gestational day; NR= not reported; PND = postnatal day.
*$p < 0.05$ vs. control exposure; formaldehyde levels are underlined.
[a]Data presented as percentage change from control, unless otherwise indicated.
[b]Additional exposure groups of 12.3 and 24.6 mg/m^3 were indicated, but data were not reported and thus, not included.
[c]Formaldehyde levels in the study converted to mg/m^3 from ppm.
[d]Actual mean analytical concentrations achieved.
[e]Active (e.g., grooming, eating, climbing, ambulating, etc.) versus inactive (i.e., immobile, sleeping).
[f]Statistical comparisons to air-air group not performed.
[g]Locomotion = crossed squares; M = changes were observed in males; F = changes were observed in females.
[h]Values presented as Trial 2 (26 hr) vs. Trial 1 (2 hr) performance in same group; * for comparisons within Trial 2.
[i]Formaldehyde levels in the study (converted to mg/m^3 from mg/L) represented the achieved analytical levels.
[j]Formaldehyde levels in the study (converted to mg/m^3 from ppm) were interpreted from the methods to represent the achieved mean analytical levels, although the range of measured concentrations was not reported.
[k]Open field activity in the short-term studies is inferred to have been conducted immediately following exposure.

Tests of learning and memory

Five studies have examined the effects of inhaled formaldehyde on learning and memory processes in experimental animals see Table 1–49). All of the studies are expected to have significant coexposures due to the formaldehyde generation methods (see Appendix A.5.7), and thus, the effects cannot be attributed to formaldehyde inhalation alone. In addition, many of the dose-response relationships are difficult to interpret and the results are occasionally inconsistent.

Decreased performance in short-term spatial memory tasks following exposure to formaldehyde has been observed in rats across two studies from coauthors in the same research

institute (Malek et al., 2003c; Pitten et al., 2000), as well as in three mouse studies (LICM, 2008). These testing paradigms involve components of memory, orientation, reward seeking, stress, olfactory and visual information processing, and motor function. In the rat studies, increased error rate and increased latency in a water maze were observed after short-term exposures to ≥0.123 mg/m^3 and ≥0.615 mg/m^3, respectively (Malek et al., 2003c), although the results were not entirely consistent across all trial days. Similarly, very brief (10-minute) formaldehyde exposures over a prolonged duration (90 days) resulted in an increased number of errors and longer running times in a land-based maze at ≥3.06 mg/m^3 (Pitten et al., 2000), with an increasing magnitude of change with increasing trial days, which suggests an additive effect of exposure. In general, excluding the latency measures reported by Malek et al. (2003c), all exposed rats were equally impaired across a broad range of exposures; no explanation for this lack of a dose-response relationship is presently available. These observations are supported by potentially related findings in mice exposed for 1 week to similar levels of formaldehyde (i.e., 2.46 to 3 mg/m^3); specifically, exposed mice exhibited decreased performance in the Morris water maze (Mei et al., 2016) and decrements in a test of recognition memory, the novel object test (Li et al., 2016). However, it is difficult to attribute these decrements to formaldehyde exposure due to notable methodological limitations (e.g., the use of formalin and the lack of observer blinding for these nonautomated measures raise substantial concerns). In addition, the data from both studies suggest possible complicating effects on behaviors other than learning or memory in the mice exposed to formaldehyde [i.e., in Mei et al. (2016), exposed mice did not exhibit improved performance across training trials and swimming tracks suggest that they avoided the target quadrant completely during the probe trial; in Li et al. (2016), even in the absence of a novel object, exposed mice spent approximately half the time exploring objects during training than did controls]. Although vision and olfaction were not evaluated in these rodent studies, possible effects on these functions are not expected to influence performance in the studies by Malek et al. (2003c), Mei et al. (2016), and Li et al. (2016), or by Pitten et al. (2000), as assessments occurred 2–3 or 22 hours after exposure(s), respectively. In contrast, supportive observations in mice (LICM, 2008) are considered even less reliable due to the short, 30-minute delay before testing following exposure to formaldehyde and other potential contaminants (formaldehyde was released from wood baseboard) at levels that are likely to induce irritation-related responses.

In rats, the increases in maze latency are most likely reflective of the increased number of errors in treated animals as errors usually increase the distance traveled, and thus the time required, for completion of the trial. However, in the absence of data on path length or motor speed in all three of the maze-based studies, it is unclear whether hyperactivity of the formaldehyde-exposed animals may have been present (e.g., increased swim time and increased number of errors due to exposed animals swimming faster in circular or back-and-forth patterns). In the study by Malek et al. (2003c), increased swim speed is indeed evident at 0.123 mg/m^3 in females: despite making approximately four more errors than control rats on trial days 4, 5, and 8,

they still had significantly shorter swimming times. Recovery following exposure was only assessed by Pitten et al. (2000), who observed that performance was still impaired 4 weeks after exposures had ended.

While the study authors interpreted these results to suggest deficits in the retention of a previously learned task or in remembering a previously explored object, these studies had significant methodological shortcomings. Thus, sole attribution of the decreases in performance to formaldehyde-induced impairment, and specifically to impairment of memory or orientation, cannot be concluded. Although two developmental studies evaluating learning and memory processes following formaldehyde exposure were identified (Liao et al., 2010; Senichenkova, 1991a), data from these studies were not considered useful for the purposes of hazard characterization (see Appendix A.5.7). Overall, while the available data suggest a potential effect on behavior in tests of learning or memory, which may or may not reflect effects on those specific cognitive processes, no studies using methanol-free formaldehyde and other more appropriate methodology were available to clarify and confirm the findings of behavioral changes from this set of *low* confidence studies.

Table 1-49. Tests of learning and memory in experimental animal studies

Reference and study design	Results (as indicated) and exposure levels			
Low confidence				
Reference: Li et al. (2016) Mouse (Kunming: outbred Swiss albino); *N* = 15 males 0, 1.23, or 2.46 mg/m^3[a] [Actual: levels confirmed] 7 days (2 hours/day) Test article: Formalin **Main limitations**: Formalin; blinding NR; possible influence of multiple behavioral tests performed in the same animals.		**0**	**1.23**	**2.46**
	Novel Object Training and Testing (~ 2 days postexposure):			
	Training exploration (time ± SEM) of Left identical object:	94 ± 14	99 ± 25	55 ± 10
	Training exploration (time ± SEM) of Right identical object:	98 ± 20	88 ± 23	51 ± 9
	Familiar object exploration (seconds) 24-hr posttraining:	69.8	47.0,	61.8
	Novel object exploration (seconds) 24-hr posttraining (*p < 0.05 versus familiar object exploration time):	149*	103*	41.6
	Discrimination Index [(novel object time ÷ total time) − (familiar object time ÷ total time) × 100]:	43.3	32.7	−12.0*
	Notes: Statistically significant differences in body-weight gain were observed at 2.46 mg/m^3 (−3.7%, as compared to + 1.82% in controls). The study authors did not provide comparisons of total exploratory activity (Left + Right object) during training.			
Reference: LICM (2008) Mouse (Kun Ming: outbred Swiss albino); *N* = 5 males 0, 1, or 3 mg/m^3 [Actual[a]: 0.020, 0.990, or 3.03] 7 days beginning at ~PND 42 Test article: Wood baseboard **Main limitations**: Undefined mixture exposure; possible impact of irritation.		**0**	**1**	**3**
	Escape latency across training trial days in the Morris water maze[b]:			
	Latency (percentage from control for averaged trial days):	0	32	74%*[c]
	Note: Magnitude of change was unrelated to duration of exposure.			
	Performance during probe trial test:			
	Time spent in the target quadrant (percentage from controls):	0	−19	−41%
	Note: Only controls spent significantly more time in the target quadrant.			

Reference and study design	Results (as indicated) and exposure levels
Reference: Mei et al. (2016) Mouse (Balb/c); *N* = 8 males 0 or 3 mg/m^3[a] [Actual: confirmed, 3.04 ± 0.13 mg/m^3] 7 days (8 hours/day) Test article: Formalin **Main limitations**: Formalin; blinding NR; details of behavioral protocols NR.	*Training trials escape latency (sec.; *p < 0.05: Dunnett's post hoc tests on ANOVA)*[e]: Control: Day 1: 58.2; Day 2: 55.4; Day 3: 55.7; Day 4: 49.4; Day 5: 38.0; Day 6: 36.3; Day 7: 33.1 3 mg/m^3: Day 1: 56.7; Day 2: 55.0; Day 3: 52.2; Day 4: 51.4; Day 5: 52.1*; Day 6: 50.4*; Day 7: 50.7* *Probe trial test performance on Day 8*[e]: Control / 3 mg/m^3 Mean (+ SE) swim distance (cm) in target quadrant: 316 (± 42) / 154* (± 16) Mean (+ SE) time (sec) in target quadrant: 27.5 (± 3.4) / 10.0* (± 0.9)
Reference: Malek et al. (2003c) Rat (LEW.1K); *N* = 15/sex 0, 0.123, 0.615, or 6.64 mg/m^3[d] 10 days Test article: Formalin **Main limitations**: Formalin; protocol deficiencies, including blinding NR.	*Latency and number of errors in a water maze:* Maze errors (as #): Males 0 / .12 / .62 / 6.6; Females 0 / .12 / .62 / 6.6 Day 1: 7 8 8 8 / 8 7 8 8 Day 2: 6 7 6 6 / 8 7* 8 6* Day 3: 5 5 6* 7* / 4 6* 7* 8* Day 4: 2 5* 5* 6* / 1 6* 5* 6* Day 5: 1 4* 3* 5* / 1 4* 4* 5* Day 6: 1 5* 4* 5* / 0 5* 5* 5* Day 7: 0 5* 4* 5* / 0 5* 4* 5* Day 8: 0 3* 3* 3* / 0 4* 3* 3* Day 9: 0 3* 3* 3* / 0 3* 3* 4* Day 10: 0 3* 2* 3* / 0 3* 2* 3* Swim time (as percentage control): Males 0 / .12 / .62 / 6.6; Females 0 / .12 / .62 / 6.6 Day 1: 0 −5 −8* 0 / 0 −7* −6* −5* Day 2: 0 −1 3 8* / 0 −4 −2 4* Day 3: 0 −2 14* 4 / 0 4 8* −2 Day 4: 0 −11 29* 14* / 0 −24* 16* 14* Day 5: 0 −11 −2 23* / 0 −13* −9 −1 Day 6: 0 6 37* 111* / 0 −2 17* 88* Day 7: 0 6 38* 94* / 0 12* 11* 62* Day 8: 0 −3 −8 41* / 0 −20* −8 15* Day 9: 0 3 17* 64* / 0 18* 11* 46* Day 10: 0 −3 21* 73* / 0 15 17* 49*
Reference: Pitten et al. (2000) Rat (Wistar); *N* = 5–8/sex[f] 0, 3.06, or 5.55 mg/m^3[d] 90 days (Note: only 10 minutes/day exposures) Test article: Formalin **Main limitation**: Formalin.	*Latency and number of errors in a land maze:* Latency (as percentage control)[g]: 0 / 3.06 / 5.55 Exposure wk 0: 0 −6 4% Exposure wk 2: 0 8 21% Exposure wk 4: 0 30 51% Exposure wk 6: 0 48 76% Exposure wk 8: 0 75* 113%* Exposure wk 10: 0 94* 143%* Exposure wk 12: 0 128* 185%* 2 wks postexposure: 0 168* 241%* 4 wks postexposure: 0 215* 303%* Errors (as percentage control): 0 / 3.06 / 5.55 Exposure wk 0: 0 −39 −7% Exposure wk 2: ND ND ND Exposure wk 4: 0 70 91% Exposure wk 6: ND ND ND Exposure wk 8: 0 116 112% Exposure wk 10: ND ND ND Exposure wk 12: 0 153* 184%* 2 wks postexposure: ND ND ND 4 wks postexposure: 0 72 89% *No CNS pathology or changes in body weight were observed.*

Results from *low* confidence studies are shaded; these findings are considered less reliable.
Abbreviations: SEM = standard error of the mean; PND = postnatal day; ND = not detected.
*p < 0.05 vs. control exposure (unless otherwise indicated); formaldehyde levels are underlined.
[a]Actual mean analytical concentrations achieved.
[b]Morris water maze: Four trials/day during training; Probe trial involved removal of the platform on Day 7.
[c]Significant differences between the 0 and 3 mg/m^3 groups by multiple comparison testing (LICM, 2008).
[d]Formaldehyde levels in the study (converted to mg/m^3 from ppm) represented the achieved analytical levels.
[e]Data digitized using Grab It!™, Datatrend Software.
[f]Male and female data were pooled for comparisons; no differences between sexes were noted.
[g]Average seconds estimated from points along the fitted linear regression curves presented by Pitten et al. (2000).

Evidence on Mode of Action for Nervous System Effects

Little mode of action (MOA) information regarding potential nervous system effects following formaldehyde inhalation is available. To date, there are no definitive data supporting a specific mechanism for effects on nervous system structure or function. As appreciable amounts of formaldehyde are not expected to reach the systemic circulation or CNS to elicit direct effects, any potential mechanisms would need to be indirect. Thus, this section focuses on mechanisms that might secondarily result from alterations to the respiratory system (see Appendix A.5.6). As such, only data from formaldehyde inhalation studies are discussed, and confidence in the findings based on individual study evaluations is emphasized (see Appendices A.5.6 and A.5.7). Although none has been confirmed experimentally, several biologically plausible, but speculative sequences of mechanistic changes that might support indirect effects can be hypothesized based on the available formaldehyde-specific data, including:

1) Repeated activation of sensory nerves (e.g., trigeminal, vagal) causing sensitization or neurogenic inflammation leading secondarily to effects on neuronal populations unrelated to pain and irritation pathways—based primarily on three *medium* (Ahmed et al., 2007; Fujimaki et al., 2004b; Kulle and Cooper, 1975) and one *low* confidence (Tsukahara et al., 2006) studies

Repeated stimulation of sensory nerve fibers relaying information related to formaldehyde exposure to neuronal nuclei might eventually lead, indirectly, to lasting changes in centrally located neurons or soluble factors; however, specific data assessing this possibility, and the downstream consequences of such potential changes, remain unexamined. Formaldehyde inhalation has been shown to increase the electrical activity of trigeminal nasal afferents at concentrations below 1 mg/m^3 (Kulle and Cooper, 1975), which appears to cause neurogenic inflammation, a process whereby stimulation of sensory nerve endings causes localized (e.g., into airway tissue) release of neuropeptides (e.g., the tachykinin, substance P) that elicit local inflammatory responses (see discussion in Section 1.2.1). In addition to the "axon reflex" that can be induced upon sensory nerve stimulation (causing a localized release of factors), if the stimulus is of sufficient intensity or duration, signaling along ascending pathways from these afferents can continue, and eventually might lead to central sensitization where the excitability or responsiveness of afferent nerve fibers is enhanced (Woolf and Salter, 2000).

While changes in neuronal nuclei associated with ascending pathways related to pain and irritation signals seems likely following formaldehyde inhalation, there are no data or hypotheses available to inform how this might indirectly affect other neuronal nuclei. Regardless of the unexplainable connection between sensory nerve stimulation and changes in presumably unrelated neuronal nuclei, hippocampal neurochemical changes which appear to be related to neurogenic inflammation, were observed in the absence of neuronal injury in a series of subchronic formaldehyde inhalation studies by Fujimaki and colleagues at formaldehyde levels as low as 0.1 mg/m^3 (Ahmed et al., 2007; Tsukahara et al., 2006; Fujimaki et al., 2004a). Importantly, these

effects were generally only observed after stimulation with foreign materials known to cause an allergic response. Although the evidence related to potential neurogenic inflammation has been primarily observed in the airways, some factors released as a result of this process can be long-lived, and receptors for these upregulated cytokines and neuropeptides, including substance P, are prevalent throughout the CNS (Douglas et al., 2008). These data suggest the possibility that sensory nerve stimulation of sufficient duration and intensity, perhaps particularly in allergic individuals, might eventually result in lasting changes in CNS regions that regulate behaviors unrelated to pain or irritation responses. However, dose-response relationships for the observed mechanistic changes were unclear and data are not available to inform some of the essential logical connections that would be necessary to connect peripheral stimulation to these central changes. An additional uncertainty with this hypothesized relationship is lack of understanding whether and to what extend this potential mechanism might be involved following chronic exposure. For example, although a related chemical, capsaicin, also causes neurogenic inflammation, no neurogenic inflammatory response to subsequent stimuli is observed following long-term exposure to capsaicin because tachykinins become depleted from sensory neurons (Kashiba et al., 1997; Cadieux et al., 1986). Further, no data are available to inform human relevance and some suggest responses might differ across species (e.g., distribution of substance P receptors in the brain can differ across species (Rigby et al., 2005)).

2) Neuronal activation following stimulation of the olfactory epithelium leading, indirectly, to alterations in neuronal targets unrelated to olfaction or, directly, to alterations in olfactory-dependent behaviors—based primarily on one *high* (Hayashi et al., 2004), one *medium* (Boja et al., 1985), and one *low* confidence (Zhang et al., 2014) study

Formaldehyde is not only a chemical irritant, it is also an odorant, and its odor is typically detectable at lower levels than those causing irritation. Repeated and prolonged stimulation of neuronal olfactory receptors in the nasal epithelium at posterior regions of the upper respiratory tract (URT) might affect neurons along ascending pathways related to olfaction; however, similar to the hypothesis presented above, no data exist to describe how such changes could indirectly affect neurons or neuronal regions unassociated with olfaction. Hayashi et al. (2004) reported that subchronic, but not acute, formaldehyde exposure increases the activity of periglomerular (PG) cells in the main olfactory bulb (OB). Increases in the number of tyrosine hydroxylase $(TH)^+$ PG cells were observed at ≥0.1mg/m^3, with no differences in PG cell number or size of the OB (indicating increased TH synthesis in TH^- PG cells rather than new cell formation). These changes might be related to observed decreases in the synapse protein, SNAP25, in the OB after periodic exposure (twice daily 30-minute exposures for 14 days) to high levels of formaldehyde (Zhang et al., 2014), although these latter results are interpreted with *low* confidence. The results in Hayashi et al. (2004) appear to highlight sensory-induced adaptive properties of the OB in relation to dopaminergic function (TH is an essential enzyme for dopamine synthesis). OB dopamine affects odor detection and can affect odor-related behaviors (e.g., impaired learning was observed with

increased dopamine D2 receptor signaling by Escanilla et al. (2009)). Thus, it is considered plausible that formaldehyde exposure could modify rodent behaviors with an olfactory component (e.g., motor-related behaviors; learning and memory in land maze tests); however, the potential for human behaviors, which are far less reliant on odorant signals, to be significantly impacted is unlikely.

It is unknown whether the adaptive changes observed in OB neurons result in alterations in neural circuitry. To date, no electrophysiological experiments have been conducted to specifically address the potential for an association between formaldehyde exposure and CNS electrophysiological changes. From the OB, olfactory signals are typically conveyed to higher order neurons, including those in the amygdala, hypothalamus, and olfactory areas of the entorhinal and piriform cortex. Possibly in relation to this, there is some suggestion of altered dopaminergic or serotonergic signaling in the hypothalamus with high-level formaldehyde exposures [6.15 mg/m^3; (Boja et al., 1985)], but these changes (increased dopamine and 5-HIAA, a serotonin metabolite) were only evaluated acutely following exposure, have not been linked to behavioral changes, and contrast somewhat with *s*uggestive observations of decreases in TH-positive cells across several brain regions at lower levels (Li et al., 2016). In addition, it remains speculative to infer that changes in olfaction-related ascending pathways after formaldehyde exposure might modify neural cell populations that are likely to be unrelated to those specific olfactory neuronal circuits. Overall, the cascade of events surrounding these adaptive changes remains unknown.

3) Altered hypothalamus-pituitary-adrenal gland (HPA) axis signaling (possibly linked to events above) causing persistent, stress-induced changes in behaviors—based primarily on one *high* (Sorg et al., 2001a) and one *medium* confidence (Sari et al., 2004) study

Stress can be a strong modifier of behavior, particularly at early lifestages. Sorg et al. (2001a; 1996) have suggested that behavioral sensitization to formaldehyde may be linked to alterations in HPA axis control of corticosterone or sensitization of limbic circuitry following repeated exposure. In support of this hypothesis, elevated numbers of corticotropin-releasing hormone (CRH)$^+$ neurons in the hypothalamus (at 0.49 mg/m^3) and adrenocorticotropic hormone (ACTH)$^+$ cells in the pituitary gland (at 0.1 mg/m^3) were observed after subchronic formaldehyde exposure (Sari et al., 2004), while increased serum corticosterone (at 0.86 mg/m^3) was evident after exposure for only 4 weeks (Sorg et al., 2001a). These findings may be related to evidence suggesting depressed hippocampal glucocorticoid responses at 2.46 mg/m^3 from a single short-term (7 day), *low* confidence study (Li et al., 2016). CRH and ACTH represent precursor steps in the release of glucocorticoids into the circulation following HPA axis stimulation, and corticosterone is the rodent glucocorticoid equivalent of cortisol in humans. Reported disruptions in sleep behavior [observed at 2.46 mg/m^3 formaldehyde by (Sorg et al., 2001b)] may also be linked to HPA axis dysfunction (Buckley and Schatzberg, 2005). In addition to highlighting the potential for formaldehyde-induced effects on allergy-related responses to impact the HPA axis, Sari et al. (2004) hypothesized that these stress-related responses might have resulted from neural

sensitization via amplification of CNS circuits with repeated exposure; however, as previously mentioned, no well-conducted formaldehyde inhalation studies assessing electrophysiological endpoints were identified. Although formaldehyde exposure appears to be correlated with HPA axis-associated changes, no studies describe exactly how these CNS-regulated HPA responses could be modified by formaldehyde, highlighting a critical information gap. Importantly, the available studies are unable to rule out the possibility that the stress responses might be caused by the animal exposure-specific phenomenon of "inescapable stress" highlighted in Sorg et al. (1996). The available studies have not fully examined the temporal profile of these changes (acute stress responses are not necessarily adverse), and no studies have demonstrated that formaldehyde-induced stress leads to persistent neurobehavioral changes, functional alterations (e.g., through impaired neurogenesis), or neuroanatomical changes.

4) Changes in neuronal health and function due to indirect CNS oxidative stress or excitatory changes (possibly linked to events described above)—based primarily on two *medium* (Songur et al., 2008; Ahmed et al., 2007) and three *low* confidence (Mei et al., 2016; LICM, 2008; Songur et al., 2003) studies

Markers of oxidative stress in the CNS are commonly associated with altered neuronal health and behavior. Songur et al. (2008) hypothesized that formaldehyde exposure may cause persistent brain changes via oxidative damage. Although a linkage between altered redox balance and hippocampal neuropathology was not tested in the stereological studies from this laboratory (Sarsilmaz et al., 2007; Aslan et al., 2006), an earlier study (Songur et al., 2003) observed reversible upregulation of hippocampal heat shock protein 70, an oxidative stress-responsive protein. Several other studies using molecular endpoints also support that formaldehyde inhalation may disrupt brain oxidative stress responses (i.e., increased malondialdehyde and nitric oxide levels; decreased superoxide dismutase activity and glutathione levels), particularly in the cerebellum, following high-level formaldehyde exposures in juvenile rats [at 7.36–14.7 mg/m^3 in (Songur et al., 2008)] and adult mice [at ~3 mg/m^3 in Mei et al. (2016)]. Songur et al. (2008) observed effects that persisted up to 60 days post-exposure. Lower level exposures (e.g., 0.123 mg/m^3) for up to 24 hours did not cause changes in brain 8OHdG: dG ratios (Matsuoka et al., 2010). The evidence for oxidative stress in the brain could be related to prolonged increases in inflammatory mediators in the blood after formaldehyde exposure, including reactive oxygen species, hormones, or other factors (see Appendix A.5.6); however, this potential linkage has not been tested. Relatedly, changes in oxidative stress markers might reflect effects on excitatory neurotransmission. Specifically, acute formaldehyde inhalation has been shown to increase expression of NMDA receptor subunits (e.g., NR2B) in nasal tissue (Hester et al., 2003) and forebrain regions (LICM, 2008), while subchronic exposure in rats sensitized to allergen increased NMDA receptor expression (Ahmed et al., 2007) but not protein levels (Tsukahara et al., 2006). However, the cause(s) and functional consequences of these reported molecular increases have not been examined. In general, an explanation for oxidative stress-related changes in the absence of

systemic distribution of formaldehyde or very high formaldehyde exposure levels is unavailable, limiting the feasibility of this potential mechanism.

Overall, no MOA for potential formaldehyde-induced nervous system effects is available.

Integrated Summary of Evidence on Nervous System Effects

Numerous human and animal studies were available and, although multiple lines of evidence suggest that some concern for nervous system effects following formaldehyde inhalation is warranted, major deficiencies in study conduct were identified and the database is considered incomplete. No experimentally supported MOA is available to explain how formaldehyde inhalation could cause nervous system effects, although some potentially relevant mechanistic changes in the brain have been observed in well-conducted studies. Summary evaluations of the evidence for potential nervous system effects of formaldehyde inhalation exposure are provided in Table 1-50.

In human studies, evidence of an association between formaldehyde exposure and ALS was suggested across four studies in different populations by two separate groups of researchers. Positive associations observed in a large prospective study were somewhat corroborated by a few (but not most) comparisons in the other studies, noting that some associations were based on a very small number of cases or secondary analyses. However, three of the studies had uncertainties in the assignment of individual exposure to formaldehyde and two of the four did not observe a dose-response relationship when the data were stratified by estimated formaldehyde levels. In addition, the results were not verified in another study in a different population, which had greater certainty in individual exposure assessments. Based on these uncertainties, the currently available human evidence is interpreted as *slight*. Importantly, however, the unexpected nature of the observed associations between formaldehyde exposure and this rare and fatal disease across a growing number of studies (the first association was reported in 2009, with some corroborating evidence in 2015 and 2016) identifies an urgent need for additional research. As no experimental animal or mechanistic studies specific to this effect were identified (i.e., *indeterminate*), overall the **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation might cause the fatal human disease, ALS, but additional study is needed for a stronger judgment. This is primarily based on epidemiological studies in occupational settings (presumably higher levels of exposure); however, there were notably uncertainties in the studies' exposure assessments.

Although numerous studies reported changes in behavior following formaldehyde exposure, the evidence was not considered adequate to support a causal hazard conclusion, as it was primarily based on rodent studies with notable methodological limitations, with more limited supporting data from studies in humans. Effects in learning and memory tests, and performance in tests of motor-related behaviors, were relatively consistent across the available animal data, and several human studies reported coherent, but more marginal, changes in related tests. However, the available experiments had significant methodological deficiencies and, overall, the data were not attributable to formaldehyde alone. Based on the methodological limitations of the available studies, both the human and animal evidence for effects in learning and memory tests, and on

motor-related behaviors, is considered *slight*. Although no established MOA exists for changes in these behaviors, several well-conducted studies reporting molecular and structural effects in relevant brain regions (e.g., limbic structures; cerebellum) provide some biological plausibility for these effects. Taken together, it was judged that the **evidence suggests**, but is not sufficient to infer, that formaldehyde exposure might cause these potential behavioral effects.

Somewhat separate from the other reported behavioral effects, formaldehyde inhalation in rodents was also reported to be associated with sensitization-related changes in behavior. While several animal studies of varying quality observed amplified behavioral responses after formaldehyde exposure, interpretation of the results is unclear. Additional data are needed to rule out any potential influence from factors other than formaldehyde exposure. No human studies were available to inform this endpoint (i.e., *inadequate*). In addition, although some biological plausibility is provided by neurochemical and hormonal changes that may be consistent with such effects, without mechanistic information to verify that formaldehyde exposure alone resulted in these effects (e.g., supporting a reasonable MOA or ruling out alternative explanations), the animal findings are considered *slight***.** As uncertainties also exist in the relevance of these tests to human exposure scenarios, based on the data overall, it was judged that the **evidence suggests** that formaldehyde might cause neural sensitization-related behavioral changes.

Thus, based on the available database of studies, it was concluded that the available **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation might cause behavioral effects. The primary support for this conclusion is from *low* confidence studies in experimental animals, many of which reported effects at ≤1 mg/m^3. Given that this judgment relates to multiple manifestations of potential behavioral toxicity (i.e., learning or memory; motor- or anxiety-related activity; and neural sensitization), with some findings reported at low-exposure levels, this represents a significant data gap.

Data from experimental animal studies also suggest that excessive formaldehyde inhalation (levels >7 mg/m^3) may cause developmental neurotoxicity. The evidence most informative to this potential health effect was a *medium* confidence study (i.e., two publications on the same experiment) examining neuropathological changes in rats; a few *low* confidence studies reporting somewhat equivocal evidence for developmental effects other than neuropathology did not contribute. While the methods used in this study to evaluate developmental neuropathology were sensitive and designed to minimize bias, and the endpoint (persistently decreased neuron number) is adverse, of clear concern to humans, and without comparable data to the contrary, there were notable uncertainties introduced by the study design that warrant replication of the results. These include a very small sample size (n = 3 litters), as well as lack of control for potential litter effects. As some mechanistic changes in the hippocampus and related brain regions after developmental exposure have been reported in well-conducted studies, indirect effects of formaldehyde exposure on the CNS have some demonstrated plausibility. In the absence of confirmatory studies (e.g., in other species; by other laboratories; using more informative study designs), the evidence for effects

in animals is considered *slight*. No studies in children were available to inform developmental neurotoxicity (i.e., *inadequate*). Overall, the **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation might cause developmental effects on the nervous system, primarily based on a set of neuropathology studies from the same laboratory. The primary support for this judgment is from animal studies of neuropathology following developmental exposure to >7 mg/m^3 of formaldehyde. Given the potential for children to be exposed to formaldehyde, this area represents a research need.

Overall, conclusive evidence of a nervous system health hazard in humans exposed to formaldehyde was not identified. Given that, across a number of studies, the **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation might cause multiple manifestations of nervous system health effects in humans given relevant exposure circumstances (see Table 1-50), and the general lack of comprehensive and rigorous experiments across the database, additional study is warranted.

Table 1-50. Evidence integration summary for nervous system effects after formaldehyde inhalation[a]

Evidence	Evidence judgment	Hazard Determination
Amyotrophic Lateral Sclerosis (ALS)		
Human evidence	*Slight*, based on: *Human health effect studies*: • Strong association in one *medium* confidence study, with more limited support from three additional *medium* confidence studies (including two studies from the same researchers). • However, no association in one *high* confidence study. • Effects were from large, well-conducted longitudinal or retrospective studies. • However, there was uncertainty in individual exposure assessments, lack of exposure-response trends in studies with adequate data to examine, inconsistency in associations with duration, and effect estimates based on a very small number of exposed cases. *Biological plausibility*: No relevant mechanistic studies in humans were identified, and this effect is surprising (i.e., plausibility is lacking) without systemic distribution.	The **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation might cause increases in ALS incidence or mortality, given the appropriate exposure circumstances[b] Primarily based on occupational studies (presumably higher levels of exposure), generally with uncertain exposure assessments. (Note: Confirmatory effects in a *medium* confidence human study with a reasonable number of exposed cases and more certain measures of exposure would be expected to adjust this to **evidence indicates [likely]**) *Potential susceptibilities*: ALS disproportionately affects males, which
Animal evidence	• *Indeterminate*, based on: No available animal studies address this outcome.	
Other inferences	• *Relevance to humans*: The effect was observed in humans. • *MOA*: No verified MOA exists for how formaldehyde could elicit effects in motor neuron-related systems without systemic distribution. Additional study into the potential involvement of systemic oxidative stress (see Appendix A.5.6) is warranted, given research interest in associations between elevated oxidative stress and ALS progression.	

		were the focus of most of the available formaldehyde studies.
Developmental Neurotoxicity		
Human evidence	• *Indeterminate*, based on: No available human studies address this outcome.	The **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation might cause developmental neurotoxicity, given the appropriate exposure circumstances[b] Based on a small set of studies from one laboratory that exposed postnatal rats to formaldehyde concentrations >7 mg/m^3. (Note: confirmatory effects in a *medium* confidence animal study from another laboratory or in another species, particularly one testing lower exposure levels, would be expected to adjust this to **evidence indicates [likely].)** *Potential susceptibilities*: The available data relate to postnatal exposure; it is unknown whether other lifestages might exhibit even greater sensitivity.
Animal evidence	*Slight* for developmental neurotoxicity, based on: *Animal health effect studies:* • Developmental neuropathology in one *medium* confidence (reported in two papers) and one *low* confidence study of the male rat hippocampus (less convincing evidence on other endpoints from other *low* confidence studies did not contribute). • No conflicting evidence (i.e., no comparable evaluations). • The stereological methods used minimize bias, and multiple indications of toxicity persisted 60 days after exposure. • However, the studies were conducted by a single laboratory, had a low sample size, were analyzed on a pup (not litter) basis, and only tested formaldehyde levels >7 mg/m^3 (which complicates interpretation). *Biological plausibility*: Several studies with well-conducted exposures (including developmental exposure) demonstrate molecular and neurochemical changes in relevant (i.e., limbic) brain regions at lower concentrations, providing plausibility.	
Other inferences	• *Relevance to humans*: Uncertainty regarding the relevance of the animal evidence exists, as the studies only tested high levels of formaldehyde expected to cause strong irritant effects that may not occur in humans; otherwise, rodent neuropathology is relevant to humans and is adverse. • *MOA*: No verified MOA exists for how formaldehyde could elicit CNS effects without systemic distribution, although evidence related to several indirect mechanisms of potential relevance was identified.	
Neurobehavioral Effects		
Human evidence	*Indeterminate* for neural sensitization, based on: No available human studies address this outcome. *Slight* for effects in tests of motor-related behaviors, based on: *Human health effects studies:* • Effects in two *low* confidence studies and slight effects (near equivocal; not dose-dependent) in one *medium* confidence study.	The **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation might cause multiple manifestations[c] of potential behavioral toxicity, given the

	• No effect in one *low* confidence study. • Effects were observed across demographics and behavioral tests. • However, likely coexposures were not always evaluated, and data are primarily based on acute exposure. *Slight* for effects in <u>tests of learning or memory</u>, based on: *Human health effects studies:* • Effects in three *low* confidence, independent studies. • No effect in one *low* confidence study. • Effects were related to duration of exposure across studies. • However, the studies had significant coexposures or poorly comparable groups, and no dose-dependent effects were observed with controlled exposure. *Biological plausibility* (for any of the above behaviors): No relevant human studies identified.	appropriate exposure circumstances[b] Primarily based on a number of *low* confidence studies in rats and mice, many of which observed effects after formaldehyde exposure ≤1 mg/m^3. (Notes: Confirmatory effects supporting neural sensitization in one *medium* confidence study from another laboratory alongside mechanistic confirmation of the human relevance and adversity of the animal findings would be expected to adjust to **evidence indicates [likely]**; as the data for other types of behavioral effects are only based on *low* confidence studies, it is expected that confirmatory effects of behavioral changes other than neural sensitization in multiple *medium* confidence studies would be needed to adjust this to **evidence indicates [likely].**) *Potential susceptibilities*: Unknown, as well-conducted developmental studies of these effects were not identified.
Animal evidence	*Slight* for <u>neural sensitization</u>, based on: *Animal health effects studies:* • Effects in one *medium* confidence and five *low* confidence studies across two species (rats and mice). • No contrary results. • Some studies show that responses increase with increasing duration of exposure and persist weeks after exposure. • However, behaviors may be complicated by possible olfaction, irritation, and stress responses specific to animal exposure scenarios that were untested. *Slight* for changes in <u>Tests of motor-related behaviors</u>, based on: *Animal health effects studies:* • Effects in seven *low* confidence studies across laboratories in both sexes of rats and mice (multiple strains). • No effect in one *medium* confidence study. • Most responses were dose-dependent and one study reported effects persisting for weeks. • However, every study had test article deficiencies or was complicated by irritation-related responses, and few tests assessed a discrete function (e.g., motor activity). *Slight* for changes in <u>Tests of learning or memory</u>, based on: *Animal health effects studies:* • Effects in five *low* confidence studies from multiple research laboratories across various durations of exposure and in both sexes of rats and mice • No contrary results • Effect magnitude increased with repeated exposure, and was sometimes dose-dependent (in two studies) and persisted weeks after exposure (in one subchronic study) • However, all studies had test article deficiencies, and most did not evaluate motor activity as a contributing factor. *Biological plausibility* (for any of the above behaviors): Several studies with well-conducted exposures demonstrate molecular and neurochemical changes in the brain at comparable or lower formaldehyde levels. Specifically, for sensitization, animal evidence of changes to circulating stress hormones provides additional plausible support.	
Other inferences	• *Relevance to humans*: For neural sensitization, translatability to human exposure scenarios and adversity in humans remains unclear, requiring further study. For the other behavioral changes, the commonly used tests and the	

	changes observed at levels not expected to induce irritation are considered relevant to humans and potentially are adverse. • *MOA (for any of these centrally mediated effects)*: No verified mechanism exists for how formaldehyde could elicit CNS effects without systemic distribution; however, several lines of evidence exist to support the potential for indirect effects on the CNS. • *Other*: The duration- and timing-dependence of these potential effects is unknown, as most of the data are from acute and short-term exposure (i.e., no chronic studies; one subchronic study of 30 min. daily exposures) of formaldehyde levels >7 mg/m^3 (which complicates interpretation).	

Abbreviations: ALS = amyotrophic lateral sclerosis; MOA = mode of action; CNS = central nervous system.
[a]In addition, a single, cursory experiment on nociception was identified; this **evidence** was considered **inadequate.**
[b]Given the uncertainty in this judgment and the available evidence, this assessment does not attempt to define what might be the "appropriate exposure circumstances" for developing this outcome.
[c]The available **evidence suggests**, but is not sufficient to infer, that formaldehdye might cause each of the evaluated manifestations of potential behavioral toxicity (i.e., neural sensitization, tests of motor-related behaviors, and tests of learning and memory), either individually or as encompassed by the broader category of neurobehavioral tests.

1.3.2. Developmental and Reproductive Toxicity

Studies in humans, and a number of animal studies have reported effects of inhaled formaldehyde on pre- and postnatal development and on the female and male reproductive systems. Three studies evaluated residential exposure during pregnancy and fetal and infant growth measures, including ultrasonographic biometric measures, birth weight and head circumference, and postnatal growth The most common outcome reported by occupational epidemiology studies was an elevated spontaneous abortion risk in different industries, with strong associations seen in the highest exposure categories. Further, maternal and paternal formaldehyde exposure was associated with decreased fecundity,[25] indicated by a longer time to achieve a pregnancy, in two studies of employees in the woodworking industry (out of a total set of three studies). The associations among female workers may reflect either toxicity to the reproductive system of the mother (ability to achieve and support the pregnancy) or the developing fetus. Together, the findings among women provide *moderate* evidence of developmental or female reproductive toxicity. In animal studies, there is *indeterminate* evidence for manifestations of developmental toxicity (i.e., decreased survival, decreased growth, or increased evidence of structural anomalies) or female reproductive toxicity (ovarian and uterine pathology, ovarian weight, and hormonal changes). All available studies were of *low* confidence, primarily due to exposure-quality concerns (i.e., the use of formalin, or an uncharacterized test substance).

Two studies of exposure to male workers from one research group provide *slight* evidence that formaldehyde exposure is associated with lower total and progressive sperm motility, and delayed fertility and spontaneous abortion. The epidemiological observations are supported by *robust* evidence from experimental studies in animals that used paraformaldehyde to expose the animals. Across this set of studies, coherent evidence for a range of effects on the male

[25]The capacity to conceive and deliver a baby.

reproductive system was demonstrated, including quantitative histopathological effects in the testes and epididymides, decreased serum testosterone (T), decreased sperm count and motility, and increased sperm morphological abnormalities. However, limitations in the animal study database for male reproductive toxicity include a general lack of functional measures in the available studies and no studies that tested formaldehyde levels below 6 mg/m^3, warranting additional study.

Overall, the **evidence indicates** that inhalation of formaldehyde likely causes increased risk of developmental or female reproductive toxicity in humans, given the appropriate exposure circumstances. This conclusion is based on *moderate* evidence in observational studies finding increases in time-to-pregnancy (TTP) and spontaneous abortion risk among women with occupational formaldehyde exposures. The evidence in animals is *indeterminate*, and a plausible, experimentally verified MOA explaining such effects without systemic distribution of formaldehyde is lacking. Likewise, the **evidence indicates** that inhalation of formaldehyde likely causes increased risk of reproductive toxicity in men, given the appropriate exposure circumstances, based on *robust* evidence in animals that presents a coherent array of adverse effects in two species testing formaldehyde concentrations >6 mg/mg^3, and *slight* evidence from observational studies of occupational exposure, and no plausible, experimentally verified MOA explaining such effects without systemic distribution of formaldehyde. However, some support for indirect effects in rodents is provided by relevant mechanistic changes in male reproductive organs.

Literature Search and Screening Strategy

The primary databases used for the literature search were PubMed, Web of Science, and ToxNet, with the last update of the search completed in September 2016 (see Appendix A.5.8), and a systematic evidence map updating the literature through 2021 (see Appendix F). This included the identification of studies of specific health outcomes and particular exposure scenarios in studies of exposed humans, studies of reproductive and developmental toxicity in animals with exposure to inhaled formaldehyde, and relevant mechanistic data. Animal studies conducted with other routes of exposure (e.g., oral, IP injection) were excluded because such studies would likely result in target organ concentrations of formaldehyde and its metabolites that would not be anticipated with inhalation exposures. The majority of health outcomes assessed in epidemiology studies of inhalation exposure that were included for further evaluation were studies of fecundability[26] (e.g., TTP), reproductive parameters in males, spontaneous abortion, and birth outcomes. Outcomes assessed in animal toxicology studies that were included in the assessment were developmental toxicity (prenatal survival, fetal and postnatal growth, and malformations), male reproductive toxicity (sperm count and morphology, testes and epididymal weight and histopathology, and functional measures), and female reproductive toxicity (hormone levels, ovarian and uterine weight and histopathology, and early embryo loss). Functional developmental

[26]A couple's probability of conception in one menstrual cycle.

outcomes (i.e., developmental neurotoxicity) were addressed in the sections on the nervous system (see Section 1.3.1).

The bibliographic databases, search terms, and specific strategies used to search them are provided in Appendix A.5.8, as are the specific PECO criteria. A literature flow diagram summarizes the results of the sorting process using these criteria and indicates the number of studies that were selected for consideration in the assessment through 2016 (see Appendix F for the identification of newer studies through 2021). These studies in animals and humans were evaluated to interpret the quality and relevance of the study results regarding hazard identification (see Appendix A.5.8 and below for details).

Methodological Issues Considered in Evaluation of Studies

A variety of different approaches to the assessment of occupational exposure were used in the epidemiological literature. These ranged from more specific, highly informative measures such as estimates of job-exposure matrix (JEM)-based TWA concentrations (based on job-specific formaldehyde measurements and the proportion of time spent at the job reported by participants) to measures subject to greater misclassification error, such as the self-reported use of specific products or chemicals, or assignment to exposures by supervisors. Four studies reported by three independent research groups assigned exposure levels to individual participants using area-level formaldehyde measurements (Wang et al., 2015; Wang et al., 2012; Taskinen et al., 1999; Seitz and Baron, 1990). Of these, three studies of wood workers used JEMs to increase the accuracy of their exposure estimates (Wang et al., 2015; Wang et al., 2012; Taskinen et al., 1999).

In the absence of formaldehyde measurements, studies assigned exposure to individuals based on self-reporting (work processes Zhu et al., 2005; Steele and Wilkins, 1996; John et al., 1994; Saurel-Cubizolles et al., 1994; Taskinen et al., 1994; Axelsson et al., 1984), an informed source (Hemminki et al., 1985; Hemminki et al., 1982) or occupation/industry codes from census data combined with expert knowledge of industry-wide concentrations (Lindbohm et al., 1991). The studies that collected information about jobs or tasks with a higher probability of formaldehyde exposure, and the amounts or frequency of exposure, were less likely to be limited by exposure misclassification (John et al., 1994; Taskinen et al., 1994). In two studies of hospital staff, Hemminki et al. (1985; 1982) identified staff who worked in specific departments and requested information about chemical exposures, including formaldehyde used as a sterilizing agent, from their supervising nurses. Supervisors were asked to assign exposures for specific periods pertaining to the first trimester of identified births that had occurred over several preceding years (Hemminki et al., 1985; Hemminki et al., 1982). In one of these studies (Hemminki et al., 1985), hospital staff were categorized as exposed if they used the sterilizing agent or merely used instruments sterilized with the agent. No information about the amount or frequency of sterilant use was incorporated in the estimates. Although relying on the nurses' supervisors for exposure information could reduce the possibility of recall bias, the actual level and frequency of exposure for some individuals categorized as exposed to formaldehyde may have been very low. Some

exposure categories were quite broad, including individuals exposed infrequently to low levels (Zhu et al., 2006, 2005; Steele and Wilkins, 1996). Exposure misclassification and the classification of individuals with probable low or infrequent exposure as exposed likely resulted in an underestimate of the effect estimate and was a major limitation in these and other studies designated as *low* confidence (Zhu et al., 2006, 2005; Lindbohm et al., 1991; Hemminki et al., 1985; Hemminki et al., 1982).

A key consideration for the interpretation of developmental and reproductive outcomes associated with inhalation exposures to formaldehyde in experimental studies was the potential for coexposure to methanol, a known developmental and reproductive toxicant (U.S. EPA, 2013), when the test article was an aqueous solution of formaldehyde. Studies that used formalin but did not control for methanol, and studies that did not characterize the formaldehyde source, are identified throughout this section. Such studies were assigned a *low* confidence rating and contributed little to the synthesis of evidence regarding formaldehyde effects on development or the reproductive system.

Developmental and Reproductive Effects in Human Studies

The observational studies of reproductive toxicity or pregnancy outcomes evaluated associations with exposure during pregnancy in three studies and with occupational exposure among cosmetologists, woodworkers, laboratory workers, and hospital staff. The evidence regarding TTP, spontaneous abortion, pre- and post-natal growth and other birth outcomes, and male reproductive toxicity was synthesized, and the studies summarized in Tables 1-51 through 1–54, ordered by the level of confidence in the study result (i.e., *high*, *medium,* or *low*) and then by publication date.

Time to pregnancy and subfertility

TTP is a measure of fertility and has been characterized in terms of number of menstrual cycles that occurred prior to conception. TTP of greater than 12 months of unprotected intercourse is indicative of infertility (Wilcox, 2010 p. 123). Increased TTP might result from potential effects on gametogenesis, transport, fertilization, migration, implantation, or survival of the embryo (Baird et al., 1986). Thus, the measure reflects a potential impact on multiple biological processes, possibly in both partners, and can be sensitive to the detection of events early during pregnancy that usually cannot be easily detected in population-based studies. Because it is evaluated in number of months or menstrual cycles, TTP is informative regarding exposures with impacts over shorter time periods (e.g., <1 year). TTP is not a measure of infertility as these studies only include women who became pregnant and had a live birth.

One *medium* confidence study (Taskinen et al., 1999) and one low confidence study (Zhu et al., 2005) were identified that evaluated effects on TTP in relation to maternal exposure to formaldehyde (see Table 1-51). TTP was retrospectively ascertained using self-completed questionnaires (Taskinen et al., 1999). Taskinen et al. (1999) used an appropriate analytical

approach, involving the comparison of fecundability[27] among four exposure groups. The association of maternal formaldehyde exposure with TTP became significantly increased in the highest exposure group with an 8-hour TWA (TWA8) exposure of 0.27 mg/m^3. The fecundability density ratio (FDR) for individuals in the highest formaldehyde exposure category compared to nonexposed individuals, adjusting for potential confounders and phenol exposure was 0.57 (95% CI 0.37, 0.85). The FDRs for organic solvents, dusts, wood dusts, and phenols in models that adjusted for potential confounders, including formaldehyde as a coexposure, were all greater than 0.90 ($p > 0.05$). Therefore, the observed association with formaldehyde was not explained by these other exposures because they were not associated with longer TTP. FDR was lowest among 17 of the 39 highly exposed women who did not wear gloves (FDR = 0.51; 95% CI 0.28, 0.92), suggesting that dermal exposure contributed to increased risk of increased TTP. In addition to the detailed exposure assignments, Taskinen et al. (1999) reduced the potential for selection bias by recruiting from female members of a woodworkers union who had been employed at least six months prior to their pregnancy. Thus, selection into the study was not conditional on being currently employed in the industry at the time of the study.

Table 1-51. Epidemiology studies describing effects on time to pregnancy in relation to formaldehyde exposure

Study and design	Results
Reference: Taskinen et al. (1999) Retrospective cohort study, Finland **Population:** Women (n = 3,772), recruited from a woodworkers' union and other businesses involving wood processing, 1,094 women eligible (born between 1946 and 1975, had a live birth at age 20–40 years during 1985–1995, had worked in the wood processing industry for at least 1 month, and had first employment in the wood processing industry beginning at least 6 months before the index pregnancy). The first eligible pregnancy was the index pregnancy. Information about personal characteristics, pregnancies, and exposures was collected from mailed questionnaires; response rate 64%. After other exclusions (primarily infertility history, unknown TTP, and contraceptive failure), the final sample included 602 women. Period of recall of TTP period: 1–11 years. **Exposure:** Questionnaire on exposure to specific agents including hours/week during TTP period. Mean daily exposure to formaldehyde was based on measurements taken at the factories where the women worked during the early 1990s or, if measurements unavailable, from comparable industries. Sampling protocol was not described. Formaldehyde concentrations were obtained from comparable industries for 46, 31, and 61% of women in low, medium, and high exposure categories, respectively. Formaldehyde concentration in factories by exposure category: Low mean 0.07 ppm (0.086 mg/m^3)*, range 0.01 to 0.3 ppm (0.012 to 0.37 mg/m^3);	TTP by formaldehyde category N / FDR[a] / 95% CI Not Exposed: 367 / 1.00 / – Low: 119 / 1.09 / 0.86, 1.37 Medium: 77 / 0.96 / 0.72, 1.26 High: 39 / 0.64 / 0.43, 0.92 [a] Fecundability density ratio adjusted for employment, smoking, alcohol consumption, irregular menstrual cycles, and number of children (recent contraceptive use not found t be a confounder). TTP among women with high formaldehyde exposure, by glove use N / FDR[a] / 95% CI Gloves: 22 / 0.79 / 0.47, 1.23 No gloves: 17 / 0.51 / 0.28, 0.92 [a]Fecundability density ratio adjusted for employment, smoking, alcohol consumption, irregular menstrual cycles, and # children.

[27]Fecundability is the probability of a couple conceiving in 1 month, calculated as the average number of menstrual cycles to achieve a pregnancy for a group divided by the total number of cycles experienced in the group.

Study and design	Results
Medium mean 0.14 ppm (0.17 mg/m^3), range 0.05 to 0.4 ppm (0.062 to 0.49 mg/m^3); High mean 0.33 ppm (0.41 mg/m^3), range 0.15 to 1.0 ppm (0.18 to 1.2 mg/m^3) Other chemicals with measurements: phenol, organic solvents, wood dust, other dusts. **Methods:** Analysis: discrete proportional hazards regression; outcome, FDR, ratio of average incidence density of pregnancies in exposed compared to employed, unexposed women); for covariates in model, see results; significance assessed by likelihood ratio test. **Evaluation:**[a]  Expect some error in individual exposure assignments.	TTP among women with high formaldehyde exposure and phenol (when included in same model)[a] N / FDR[b] / 95% CI Phenol: 68 / 1.56 / 0.93, 2.53 Formaldehyde: NR[c] / 0.57 / 0.37, 0.85 [a]All women exposed to phenols were also exposed to formaldehyde, but not vice versa. Fecundability density ratio adjusted for employment, smoking, alcohol consumption, irregular menstrual cycles, and # children. [c]Not reported.
Reference: Zhu et al. (2005) Cohort study, Denmark **Population:** Exposed were female laboratory technicians, identified through the Danish National Birth Cohort, who had only held one job (*n* = 1,069); 1st interview in June 1997–February 2003 (at week 12–25 of gestation); excluded women with endometriosis, ovarian or cervical cancer, unplanned or partly planned pregnancies, and included only 1st pregnancy in study period for each woman (final *n* = 829, 77.5% of initial study cohort); 8.6% ≥35 years old, 13.9% smoker during 1st trimester; 29.3% previous spontaneous abortion. Referents were teachers identified in same manner; *n* = 6,250 (73.9% of initial cohort of 8,461); 12.7% ≥35 years old, 20.1% smoker during 1st trimester; 31.1% previous SA **Exposure:** Queried at gestation week 12–25 (median week 17). Self-report on laboratory work processes during pregnancy and 3 months before, including frequency and use of protective measures. EI calculated as exposure level × frequency of work contact, using scores for exposure level and frequency: Formaldehyde exposure level (low = 1, medium = 2), assigned by study researchers as follows: Low: human blood and tissue processing, work with experimental animals, work with microorganisms; medium: preparation of slides for microscopy. No work processes were identified considered to involve high exposure to formaldehyde. Frequency: everyday = 4, several times per week = 3, several days per month = 2, and rarely = 1. Exposure Index categories: 1–5 and ≥6 **Methods:** Self-report of TTP (4 categories: 0–2 months, 3–5 months, 6–12 months, and >12 months); Fecundability ratios analyzed using discrete-time survival analysis (complementary log-log link); comparisons between laboratory technicians and referents (teachers) and among laboratory technicians; covariates in model see results. **Evaluation:**[a]  	Fecundability ratio for 1st pregnancies among 829 laboratory technicians, by formaldehyde exposure index EI / N / cFR / aFR[a] / 95% CI 1–5: 112 / 1.0 / 0.92 / 0.69, 1.22 ≥6: 74 / 1.18 / 1.03 / 0.74, 1.43 [a]aFR: adjusted for maternal age, gravidity, smoking, prepregnancy BMI, and paternal job (also evaluated history of spontaneous abortion and alcohol consumption). Fecundability ratios for 1st pregnancies: labora technicians compared to teachers N / cFR / aFRb / 95% Teacher: 6,250 / 1.00 / 1.00 Lab technician: 829 / 1.01 / 0.98 / 0.86, 1.13 [b]FRa: adjusted for maternal age, gravidity, smoking, prepregnancy BMI, and paternal job (also evaluated history of spontaneous aborti and alcohol consumption).

Study and design	Results
Categorized TTP (decreased precision), missed pregnancies that ended before 1st interview. Variation in probability or intensity of formaldehyde exposure possible for work processes across different types of labs and high likelihood of exposure misclassification (likely underestimating the effect estimate), did not account for large proportion of participants who used protective measures to prevent inhalation exposure. JEM was not validated for formaldehyde.	

[a]Evaluation of sources of bias or study limitations (see details in Appendix A.5.8). SB = selection bias; IB = information bias; Cf = confounding; Oth = other feature of design or analysis. Extent of column shading reflects degree of limitation. Direction of anticipated bias indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact would be likely to be away from the null (i.e., spurious or inflated effect estimate).
Results from *low* confidence studies are shaded; these findings are considered less reliable.
Abbreviations: TTP = time to pregnancy; CI = confidence interval; EI = exposure index; JEM = job-exposure matrix; FDR = fecundability density ratio; BMI = body mass index.
[*]Converted study exposure values are presented in [italics]. Conversion factors for formaldehyde in air (at 25°C): 1 ppm = 1.23 mg/m^3.
Results from *low* confidence studies are shaded; these findings are considered less reliable.

Spontaneous abortion

Two *medium* confidence studies provide evidence (see Table 1-52) that formaldehyde exposure to female workers is associated with an increased risk of spontaneous abortion. A third *low* confidence study contributed information about exposure-response patterns, which was included as a consideration in the synthesis. These studies examined diverse occupational groups exposed to different combinations of chemical exposures and products containing formaldehyde (wood working, cosmetology, research laboratories). Relatively high odds ratios (ORs) of 2–3.5 in the highest exposure categories were observed (Taskinen et al., 1999; John et al., 1994; Taskinen et al., 1994). Studies of hospital, nursing, or medical employees generally did not report an association with formaldehyde exposure, although these *low* confidence studies tended to use less precise exposure assessment methods, a major limitation that reduced the sensitivity of these studies.

All of the studies defined spontaneous abortion, also called miscarriage, as a pregnancy loss before the 20th week of gestation. Spontaneous abortions were ascertained retrospectively, primarily using questionnaires, and in several studies these self-reports were included for analysis only if they could be verified using additional information. Some studies included all eligible spontaneous abortions recalled by participants (Taskinen et al., 1999; Steele and Wilkins, 1996). These studies had greater sensitivity (ascertained early pregnancies prior to clinical recognition). Validity studies indicate that recall of previous spontaneous abortions is relatively complete, particularly for losses that occurred after the 8th week of gestation (>80% of recorded spontaneous abortions were recalled) (Wilcox and Horney, 1984). Other studies identified spontaneous abortions directly from a hospital discharge register (Lindbohm et al., 1991; Hemminki et al., 1985), an approach that avoids the limitations of recall bias but is prone to underascertainment of early recognized losses that do not merit medical attention (Wilcox, 2010).

All of the studies focused their exposure assessments on the first trimester of pregnancy (women). The assignment of formaldehyde exposure during this period of susceptibility for spontaneous abortion (Wilcox and Horney, 1984) was less certain for two *low* confidence studies, possibly resulting in misclassification and reduced study sensitivity (Steele and Wilkins, 1996; Lindbohm et al., 1991).

Two *medium* confidence studies conducted analyses or provided details to evaluate potential confounding by coexposures and found that formaldehyde exposure posed an independent risk. One study adjusted for other coexposures in the workplace that also posed a possible risk of spontaneous abortion (John et al., 1994). In this evaluation of cosmetologists, an adjusted OR of 2.1 was reported for use of formaldehyde-based disinfectants (95% CI 1.0, 4.3). Taskinen et al. (1999) evaluated previous spontaneous abortions reported by female woodworkers, all of whom had a live birth, using unconditional logistic regression, and adjusted for age, employment, smoking, and alcohol consumption. No associations were observed for exposure to phenol, organic solvents, wood, and other dusts. Because formaldehyde was the only exposure associated with spontaneous abortion, these other work exposures were not confounders in this analysis. Potential confounding was identified to be a limitation for a study of laboratory technicians (Taskinen et al., 1994). This study observed a strong association between formalin exposure at a frequency of 3–5 days per week and spontaneous abortion (OR = 3.5; 95% CI 1.3, 7.5), but most of the participants exposed to formalin also reported exposure to xylene, which also was strongly associated with spontaneous abortion (OR = 3.1; 95% CI 1.3, 7.5). Although potentially confounded by xylene, the results of this study were compared to those of John et al. (1994) and Taskinen et al. (1999) to assess a potential bias away from the null. Other studies did not provide information to evaluate confounding by coexposures and did not provide risk estimates adjusted for coexposures.

ORs for spontaneous abortion risk in relation to maternal formaldehyde exposure are plotted in Figure 1–31 and are grouped by industry. The three studies indicate that maternal formaldehyde exposure is associated with risk of spontaneous abortion among woodworkers, laboratory workers, and cosmetologists (Taskinen et al., 1999; John et al., 1994; Taskinen et al., 1994). Two studies evaluated multiple exposure groups and found that stronger associations were observed among women in the highest exposure groups (OR range 3.2–3.5). Although Taskinen et al. (1994) did not control for xylene exposure, which also was associated with spontaneous abortion risk, the magnitude of the OR among laboratory workers with the most frequent exposure was comparable to the two higher confidence studies.

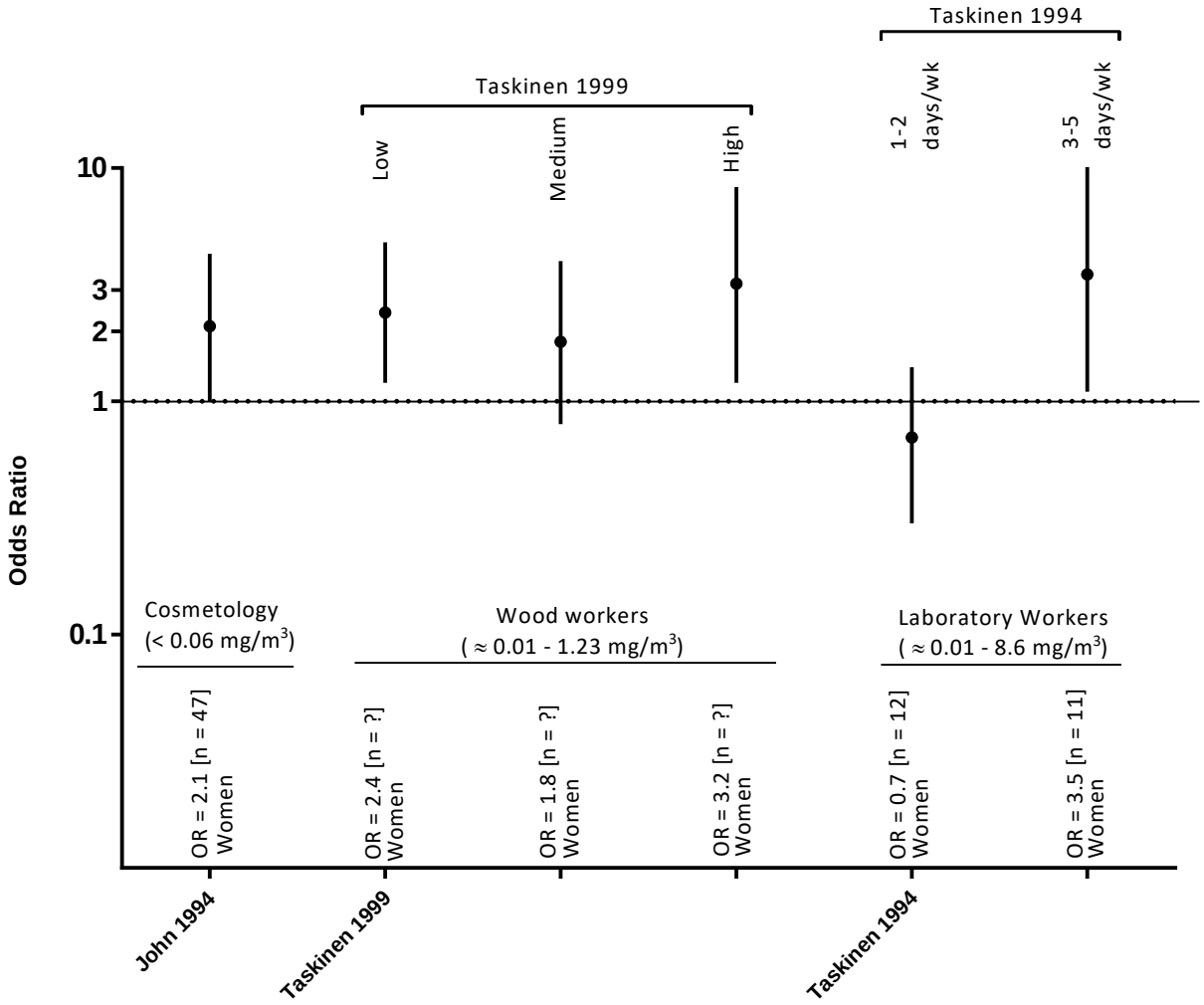


Figure 1-31. Risk of spontaneous abortion associated with maternal occupational formaldehyde exposure.

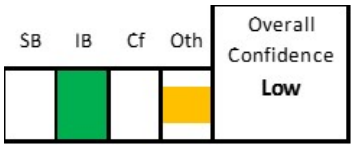
OR and number of exposed cases are presented for each study. Taskinen et al. (1999) and John et al. (1994) were *medium* confidence studies, and Taskinen et al. (1994) was a *low* confidence study due to potential confounding possibly resulting in bias away from the null. The number of exposed cases was not reported by Taskinen et al. (1999). A range of formaldehyde exposure concentrations experienced in specific industries is presented. Formaldehyde concentration ranges reported or cited by the authors are presented (Taskinen et al., 1999; Taskinen et al., 1994), or were obtained from the literature for cosmetology (Tsigonia et al., 2010; Labrèche et al., 2003).

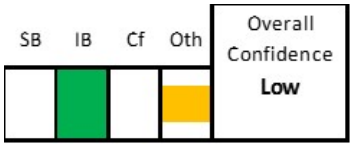
Table 1-52. Epidemiology studies describing effects on spontaneous abortion in relation to formaldehyde exposure

Study and design	Results
Reference: John et al. (1994) United States Case-control study **Population:** 6,202 of 8,356 women (74%) in North Carolina cosmetology license registry responded to screening questionnaire; 1,249 of 1,696 women (74%) with eligible pregnancy (most recent pregnancy for which last menstrual period occurred between April 1983 and March 1988) completed detailed questionnaire. Data obtained on 191 of 267 eligible spontaneous abortions, and 1,058 of 1,429 eligible live births (1,696 total abortions and live births); 87% white, 92% high school education, 65% income <$20,000, mean age 25.9 years. **Exposure:** Self-reported exposure through mailed questionnaire to formaldehyde-based disinfectant products during first trimester. Other measures of exposure intensity: number of customers, number and type of chemical services performed per week, number of hours per day spent standing, disinfection products used, and glove use. **Methods:** Three spontaneous abortions were excluded because no positive pregnancy test or subsequent medical care was reported. Women working ≥35 hrs/week as cosmetologists, with or without use of formaldehyde disinfectants, were compared to women working in other jobs (referent) during first trimester, and cosmetologists working with formaldehyde disinfectants were compared with those who did not. Multivariate unconditional logistic regression. **Evaluation:**[a]  Selection of most recent eligible pregnancy (potential underascertainment); no ambient measurements; adjustment for previous pregnancy loss may introduce bias.	Spontaneous abortions in 7.8% of most recent pregnancies; mean gestational age for spontaneous abortion: 9.8 weeks. Spontaneous abortion among women working full-time (≥35 hr/week) during 1st trimester | | # SA | OR[a] | 95% CI | | Other jobs | 26 | 1.0 | Referent | | Cosmetology work and no formaldehyde-based disinfectant use | 16 | 0.8 | 0.4, 1.6 | | Cosmetology work and use of formaldehyde-based disinfectant | 51 | 1.7 | 1.0, 3.0 | [a]Adjusted for mother's age at conception, previous pregnancy loss, and cigarette smoking. Spontaneous abortion among women working full-time (≥35 hr/week) as cosmetologists during 1st trimester | formaldehyde disinfectant use | # SA | OR[a] | 95% CI | | No | 14 | 1.0 | | | Yes | 47 | 2.1 | 1.0, 4.3 | [a]Adjusted for variables listed above and other work exposures (hours worked, hours standing, chemical services, formaldehyde-based disinfectant, alcohol-based disinfectant, and nail sculpturing). ORs increased with standing ≥8 hours a day and the number of chemical services/week. Previous pregnancy loss, ≥3 pregnancies, and cigarette smoking were more prevalent among women with spontaneous abortion.
Reference: Taskinen et al. (1999) Retrospective cohort study, Finland **Population:** Women (*n* = 3,772), recruited from a woodworkers' union and other businesses involving wood processing. 1,094 women eligible (born between 1946 and 1975, had a live birth at age 20–40 years during 1985–1995, had worked in the wood processing industry for at least 1 month, and had first employment in the wood processing industry beginning at least 6 months before the index pregnancy). The first eligible pregnancy was the index pregnancy. Information about personal characteristics,	For 52 pregnancies with report of previous spontaneous abortion and same place of employment for both events (95% CI) | Exposure | OR | 95% CI | | Low | 2.4 | 1.2, 4.8 | | Medium | 1.8 | 0.8, 4.0 | | High | 3.2 | 1.2, 8.3 | Organic solvents, dusts, wood dusts, and phenols were not associated with spontaneous abortions.

Study and design	Results
pregnancies, and exposures was collected from mailed questionnaires; response rate 64%. After other exclusions (primarily infertility history, unknown TTP, and contraceptive failure), the final sample included 602 women. **Exposure:** Questionnaire on exposure to specific agents including hours/week during the period pertaining to TTP. Exposures during critical exposure period(s) for spontaneous abortion were not estimated. Mean daily exposure to formaldehyde was based on measurements taken at the factories where the women worked during the early 1990s or, if measurements unavailable, from comparable industries. Sampling protocol was not described. Formaldehyde concentrations were obtained from comparable industries for 46, 31, and 61% of women in low, medium, and high exposure categories, respectively. Formaldehyde concentration in factories by exposure category: Low mean 0.07 ppm (0.086 mg/m^3)[a], range 0.01 to 0.03 ppm (0.012 to 0.37 mg/m^3); Medium mean 0.14 ppm (0.17 mg/m^3), range 0.05 to 0.4 ppm (0.062 to 0.49 mg/m^3); High mean 0.33 ppm (0.41 mg/m^3), range 0.15 to 1.0 ppm (0.18 to 1.2 mg/m^3) Other chemicals with measurements: phenol, organic solvents, wood dust, other dusts. **Methods:** Self-reported spontaneous abortions occurring prior to the index pregnancy and at the same workplace were evaluated. Unconditional logistic regression, ORs, adjusted for age, employment, smoking, and alcohol; # exposed cases not reported. **Evaluation:**[a]  Uncertainty regarding exposure measurements with regard to critical exposure period(s) for spontaneous abortion; excluded women with no live birth (missing spontaneous abortions to women with no live births).	
Reference: Taskinen et al. (1994) Finland, Retrospective case-referent **Population:** Sampled from payroll of state lab personnel (1970, 1975–1986), Finnish Union of Laboratory Assistants (1987), and Register of Employees Occupationally Exposed to Carcinogens (1979–1986) **Exposure:** Self-reported exposure from mailed questionnaire. Substances listed in questionnaire or open-ended question Frequency: Rare: 1–2 days/week Frequent: 3+ days/week Reviewed by two occupational hygienists blinded to case status; 8/10 cases and 5/7 referents exposed to formalin were also exposed to xylene. **Methods:** Participants responded to mailed questionnaire regarding occupational exposure, health status, medications, contraception use, smoking, and alcohol consumption during 1st trimester (824 returned/1,000 mailed (82.4%)). Sample linked to Hospital Discharge Register and database of spontaneous abortions treated at hospital outpatient clinics, 1973–1986. Cases: 206 women aged 20–34 years with one spontaneous abortion during study period; 329 referents: 2/case	Spontaneous abortion risk by frequency of formaldehyde exposure Exposure / Cases/ Referent / OR / 95% CI Employed — 0.9 — 0.5, 1.7 Laboratory — 1.4 — 0.9, 2.2 Formalin 1–2 days/wk — 12/28 — 0.7 — 0.3, 1.4 3–5 days/wk — 11/8 — 3.5[a] — 1.1, 11.2 [a]$p < 0.05$ Other substances also were associated with spontaneous abortion during 1st trimester; xylene 3–5 days/week (OR 3.1; 95% CI 1.3, 7.5), toluene 3–5 days/week (OR 4.7; 95% CI 1.4, 15.9).

Study and design	Results
selected from registered births and not a case, matched on age (24 months) and year of end of pregnancy. Logistic regression for matched data adjusting for parity, previous miscarriage, febrile diseases during pregnancy, used contraception at beginning of pregnancy, alcohol consumption, and employment status. **Evaluation:**[a]  Adjustment for parity and previous miscarriage may introduce bias; lack of adjustment for xylene, an exposure associated with the spontaneous abortion and formalin exposure. Evaluation of increasing frequency of use a strength.	
Reference: Steele and Wilkins (1996) United States **Population:** 85% of 2,978 eligible women graduating from U.S. colleges of veterinary medicine during 1970–1980, mean age 36.1 years, 96.2% White; 1,444 women reported 3,098 pregnancies, 2,375 after graduation. **Exposure:** Self-reported job exposure to specific listed chemical or physical agents (yes, no, don't know). Exposed pregnancy defined if estimated time of conception was during the reported years of a job for which exposure also was reported. Definitions of exposure: 1. Job classification associated with the index pregnancy (type of clinical practice). Referent pregnancies: women unemployed when pregnancies began. 2. Specific chemical and physical agents. Referent: employed women reporting no exposure to that agent or unemployed while pregnant. Thirteen exposure categories examined: disinfectants, antibiotics, animal insecticides, formaldehyde, non-DES hormones, solvents, radiation, diethylstilbestrol, nonhalothane anesthetics, halothane, antineoplastics, heavy metals, and ethylene oxide. **Methods:** Self-reported (via mailed questionnaire in 1987) pregnancy and employment history. Evaluated eligible pregnancies (live births, induced abortions, spontaneous abortions) in relation to postgraduate employment. Spontaneous abortion defined as fetal death prior to 20 weeks. Unconditional multiple logistic regression of spontaneous abortion in relation to clinical practice type or self-reported exposures adjusting for maternal age, gravidity, history of spontaneous abortion, history of smoking, and alcohol use. **Evaluation:**[a]  No information on intensity and frequency of formaldehyde exposure, which would likely be variable among veterinarians (exposure misclassification–decreased sensitivity). Adjustment for gravidity and previous spontaneous abortion may introduce bias.	264 (11.1%) spontaneous abortions. Analysis limited to women holding only one job at the time of conception (1,813 pregnancies). Spontaneous abortions in veterinarians with self-reported exposure to formaldehyde, adjusted[a] OR (95% CI) Clinical practice / Exposed pregnancies (*N*) / OR / 95% CI All types / 172 / 0.9 / 0.6, 1.5 All small animal / 115 / 1.1 / 0.6, 2.0 [a]adjusted for age, history of spontaneous abortion, gravidity, smoker, drinker.
Reference: Hemminki et al. (1982) Finland Retrospective cohort	Adjusted spontaneous abortion rate (total pregnancies (*N*) and adjusted rate) among women not exposed and exposed to formaldehyde during pregnancy

Study and design	Results
Population: Female nursing staff working in sterilizing units (exposed) or auxiliary units (referent) in all (approx. 80) general hospitals; 50 exposed pregnancies, 1,100 unexposed pregnancies. **Exposure:** Exposure to sterilizing agents (formaldehyde, ethylene oxide, glutaraldehyde) at beginning of pregnancy (1960−1980) assigned by supervising nurse. Blind to case status; 50 formaldehyde-exposed pregnancies out of 545 total exposed group (9%). No air monitoring conducted. **Methods:** Questionnaire mailed to current supervising nurses to identify nurses exposed to chemical sterilizing agents and nurses not exposed to sterilizing agents, X-rays, or anesthetic gases; response in exposed 91.6%; referent 90.6%. Spontaneous abortions, 1960−1980, identified via questionnaire sent to nurses (self-report); compared to Finland hospital discharge register, 1973−1979. Spontaneous abortion rate (compared to total pregnancies, live births, induced abortions, spontaneous abortions), logistic regression adjusting for age, parity, decade of pregnancy, smoking habits, alcohol, and coffee consumption. **Evaluation:**[a]  Adjustment for parity may introduce bias. Assumed sterilant use was same throughout period; no information on intensity and frequency of formaldehyde exposure (exposure misclassification–decreased sensitivity); no adjustment for other sterilants.	Not Exposed / Exposed Agent: HCHO[a] — Not Exposed *N* 1,100, Rate 8.3; Exposed *N* 50, Rate 8.4 [a] Some individuals used more than one sterilizing agent Adjusted rates among women exposed to ethylene oxide were higher 16.1% versus 7.8%, $p < 0.01$.
Reference: Hemminki et al. (1985) Finland Case-control study **Population:** Pregnancies during 1973−1979 among women who worked in anesthesia surgery, intensive care, operating room or internal medicine departments of a general hospital. **Exposure:** Exposure assessment via questionnaire sent to head nurses at all general hospitals in Finland. For each study subject, requested occupation and exposure (yes, no) to any of the listed substances during a stated 3-month period (1st trimester); blind to case status. Listed substances were anesthetic gases (nitrous acid, halothane, other), sterilizing agents (ethylene oxide, glutaraldehyde, formaldehyde), disinfectant soaps (requested names), cytostatic drugs, and X-rays. Included information about job: shift work, night shift, rotating etc. Occupation identified during 1st trimester for 87.1% cases and 87.8% controls. Information on employment and exposure obtained for 81% of case:control sets. No air monitoring conducted. **Methods:** Spontaneous abortions identified by linking Finnish Hospital Discharge Register with Central Register of Health Care Personnel; 217 cases identified from register as treated for spontaneous abortion 1973−1979 (ICD8 643 & 645). Controls (*n* = 571) were nurses who gave birth to a healthy infant 1973−1979 and other pregnancies who were not cases. Selected three controls per case, matched on age (± 1.5 years), among nurses from same hospital as case. Relationships between spontaneous abortion and formaldehyde analyzed using an unmatched crude analysis.	Spontaneous abortion Crude rate (# cases/# all pregnancies): 8.3%; not different from Finnish rate: 8.4% Exposed pregnancies (#) (at least once per week) among cases and controls (unadjusted OR) Agent: HCHO — Cases # 6, % 3.7; Controls # 24, % 5.2; OR 0.6 Exposure defined as whether subject used sterilizing agent or sterilized instruments

Study and design	Results
Evaluation:[a]  No information on intensity or frequency (exposure misclassification–decreased sensitivity); very small number of exposed cases.	

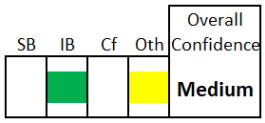
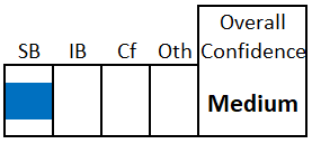
[a]Evaluation of sources of bias or study limitations (see details in Appendix A.5.8). SB = selection bias; IB = information bias; Cf = confounding; Oth = other feature of design or analysis. Extent of column shading reflects degree of limitation. Direction of anticipated bias indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact would be likely to be away from the null (i.e., spurious or inflated effect estimate).
Results from *low* confidence studies are shaded; these findings are considered less reliable.
Abbreviations: SA = spontaneous abortion; OR = odds ratio; CI = confidence interval; HCHO = formaldehyde.

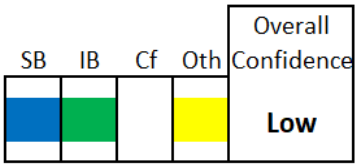
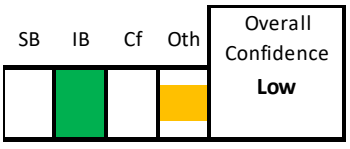
Birth outcomes

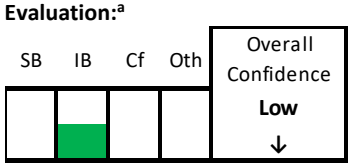
The epidemiology literature is very limited regarding formaldehyde exposure and birth outcomes (see Table 1-53). One birth cohort study reported decreases of 0.044 and 0.056 in the z-scores for birth weight and head circumference, respectively, with each 1 μg/m^3 unit increase in formaldehyde concentration measured in the mother's homes at 34 weeks gestation (Franklin et al., 2019). Gestational age was not associated with exposure. The median concentration in the homes was 0.0028 mg/m^3 and 23.3% of samples were below the LOD in this relatively small study. Another pregnancy cohort study in South Korea observed lower birth weights associated with increasing formaldehyde concentration measured at mid to late pregnancy (mean concentrations were 0.08 mg/m^3), although the associations were of greater magnitude for total volatile organic compounds, which were correlated with formaldehyde levels (Chang et al., 2017). Another study of pregnant women in the southeastern United States, rated as *low* confidence, reported an association of biparietal diameter, suggestive of intrauterine growth retardation, with personal formaldehyde exposure >0.037 mg/m^3, both measured in the second trimester (Amiri and Turner-Henson, 2017). Preterm birth and low birth weight were not associated with exposure to high formaldehyde concentrations among a cohort of male woodworkers in China (Wang et al., 2012).

An elevated association with congenital malformations and maternal exposure was reported by a limited set of *low* confidence studies among female hospital or laboratory workers (Zhu et al., 2006; Hemminki et al., 1985). The precision of the ORs was low, as indicated by the wide CIs generally overlapping 1.0. In addition, the studies evaluated associations for all or major malformations grouped together. These outcomes may be etiologically distinct, so this lack of specificity limits the ability to interpret these results. The probability or frequency of exposure to formaldehyde likely was low in these studies, which would have limited the ability to detect differences across various exposure groups for these rare outcomes (Hemminki et al., 1985; Ericson et al., 1984).

Table 1-53. Epidemiology studies describing effects on prenatal growth and births outcomes in relation to formaldehyde exposure

Study and design	Results
Reference: Franklin et al. (2019) Birth cohort study, Australia **Population:** Pregnant women, all nonsmokers, recruited prior to 18 weeks gestation. 305 of 373 recruited, 81.7% participation; Birth data available for 262 live births. N=129 males and N=133 females, gestational age 38.97 weeks (6 infants born at 36–37 weeks). **Exposure:** Air monitoring in homes at 34 weeks gestation, 7-day sampling duration using validated passive samplers in bedroom and living room. LOD 2.4 µg/m^3; used LOD/2 for values <LOD. House average Median (range) 2.81 (LOD–17.33) µg/m^3; 23.3% < LOD. **Methods:** Gestational age (untransformed), birth weight, birth length and head circumference (all z-scores) obtained from birth records. **Evaluation:**[a]  Uncertainties in exposure distribution due to large % < LOD, small sample size, uncertain relationship between outcomes and window of exposure (3rd trimester).	**Prenatal growth** Regression coefficients (95% CI) per µg/m^3 Birth weight (z-score) -0.044 (-0.085, -0.004; p =0.033) Head circumference (z-score) -0.056 (p = 0.06) General linear models adjusted for maternal age, parity, maternal asthma, maternal diabetes, maternal hypertension and season of birth. ETS and distance to roads evaluated but not included in final model. No associations with gestational age or birth length (results not reported)
Reference: Chang et al. (2017) (Pregnancy cohort) South Korea **Population:** Women were selected from hospital-based pregnancy cohort (n = 383), Mother and Childrens Environmental Health Study. Infants followed at 6 (n=262), 12 (n=234), 24 (n=199), and 36 months (n=92). **Exposure:** Personal formaldehyde measurements during mid- or late pregnancy, 3 days. Categorized into two groups below and above the 75th percentile and also continuous variable with log transformation. Mean (SD) 0.082 (0.052) mg/m^3, geometric mean 0.067, 75th percentile 0.106 mg/m^3. Correlation between TVOCs and formaldehyde 0.22, p<0.01. **Methods:** Birth weight from medical records; Age-specific postnatal weight at 6, 12, 24, and 36 months by gender using growth standard for Korean children. **Evaluation:**[a]  Hospital-based cohort with potential selection bias, notable attrition over time	**Birth weight** Regression coefficient (SE), p value -37.98 (39.55), 0.34 per 1 log unit change in formaldehyde Multiple linear regression adjusted for maternal age, body mass index, education level, parity, infant's gender, and gestational age at delivery. Postnatal weight Mean difference by exposure group, p value, at 6 months -0.09, 0.529 12 months -0.25, 0.149 24 months -0.04, 0.860 36 months 0.22, 0.702 Multiple linear regression adjusted for birth weight with maternal age, gestational age at delivery, pre-pregnancy BMI, educational level, parity, and infant's gender plus, air cleaner use and house age. Association with greater magnitude observed for TVOCs for birth weight and postnatal weight Prevalence LBW 2.5% Prevalence gestational age <37 weeks, 3.6%
Reference: Amiri and Turner-Henson (2017) Cross sectional study (Southeastern United States) **Population:** Pregnant women in 2nd trimester (n = 140) recruited from obstetrics and gynecology clinics with no history of chronic disease or high-risk pregnancy, 19 - 40 years old, 46% White, 37% African American, 16% other race. Participation 63% (n = 88).	**Ultrasonographic biometry** BPD percentile lower by 0.271% among infants with maternal exposure >0.03 ppm (0.037 mg/m^3), (p < 0.013). Multiple linear regression adjusted for race. Maternal age and fetal sex were not associated.

Study and design	Results
Exposure: Personal exposure during 2nd trimester, vapor monitor badges, 24-hour period, detection limit 0.003 ppm. Mean (SD) 0.04 (0.06) ppm; 0.049 (0.074) mg/m^3 **Methods:** Ultrasonographic biometry during 2nd trimester for head circumference, abdominal circumference, femur length, biparietal diameter, estimated fetal weight, and ratio of abdominal circumference to femur length. Measurements in mm converted to percentiles using gestational age and the Hadlock formulas. **Evaluation:**[a]  Low participation rate with no comparisons of participants with nonparticipants raises concern for selection bias. Small sample size with reduction in sensitivity. Reference population for BPD measure was not appropriate for >50% of participants. Potential incomplete control for smoking; collection methods and timing were not described.	Other biometric measures were not associated with formaldehyde exposure.
Reference: Hemminki et al. (1985) Case-control study, Finland **Population:** Pregnancies during 1973−1979 among women who worked in anesthesia surgery, intensive care, operating room, or internal medicine departments of a general hospital. **Exposure:** Exposure assessment via questionnaire sent to head nurses at all general hospitals in Finland. Reported occupation for each name and whether exposed to listed substance during a stated 3-month period (1st trimester); blind to case status. Substances were anesthetic gases (nitrous acid, halothane, other), sterilizing agents (ethylene oxide, glutaraldehyde, formaldehyde), disinfectant soaps (requested names), cytostatic drugs, and X-rays. Included information about job: shift work, night shift, rotating etc. Occupation identified during 1st trimester for 87.1% cases and 87.8% controls. No air monitoring conducted. **Methods:** Congenital malformations identified by linking with Register of Congenital Malformations; 46 cases 1973−1979. Controls were nurses who gave birth to a healthy infant 1973−1979 and other pregnancies were not cases. Selected three controls per case, matched on age (± 1.5 years), among nurses from same hospital as case. Congenital malformation controls: 128. **Evaluation:**[a]  No information on intensity or frequency (exposure misclassification–decreased sensitivity); very small number of exposed cases.	**Congenital Malformations** Exposed pregnancies (E) (at least once per week) and total pregnancies (T) among cases and controls (unadjusted OR) **Agent** / **Cases** E/T / % / **Controls** E/T / % / **OR** HCHO 3/34 8.8 5/95 5.3 1.8 Exposure defined as whether subject used sterilizing agent or used sterilized instruments (only one nurse sterilized instruments)

Study and design	Results
Reference: Zhu et al. (2006) Cohort study **Population:** Source: Danish National Birth Cohort; 30–40% of all pregnant women in Denmark, 1st interview June 1997–February 2003; 1,025 of 1,069 pregnancies of laboratory technicians with one job at interview and 1st pregnancy; excluded induced abortions, hydatidiform mole, or unknown outcomes of pregnancy (95.9% of eligible); 9.7% ≥35 years old, 14.9% smoker during 1st trimester; 27.7% previous spontaneous abortion. Referent: 8,037 of 8,461 teachers; 14.6% ≥35 years old, 22.1% smoker during 1st trimester; 29.6% previous spontaneous abortion. **Exposure:** Queried at gestation week 11–25 (median week 16). Self-report on laboratory work processes during pregnancy and 3 months before including frequency and use of protective measures. JEM: EI = Exposure level times Frequency of work contact Exposure level: low (1), medium (2), and high (3); assigned by study researchers For formaldehyde: low: human blood and tissue processing, work with experimental animals, work with microorganisms; medium: preparation of slides for microscopy. No work processes were identified with high exposure to formaldehyde. Frequency: everyday (4), several times per week (3), several days per month (2), and rarely (1); EI categorized into two levels: 1–5 and ≥6. **Methods:** Cohort linked to National Hospital Register and Medical Birth Register, Cox regression and hazard ratios for late fetal loss and congenital malformations; laboratory technicians compared to teachers and comparisons within laboratory technicians. Adjusted for maternal age, history of spontaneous abortion, gravidity, prepregnancy BMI, smoking, paternal laboratory job, alcohol consumption, child's sex (some models). **Evaluation:**[a]  Variation in probability or intensity of formaldehyde exposure possible for work processes across different types of labs, did not account for large proportion of participants who used protective measures to prevent inhalation exposure. JEM was not validated for formaldehyde.	ORs for 1st pregnancies among 991 laboratory technicians by formaldehyde exposure category (*N*, adjusted OR, [95% CI]). **Exposure Index** **0** **1–5** **≥6** **"Major" malformation** 20, 1.0 20, 1.2 (0.6, 2.1) 16, 1.5 (0.8, 2.9) Unexposed technicians were exposed to other work processes.

[a]Evaluation of sources of bias or study limitations (see details in Appendix A.5.8). SB = selection bias; IB = information bias; Cf = confounding; Oth = other feature of design or analysis. Extent of column shading reflects degree of limitation. Direction of anticipated bias indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact would be likely to be away from the null (i.e., spurious or inflated effect estimate).
Results from *low* confidence studies are shaded; these findings are considered less reliable.
Abbreviations: OR = odds ratio; EI = exposure index; BMI = body mass index; JEM = job-exposure matrix.

Male reproductive toxicity

Two studies (one *medium* and one *low* confidence) of male woodworkers in China from one research group reported associations with lower sperm motility (total and progressive), delayed fertility and spontaneous abortion (Wang et al., 2015; Wang et al., 2012). Eligible participants were

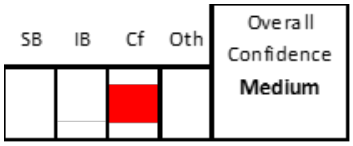
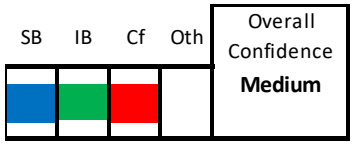
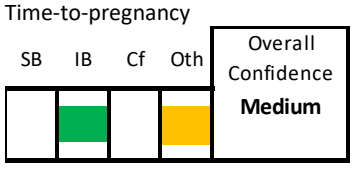
of Han Chinese ethnicity and were occupationally exposed for at least 24 months. A detailed exposure assessment involved formaldehyde measurements and individual information regarding workplace, work tasks, time spent at work tasks, and duration of employment. Progressive motility and total motility were inversely associated with formaldehyde exposure index, a cumulative measure of exposure, and a strong association with this exposure metric also was observed in logistic models of below-normal values of these motility measures. For example, ORs of 2.58 and 3.41 were found for progressive motility less than 32% in the low and high exposure groups, respectively, compared to the community-based referent group. Lindbohm et al. (1991) reported no association with spontaneous abortion identified from a nationwide hospital discharge register in relation to male formaldehyde exposure assessed using census data. There was a high likelihood of exposure misclassification using this assessment method, which reduced the sensitivity of the study (i.e., judged as *low* confidence) to identify an association with developmental endpoints. In another study, no statistically significant differences in sperm counts or percentage of abnormal sperm were observed in an underpowered, *low* confidence study of autopsy workers (Ward et al., 1984) (see Table 1-54).

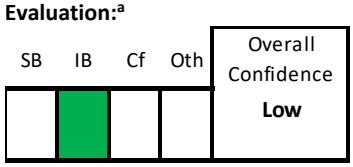
Table 1-54. Epidemiology studies describing male reproductive toxicity in relation to formaldehyde exposure

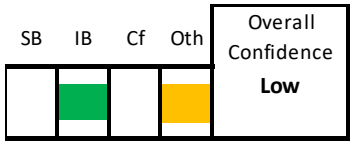
<table>
<tr><th>Study and design</th><th>Results</th></tr>
<tr><td>Reference: Wang et al. (2015) China
Prevalence
Population: Woodworkers; N = 124 participated (62.3%), N = 10 with missing semen data, aged 23–40, Chinese Han ethnicity, occupational exposure at least 24 months; excluded men living in newly built or recently remodeled house, men with genital malformations or other chronic disease; N = 81 (40.5%) recruited referent group age-matched, male Han volunteers from same area (salesmen and clerks), N = 5 with missing semen data.
Exposure: Sampling: 25-minute samples at three times on one workday, same day as questionnaire. Exposure information based on workplace, work tasks, work duration, and time (referenced Wang et al., 2012). Exposure index based on formaldehyde concentration (mean of three samples) multiplied by exposed work time during work day and exposure duration (years). Two categories with cutpoint at median. Concentrations: Exposed 0.22–2.91 mg/m^3, exposure index 4.54–195.08, median 56.55; referent 0–0.02 mg/m^3. Measurement and adjustment for other contaminants was not described (e.g., phenols).
Methods: Semistructured interview questionnaire, genital examination, semen collection (2–7 days after abstinence), and analysis (within 2 weeks of formaldehyde sampling); parameters were semen volume, sperm concentration, total sperm count, sperm progressive motility, total sperm motility, and kinematic parameters (WHO, 2010). Linear regression Ln-transformed semen parameters and formaldehyde exposure and logistic regression of abnormal semen parameters. Models adjusted for age, BMI, education, income, smoking, alcohol, and abstinence duration.
Evaluation:[a]</td><td>Regression analysis of sperm parameters and formaldehyde exposure index
<table>
<tr><th></th><th>β</th><th>95% CI</th></tr>
<tr><td>Volume (mL)[a]</td><td>−0.02</td><td>−0.08, 0.03</td></tr>
<tr><td>Concentration (106/mL)[a]</td><td>−0.02</td><td>−0.19, 0.14</td></tr>
<tr><td>Total sperm count[a]</td><td>−0.20</td><td>−0.68, 0.29</td></tr>
<tr><td>Sperm progressive motility (%)[b]</td><td>−0.19</td><td>−0.25, −0.12</td></tr>
<tr><td>Total motility[b,c]</td><td>−0.23</td><td>−0.30, −0.16</td></tr>
</table>
[a]Relative percentage change
[b]Absolute change
[c]Progressive motility plus nonprogressive motility

No association with kinematic parameters

Logistic regression of below-normal values of sperm parameters and formaldehyde exposure index (below and above median, compared to referent (N = 76)
<table>
<tr><th></th><th>Low (N = 57)</th><th>High (N = 57)</th></tr>
<tr><td>Semen volume (<1.5 mL)</td><td>1.83 (0.63, 5.36)</td><td>2.28 (0.75, 6.91)</td></tr>
<tr><td>Concentration (<15 × 106/mL)</td><td>1.67 (0.33, 8.43)</td><td>1.25 (0.21, 7.35)</td></tr>
<tr><td>Total sperm count (<39 × 106)</td><td>1.59 (0.45, 5.61)</td><td>1.73 (0.49, 6.15)</td></tr>
</table></td></tr>
</table>

Study and design	Results
 Other workplace exposures in woodworking industry (solvents) have been associated with sperm motility but not accounted for; however, otherwise strong design and analysis, including evaluation of increasing exposure-response relationship.	Progressive motility (<32%) 2.58 (1.11, 5.97) 3.41 (1.45, 7.92) Total motility (<40%) 3.21 (1.24, 8.28) 4.84 (1.83, 12.81)
Reference: Wang et al. (2012), Retrospective cohort, 2007–2009 China **Population:** Woodworkers; 302 eligible of 1,035 married men, aged 23–40, Chinese Han ethnicity, occupational exposure at least 24 months; excluded 733 couples living in newly built or recently remodeled house before and during pregnancy, couples who never tried to conceive, couples with genital malformations or other chronic disease, wives with occupational exposure to reproductive toxicants, pregnancies before husband's formaldehyde exposure and data incomplete; 305 of 816 recruited referent group age-matched, married male Han volunteers from same area (salesmen and clerks) **Exposure:** Mean daily exposure for each worker: Reported workplace, work tasks, and hour per day exposed to formaldehyde; concentration monitored three times during different periods. Daily exposure index: Mean formaldehyde concentration times proportion of exposed work time during work day multiplied by 100 [cited exposure assessment by Taskinen et al. (1999)]. Daily mean concentration categorized in low (n = 151) and high (n = 151), equal number in each group. Formaldehyde sampling details not provided (concentrations, sampling protocols, sampling locations, etc.). TWA formaldehyde concentrations were not reported. Measurement and adjustment for other contaminants was not described (e.g., dust, phenols) **Methods:** Semistructured interview questionnaire. Most recent pregnancy; TTP: # months of unprotected intercourse leading to pregnancy; spontaneous abortion defined as termination of pregnancy prior to 20th week gestation; preterm: <37 weeks; low birth weight: 2,500 g; major structural birth defects. Spontaneous abortion **Evaluation:**[a]  Other workplace exposures in woodworking industry (solvents) have been associated with spontaneous abortion but not accounted for; Analysis of most recent pregnancy: possible selection for live births (time-lapse bias) and impact of gravidity on spontaneous abortion Time-to-pregnancy 	OR (95% CI) associated with paternal formaldehyde exposure Exposed: Referent — High: Low TTP >12 months: 2.83 (1.08, 7.41) — 2.29 (0.78, 6.77) Spontaneous abortion: 1.92 (1.10, 3.33) — 1.78 (0.88, 3.62) Preterm birth: 1.25 (0.55, 2.84) — 0.85 (0.28, 2.60) Low birth weight: 1.26 (0.59, 2.66) — 1.0 (0.37, 2.74) Birth defects: 2.61 (0.79, 8.65) — 1.26 (0.33, 4.78) [a]Significant covariates: BMI, alcohol [b]Significant covariates: Cigarette smoking [c]Significant covariates: Education [d]Significant covariates: Alcohol Logistic regression model adjusted for confounders identified through univariate analyses. Confounders considered: age, BMI, education, income, smoking, alcohol, and frequency of intercourse. The numbers of exposed and referent cases were not presented.

Study and design	Results
Exposure levels not reported (but robust assessment method). Dichotomized TTP in analysis (low sensitivity).	
Reference: Lindbohm et al. (1991) Finland; Registry linkage **Population:** All Finnish women with diagnosis of spontaneous abortion (ICD−8 643, 645), induced abortion (ICD−8 640−642), or birth (ICD−8 650−662) between 1973 and 1982 were identified using the nationwide Hospital Discharge Register and hospital outpatient records. Information on occupation and industry of women and their husbands, and SES (women only), was obtained from Finnish national censuses from 1975 to 1980. Excluded pregnancies among women <12 years or >50 years of age, and those lacking data on occupation, industry, or SES. Final study population included 99,186 pregnancies ending Jan. 1–Dec. 31, 1976 or May 1, 1980−Apr. 30, 1981. **Exposure:** Job-exposure classification developed by two industrial hygienists using combinations of occupation and industry with similar type of exposure. Identified jobs held during census period close to period of susceptibility. List of toxic agents associated with job groups developed using air sampling data from Finnish occupational health agency and register of employees occupationally exposed to carcinogens. Exposure categories: 1. Not exposed 2. Potential, low: jobs with low levels but high prevalence of exposure, jobs without exposure data but in register of occupational exposure to carcinogens, or jobs with high level but unknown prevalence of exposure 3. Moderate or high: jobs with levels ≥TLV, or periodically ≥TLV and high prevalence Paternal exposure to any mutagenic agent: Not exposed: 87,616 Potential, low: 9,930 Moderate/high: 1,640 **Methods:** Logistic regression models were used to evaluate association between spontaneous abortion and paternal occupation or industry during period of susceptibility (spermatogenesis 80 days prior to conception, or 1st trimester). **Evaluation:**[a]  Industry/occupation coding has low specificity; potential exposure misclassification and imprecise assignment of exposure period to period of spermatogenesis relevant to identified pregnancy.	Spontaneous abortion rate 8.8% (including induced abortions in denominator). Spontaneous abortion risk by paternal exposure to formaldehyde[a] Group — *N* — Cases — OR[b] — 95% CI Not exposed — 87,616 — 7,772 — 1.0 — Potential, low — 1,212 — 110 — 1.1 — 0.9, 1.4 Mod/High — 596 — 54 — 1.0 — 0.8, 1.4 [a]Among 25 evaluated exposures. [b]Adjusted for maternal age, socioeconomic status, and maternal exposure to potential reproductive hazards. Paternal exposures to solvents (petroleum refineries), rubber production solvents, rubber chemicals, and ethylene oxide were associated with increased odds of spontaneous abortion ($p < 0.05$).
Reference: Ward et al. (1984) Texas **Population:** Exposed: 11 male pathologists and coworkers at university autopsy service. Matched referent: 11 staff and students in medical branch; matched on sex, age, tobacco, alcohol, and recreational drug use. **Exposure:** Area and personal breathing zone samples; exposures episodic, maximum 5.8 ppm (*7.13 mg/m³*),* LOD = *0.12 mg/m³* TWA 0.61–1.32 ppm (*0.75–1.62 mg/m³*) **Methods:** Morning semen samples every 2−3 months. Sperm counts and morphology (percentage abnormal); three samples per subject at 2-	Sperm abnormalities (mean [SD]) by exposure group Exposed — Referent Count[a] — 62.9 (49.9) — 87.4 (75.0) percentage abnormal — 44.5 (13.4) — 53.5 (16.2) [a] millions/cc of semen Differences between exposed and referent were reported to be not statistically significant.

Study and design	Results
to 3-month intervals; mean value analyzed; Pearson correlation coefficients. **Evaluation:**[a]  Small sample size; uncertainty regarding reliability of morphology scoring.	

[a]Evaluation of sources of bias or study limitations (see details in Appendix A.5.8). SB = selection bias; IB = information bias; Cf = confounding; Oth = other feature of design or analysis. Extent of column shading reflects degree of limitation. Direction of anticipated bias indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact would be likely to be away from the null (i.e., spurious or inflated effect estimate).
Results from *low* confidence studies are shaded; these findings are considered less reliable.
Abbreviations: BMI = body mass index; TWA = time-weighted average; SD = standard deviation.
Converted study exposure values are presented in (*italics*). Conversion factors for formaldehyde in air (at 25°C): 1 ppm = 1.23 mg/m^3.

Developmental and Reproductive Effects in Animal Studies

This section provides a separate discussion of the available experimental animal studies on developmental toxicity, female reproductive toxicity, and male reproductive toxicity, which are separately summarized in Tables 1-55, 1-56, and 1-57, respectively. For each of these three categories of health effects, the discussion is organized based on the types of endpoints evaluated, and the evidence tables are organized by endpoint, study confidence (if applicable; see Appendix A.5.8 for details), species, and lowest formaldehyde exposure level tested.

Two of the studies that assessed developmental toxicity evaluated a standard battery of developmental endpoints following inhalation exposure of formaldehyde to rats on gestation days (GDs) 6–15 (Martin, 1990) or GD 6–20 (Saillenfait et al., 1989) (i.e., during [at a minimum] the period of major organogenesis in the rat). Both of these studies had limitations. Martin (1990) employed robust exposure methods, but failed to report methodological details and quantitative results. In contrast, Saillenfait et al. (1989) was well reported, but rodents were exposed to formalin (including 10% methanol), which introduces substantial uncertainty regarding the role of formaldehyde in the observed effects. Importantly, of these two studies, only Saillenfait et al. (1989) identified adverse developmental outcomes. There are also reports identifying developmental effects resulting from formaldehyde exposures administered throughout gestation to rats (Monfared, 2012; Kum et al., 2007; Senichenkova and Chebotar, 1996a; Senichenkova, 1991a; Kitaev et al., 1984; Sheveleva, 1971; Gofmekler et al., 1968; Pushkina et al., 1968). Evidence that inhalation exposures to formaldehyde might affect the female reproductive system in rats is limited to three studies that are considered to be *low* confidence (Wang et al., 2013; Maronpot et al., 1986; Kitaev et al., 1984). However, all of the available animal studies of female reproductive

toxicity and developmental toxicity had serious methodological limitations, most notably poor methods used in conducting formaldehyde exposures, and are all interpreted with *low* confidence.

Additionally, studies in rodents demonstrated that formaldehyde adversely affects the male reproductive system after inhalation exposures of varied durations. Some of the studies were considered as *high* to *medium* confidence (Vosoughi et al., 2013; Vosoughi et al., 2012; Ozen et al., 2005; Ozen et al., 2002; Sarsilmaz et al., 1999); however, all of the available *medium* and *high* confidence studies exposed animals to high formaldehyde concentrations (>5 mg/m^3). The other available studies, including many testing lower formaldehyde levels, had methodological limitations that resulted in their consideration as *low* confidence studies (Han et al., 2015; Zhou et al., 2011a; Zhou et al., 2011b; Golalipour et al., 2007; Xing et al., 2007a; Zhou et al., 2006; Appelman et al., 1988). Studies examining developmental immunotoxicity following gestational exposure and developmental neuropathology following postnatal exposure were discussed previously (see Sections 1.2.3 and 1.3.1, respectively).

Developmental toxicity

The formaldehyde database contains results of studies that evaluated effects on pre- or postnatal development following inhalation exposures (see Table 1-55; Figure 1-32). The evidence table is organized by several major manifestations of developmental toxicity (U.S. EPA, 1991): survival, growth, and morphological development. (Functional developmental toxicity is not addressed here.) Because all of the developmental toxicology studies have limitations that result in *low* confidence ratings, studies within each category are presented in alphabetical order by author in the table. The results of these studies are presented in Figure 1-32.

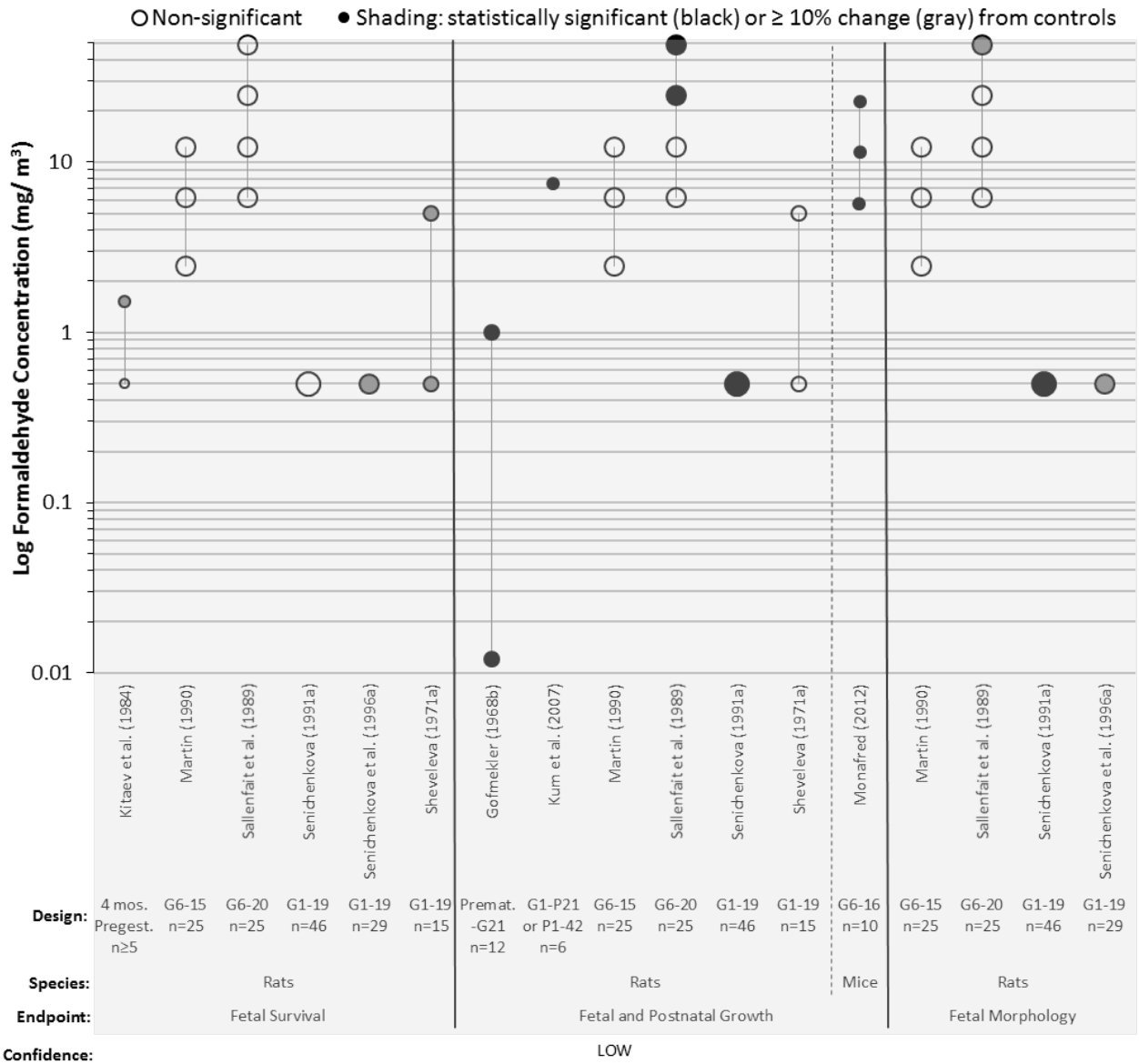


Figure 1-32. Animal studies evaluating the effects of formaldehyde inhalation exposure on developmental toxicity.

Low confidence animal studies of developmental toxicity are presented. As no *high* or *medium* confidence experimental animal studies were identified (see Appendix A.5.8), the available studies are organized by endpoint, then species, then by timing of exposure (e.g., premating [premat.] or pregestational [pregest.]; gestational [g= gestational day]; or postnatal [p = postnatal day] exposure). Filled shapes indicate statistical significance, as indicated by the study author (black), or ≥10% change from control groups (gray). The size of the points reflecting the sample size for that particular exposure group (larger size = larger *n*). The *low* confidence experiments are shown on a gray background, as the identified study limitations substantially reduce confidence in the reliability of the results; these low confidence experiments contribute very little to the weight of evidence for developmental toxicity.

Fetal survival

Decreased prenatal survival following developmental exposures was observed as increased preimplantation loss by Kitaev et al. (1984) at 1.5 mg/m^3 and by Sheveleva (1971) at 0.5 mg/m^3 or increased postimplantation loss at 0.5 mg/m^3 by Senichenkova and Chebotar (1996b). The evidence for these outcomes across the available studies is inconsistent. For example, only Kitaev et al. (1984), Senichenkova (1991b), and Sheveleva (1971) treated the dams during the preimplantation period (i.e., GD 0–6 in rats) and specifically indicated that preimplantation loss was examined. Kitaev et al. (1984) found degenerated embryos on GD 3, but not GD 2 (which could reasonably have been the result of continued exposure of the embryos to stressors resulting from formaldehyde exposure, and may not have been an inconsistency in response); however, increased preimplantation loss was not observed by Senichenkova (1991b). The increased postimplantation loss reported by Senichenkova and Chebotar (1996a) was not observed by Senichenkova (1991b), in spite of the fact that these two studies used the same procedures and exposure levels, nor was it reported by Sheveleva (1971), Saillenfait et al. (1989), or Martin (1990). The reason for these varied responses is unknown, although they might have been influenced by differences in study protocols or study conduct that are not transparently elucidated in the publications. Because of limitations in the description of methods or results for most of these studies, it is not possible to conduct an in-depth evaluation of this issue.

Fetal and postnatal growth

Evidence of decreased or delayed fetal or early postnatal growth was noted in a number of studies, but a consistent pattern of response was difficult to identify due to differences in study protocols and study quality. Following gestational formaldehyde exposure, significant 24–32% decreases in fetal body weight (accompanied by alterations in placental weight and ultrastructural conformation of the placenta) were observed in mice at exposure levels of ≥5.68 mg/m^3 by Monfared (2012). Saillenfait et al. (1989) reported significant fetal weight decreases in rats of 5% at 24.6 mg/m^3 and of 19–21% at 49.2 mg/m^3. However, fetal weight deficits were not noted by Martin (1990) at exposure levels up to 12.3 mg/m^3 or by Sheveleva (1971) at 5 mg/m^3. Conversely, significantly increased fetal body weight was noted in some studies following gestational exposure to comparatively lower exposure levels of formaldehyde, e.g., Gofmekler et al. (1968) (7% and 13% increased fetal weight at 0.012 and 1 mg/m^3, respectively) and Senichenkova (1991b) (a 5% increase at 0.5 mg/m^3). It is possible that such findings might be more subtle signals for developmental disruption of metabolic regulation and function. At 7.38 mg/m^3, Kum et al. (2007) found significant 31% decreases in rat pup weights at 3 weeks of age following in utero and lactational exposures and significant 14% decreases at 6 weeks of age (i.e., around the time of puberty) following 6 weeks of exposure starting at birth. Body weight decreases (9%) in young adult rats after 6 weeks of exposure starting at 4 weeks of age did not reach statistical significance. Notably, the same outcome did not occur when adult rats on the study were treated for 6 weeks.

These findings suggest the possibility of a life stage-related susceptibility to formaldehyde exposures. Gofmekler et al. (1968) reported significantly decreased neonatal relative liver and lung weights (~5 and 20%, respectively) following gestational exposures to ≥0.012 mg/m^3. A 2–3-day increase in the mean postnatal day on which incisor eruption occurred, another indicator of delayed postnatal growth, was reported in rat pups that had been exposed in utero to 0.5 mg/m^3 (Senichenkova, 1991a).

Fetal morphological development

Morphological alterations of fetuses exposed in utero were reported in three studies (Senichenkova and Chebotar, 1996a; Senichenkova, 1991a; Saillenfait et al., 1989). Senichenkova (1991b) and Saillenfait et al. (1989) observed delayed skeletal ossification of various bones, some of which are generally consistent with developmental delays, at 0.5 and 49.2 mg/m^3, respectively. However, Senichenkova (1991b) noted significantly increased metatarsal and metacarpal ossification centers; this finding suggests more advanced ossification states rather than a delay in development and is consistent with the finding of increased fetal weights in that study. Senichenkova (1991b) also reported an increase in litters with uncharacterized internal organ anomalies at 0.5 mg/m^3. The only outcome specific to reproductive system development was a reported ~20% increase in "cryptorchidism" by Senichenkova and Chebotar (1996a) and Senichenkova (1991b) at 0.5 mg/m^3; this was interpreted as evidence of a delay in fetal (i.e., 1st stage) testes descent. No study in the available database specifically examined the second stage of postnatal testes descent in pups. Thus, there is no evidence to determine if the observed effect represented a developmental delay or if it was related to disruptions in male reproductive tract ontogeny, which is dependent on normal levels of fetal testicular testosterone and on the expression of insulin-like hormone-3 (*insl3*) in fetal Leydig cells (Klonisch et al., 2004). This abnormality was not observed in any other study in the formaldehyde database; however, no single or multigeneration reproduction studies were available, and it is with this type of protocol that such a finding would more likely be detected. Martin (1990) did not report any structural anomalies resulting from inhalation exposures during gestation up to exposure levels of 12.3 mg/m^3.

The potential influence of maternal toxicity on developmental findings was considered in the review of the available data. For several studies, information on maternal toxicity was not reported (Monfared, 2012; Senichenkova and Chebotar, 1996b; Senichenkova, 1991a) although for these studies, it is not known whether (1) maternal toxicity was not assessed or (2) maternal toxicity was assessed, but results were not reported. Kum et al. (2007) measured maternal body and liver weight but found no treatment-related effects. In Kitaev et al. (1984), increased luteinizing hormone (LH) or follicle-stimulating hormone (FSH) levels were observed in dams at 0.5 and 1.5 mg/m^3, with compromised preimplantation survival noted at the highest exposure level. Although the maternal hormonal alterations could have been related to the embryo loss, there was no confirmation in other studies. Gofmekler et al. (1968) noted increased gestation duration at

0.012 and 1 mg/m^3, with corollary evidence of increased newborn body and organ weights at those exposure levels. Sheveleva (1971) reported evidence suggesting maternal toxicity at 5 mg/m^3, including a decreased threshold of neuromuscular excitability, increased rectal temperature, and increased hemoglobin in dams; however, developmental toxicity (i.e., increased preimplantation loss) was observed at both 0.5 and 5 mg/m^3. Martin et al. (1990) reported significantly decreased maternal weight gain and food consumption only at the highest exposure level (12.3 mg/m^3), but no developmental toxicity was observed in the study. In the Saillenfait et al. (1989) study, significantly decreased maternal body-weight gain was observed only at the highest exposure level (49.2 mg/m^3); however, significantly decreased fetal weight was observed at both 24.6 and 49.2 mg/m^3. Thus, in the limited developmental toxicity database available for evaluation, there was little evidence that maternal toxicity was a major contributing factor to observations of developmental toxicity.

Overall, the database for the evaluation of developmental toxicity (survival, growth, and morphological alterations) consisted of weak (*low* confidence) studies that had methodological limitations, primarily lack of information about the test substance or the described use of formalin, with known or presumed methanol coexposures. Effects on fetal survival, pre- or postnatal growth, or morphological alterations were observed in several studies and sometimes more than one rodent species, and maternal toxicity did not appear to be a confounding influence. However, inconsistencies in response were also observed, and clear dose-response relationships were not discernable. Additional experiments using stronger study designs are needed to more thoroughly assess the effect of formaldehyde exposure on development.

Table 1-55. Summary of developmental effects observed in animal studies following inhalation exposure to formaldehyde

Reference and study design[a]	Results[b] and exposure levels (mg/m^3)				
Low confidence (all animal studies of developmental toxicity)					
Fetal survival					
Reference: Kitaev et al. (1984) Rats (Wistar), 200 females total 4 hr/day, 5 days/wk, for 4 months 0, 0.5 or 1.5 mg/m^3 Test article: Not characterized Maternal tox: Altered LH and FSH levels in treated dams **Main limitations**: Test article NC; limited description of methods.		**0**	**0.5**	**1.5**	
	Number (percentage) degenerated embryos GD 2 (*n* = 5–8)	2 (5.1)	3 (3.8)	5 (10.2)	
	Number (percentage) degenerated embryos GD 3 (*n* = 5–9)	3 (4.4)	4 (9.1)	10 (14.9)	
Reference: Martin (1990) Rats (Sprague Dawley), 25/group 6 hr/day, GD 6–15 0, 2.46, 6.15, 12.3 mg/m^3 Test article: Paraformaldehyde Maternal tox: Significantly decreased maternal body-weight gain and food consumption at 12.3 mg/m^3 **Main limitations**: Inadequate reporting of methods and quantitative results.	Report states that there was no evidence of decreased fetal survival; no data were presented.				
Reference: Saillenfait et al. (1989) Rats (Sprague Dawley), 25/group 6 hr/day, GD 6–20 0, 6.15, 12.3, 24.6, or 49.2 mg/m^3 Test article: Formalin Maternal tox: Significantly decreased maternal body-weight gain at 49.2 mg/m^3 **Main limitation**: Formalin.		**0**	**6.15**	**12.3**	**24.6**	**49.2**
	Mean total fetal loss/litter[c]	–	−33	0	0	0%
Reference: Senichenkova (1991b) Rats (white mongrel), 137 dams total, ≈46 dams/group 4 hr/day, GD 1–19 (C-section GD 20) 0 or 0.5 mg/m^3 Test article: Not characterized Maternal tox: Not reported **Main limitations**: Test article NC; exposure generation, animal strain/source, # dams/group, maternal tox NR; limited description of methods.		**0**	**0.5**		
	Number (percentage) preimplantation loss	38/381 (10.0)	25/304 (8.2)		
	Number (percentage) postimplantation loss	26/343 (7.6)	12/279 (7.3)		
	Mean preimplantation loss	–	−3%		
	Mean postimplantation loss	–	−15%		
Reference: Senichenkova and Chebotar (1996a) Rats (mongrel, strain not reported), 29/group 4 hr/day, GD 1–19 (C-section GD 20) 0 or 0.5 mg/m^3 Test article: Not characterized Maternal tox: Not reported **Main limitations**: Test article, exposure generation, animal strain/source, # dams/group, maternal tox NR; limited description of methods.		**0**	**0.5**		
	Mean postimplantation loss[c]	-	29%		

Reference and study design[a]	Results[b] and exposure levels (mg/m^3)			
Reference: Sheveleva (1971) Rats (mongrel, strain not reported), 15/group terminated GD 20, 6/group littered 4 hr/day, GD 1–19 0, 0.5, or 5 mg/m^3 Test article: Not characterized Maternal tox: Decreased threshold of neuromuscular excitability, rectal temperature, and hemoglobin in dams at 5 mg/m^3 **Main limitations**: Test article NC; exposure generation, animal strain/source NR; limited description of methods.		**0**	**0.5**	**5**
	Mean preimplantation loss[c]	-	50	70%
	Mean postimplantation loss[c]	-	0	0%
Fetal and postnatal growth				
Reference: Gofmekler et al. (1968) Rats (strain not specified), 12 females/group Continuous exposure 10–15 days prior to mating and throughout gestation 0, 0.012, or 1 mg/m^3 Test article: Not characterized Maternal tox: Increased duration of gestation at both dose levels **Main limitations**: Test article NC, exposure generation, animal strain/source NR; limited description of methods; limited reporting.		**0**	**0.012**	**1**
	Mean newborn weight (g)	-	7*	13%*
	Mean relative neonatal lung weight (mg/10 g BW)	-	-20*	-19%*
	Mean relative neonatal liver weight (mg/10 g BW)	-	-5*	-6%*
Reference: Kum et al. (2007) Rats (Sprague Dawley), 6/group 8 hr/day, 7 days/wk, for 6 weeks starting at GD 1, PND 1, Wk-4, or Adult 0 or 7.38 mg/m^3 Test article: Formalin Maternal tox: Not reported **Main limitations**: Formalin; limited description of methods; maternal tox NR.		**0**	**7.38**	
	Decreased pup weight (g) (3-wk old pups that were exposed in utero and during lactation)	-	-31%*	
	Decreased pup weight (g) (6-wk old pups that were exposed during lactation and for 3 weeks postweaning)	-	-14%*	
	Decreased young adult weight (g) (10-wk old young adults that were exposed starting at 4-weeks of age)	-	-9%	
	Mature adult weight (g) (6 weeks of exposure to adult rats)	-	7%	
Reference: Martin (1990) Rats (Sprague Dawley), 25/group 6 hr/day, GD 6–15 0, 2.46, 6.15, 12.3 mg/m^3 Test article: Paraformaldehyde Maternal tox: Significantly decreased maternal body-weight gain and food consumption at 12.3 mg/m^3 **Main limitations**: Inadequate reporting of methods and quantitative results.	Report states that fetal weights were not affected by treatment; no data were presented.			
Reference: Monfared (2012) Mice (Balb/C), 10/group 8 hr/day, GD 6–16 (C-section GD 17) 0, 5.68, 11.38, or 22.76 mg/m^3		**0**	**5.68**	**11.38**	**22.76**
	Mean fetal weight (g)	-	-24*	-27*	-32%*
	Mean placental weight (g)	-	35*	57*	39%*

Reference and study design[a]	Results[b] and exposure levels (mg/m^3)				
Test article: Not characterized Maternal tox: Not reported **Main limitations**: Test article NC; maternal tox: NR.	Thickness of placental trophoblastic basement membrane (nm) Thickness of placental labyrinth interhemal membrane (µm)	- -	148* 45*	177* 42*	203%* 49%*
Reference: Saillenfait et al. (1989) Rats (Sprague Dawley), 25/group 6 hr/day, GD 6–20 0, 6.15, 12.3, 24.6, or 49.2 mg/m^3 Test article: Formalin Maternal tox: Significantly decreased maternal body-weight gain at 49.2 mg/m^3 **Main limitation**: Formalin.		**0**	**6.15**	**12.3**	**24.6**	**49.2**
	Mean fetal body weight/litter – males	-	-1	-2	-5*	-21%*
	Mean fetal body weight/litter – females	-	1	0	-3	-19%*
Reference: Senichenkova (1991b) Rats (white mongrel), 137 dams total, ≈46 dams/group 4 hr/day, GD 1-19 (C-section GD 20) 0 or 0.5 mg/m^3 Test article: Not characterized Maternal tox: Not reported **Main limitations**: Test article NC; exposure generation, animal strain/source, # dams/group, maternal tox NR; limited description of methods.		**0**	**0.5**			
	Mean fetal body weight (g)	-	5%*			
	Mean fetal length (mm)	-	0%			
	Mean day of upper incisor eruption	-	17%*			
	Mean day of lower incisor eruption	-	25%*			
Reference: Sheveleva (1971) Rats (mongrel, strain not reported), 15/group terminated GD 20, 6/group littered 4 hr/day, GD 1–19 0, 0.5, or 5 mg/m^3 Test article: Not characterized Maternal tox: Decreased threshold of neuromuscular excitability, rectal temperature, and hemoglobin in dams at 5 mg/m^3 **Main limitations**: Test article NC; exposure generation, animal strain/source NR; limited description of methods.		**0**	**0.5**	**5**		
	Mean fetal weight (g)	-	0	3%		
	Mean fetal length (mm)	-	0	0%		
Fetal morphological development						
Reference: Martin (1990) Rats (Sprague Dawley), 25/group 6 hr/day, GD 6–15 0, 2.46, 6.15, 12.3 mg/m^3 Test article: Paraformaldehyde Maternal tox: Significantly decreased maternal body-weight gain and food consumption at 12.3 mg/m^3 **Main limitations**: Inadequate reporting of methods and quantitative results.	Fetal incidences of major malformations, minor external and visceral anomalies, and minor skeletal anomalies.	Report states that fetal incidences were not affected by treatment; no data presented.				
Reference: Saillenfait et al. (1989) Rats (Sprague Dawley), 25/group 6 hr/day, GD 6–20 0, 6.15, 12.3, 24.6, or 49.2 mg/m^3 Test article: Formalin Maternal tox: Significantly decreased maternal body-weight gain at 49.2 mg/m^3		**0**	**6.15**	**12.3**	**24.6**	**49.2**
	Unossified sternebrae [fetal(litter) incidence]	3(3)	1(1)	6(3)	6(3)	15(7)
	Unossified sternebrae [fetal percentage]	0.9	0.4	1.9	2	4.4%
	Unossified sternebrae [litter percentage]					

Reference and study design[a]	Results[b] and exposure levels (mg/m^3)					
Main limitation: Formalin.		12.5	4.8	13	14.3	29.2%
Reference: Senichenkova (1991b) Rats (white mongrel), 137 dams total, ≈46 dams/group 4 hr/day, GD 1–19 (C-section GD 20) 0 or 0.5 mg/m^3 Test article: Not characterized Maternal tox: Not reported **Main limitations**: Test article NC; exposure generation, animal strain/source, # dams/group, maternal tox NR; limited description of methods.		**0**		**0.5**		
	Mean percentage fetuses with cryptorchidism	-		20%*		
	Number of litters with internal organ anomalies	2		8%		
	Mean number of litters with internal organ anomalies	-		914%*		
	Number (percentage) embryos with ossification centers in the hyoid bone	145(100)		61(91)*		
	Mean number of metacarpal bone centers	-		13%*		
	Mean number of metatarsal bone centers	-		9%*		
Reference: Senichenkova and Chebotar (1996a) Rats (mongrel, strain not reported), 29/group 4 hr/day, GD 1–19 (C-section GD 20) 0 or 0.5 mg/m^3 Test article: Not characterized Maternal tox: Not reported **Main limitations**: Test article NC; exposure generation, animal strain/source, # dams/group, maternal tox NR; limited description of methods.		**0**	**0.5**			
	Mean percentage litters with hydronephrosis	-	5%			
	Mean percentage litters with cryptorchidism	-	21%			

Results from *low* confidence studies are shaded; these findings are considered less reliable.
Abbreviations: GD = gestational day; LH = luteinizing hormone; FSH = follicle-stimulating hormone; NC = not characterized; NR = not reported.
[a]Studies with gestational or lactational exposures and evaluation of pre- or postnatal developmental outcomes are included in this table.
[b]Response relative to control for mean data, or incidence data.
[c]Incidence data not reported.
*Statistically significant difference from control value, as reported by the study author.
Study exposure levels converted from ppm to mg/m^3 are presented in italics (1 ppm = 1.23 mg/m^3).

Female reproductive toxicity

Information on female reproductive toxicity in the formaldehyde database is minimal (see Table 1-56; Figure 1-33). For the three *low* confidence studies that noted effects on the female reproductive system, the test substance was either not characterized (Wang et al.; Kitaev et al., 1984) or was reported to be formalin (Maronpot et al., 1986).

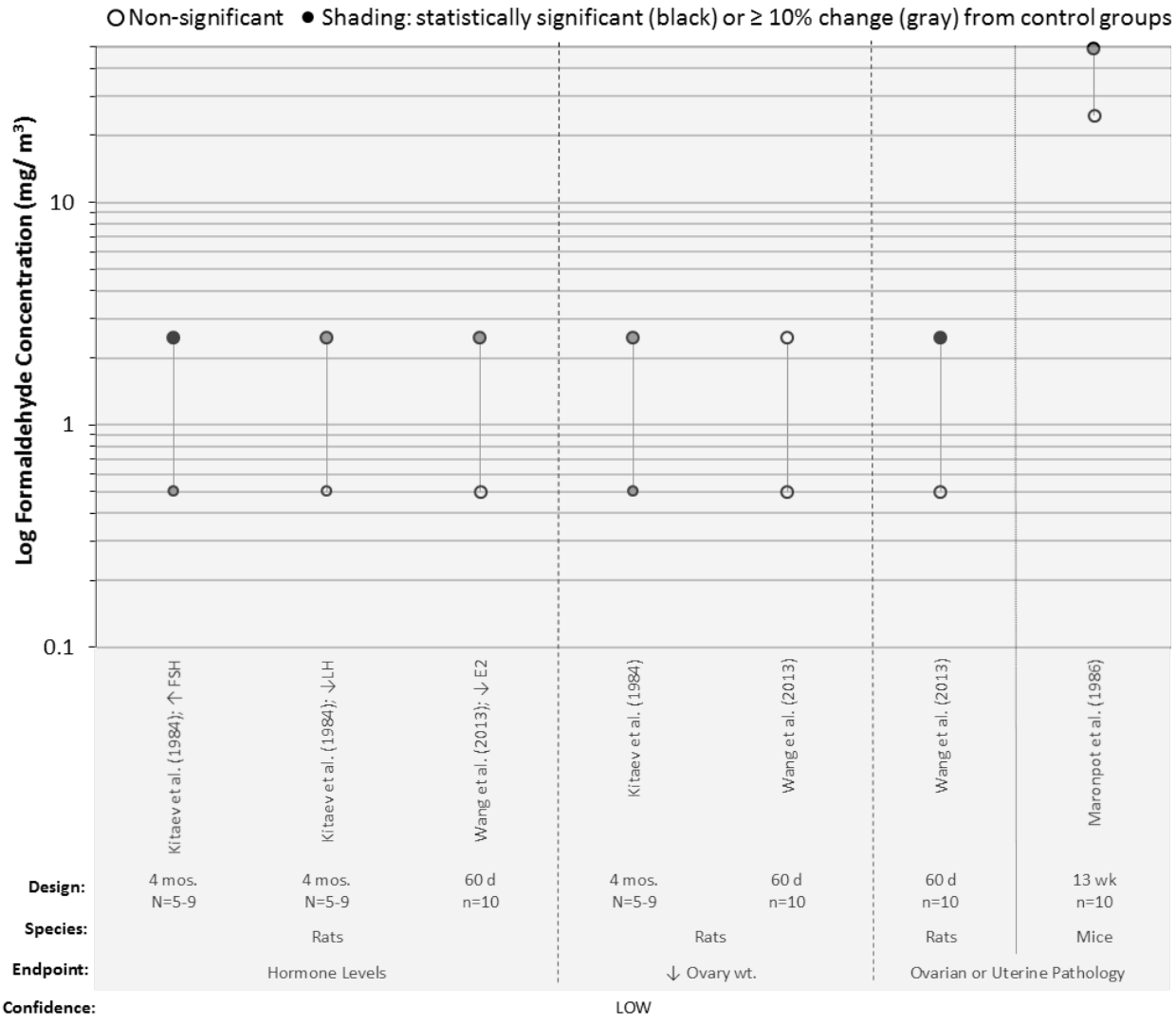


Figure 1-33. Animal studies evaluating female reproductive toxicity.

As no *high* or *medium* confidence experimental animal studies were identified (see Appendix A.5.8), the available studies are organized by endpoint, species, and then by duration of exposure. Shading indicates statistically significant (black) or ≥10% change (gray) from controls, and the size of the points reflects the sample size for that exposure group (larger size = larger *n*). The *low* confidence experiments are shown on a gray background, as the identified study limitations substantially reduce confidence in the reliability of the results; these *low* confidence experiments contribute very little to the weight of evidence for female reproductive toxicity.

Uterine and ovarian hypoplasia was observed by Maronpot et al. (1986) in 100% of the mice on study at 49.2 mg/m^3 following 13 weeks of inhalation exposure; the incidence of these findings was zero at the next lower exposure level of 24.6 mg/m^3. Histopathological evaluation conducted by Wang et al. (2013) did not confirm these findings, but identified a significant decrease in the number and size of mature ovarian follicles with a concomitant increase in the number of atretic follicles, and disruptions in structural integrity of the ovary in rats after 8 weeks of

formaldehyde exposure. Kitaev et al. (1984) reported a 56% increase in relative ovarian weight, accompanied by increased blood LH and FSH levels (11 and 36%, respectively) and significantly increased ovulation (not shown in evidence table), at the lowest dose tested (0.5 mg/m^3) in rats following 4 months of inhalation exposure; these findings are suggestive of a treatment-related disruption of the hypothalamic-pituitary-ovarian (HPO) axis. At the highest dose tested in the same study (1.5 mg/m^3), ovarian weights and LH levels were decreased by 33 and 17%, respectively, as compared to control, and FSH levels were statistically significantly increased (191%); these findings might represent evidence of direct ovarian toxicity and the consequences of disturbed early embryo development in addition to effects on the HPO axis. However, a lack of information about sample collection and analytical methods render it difficult to interpret these data with confidence. The nonmonotonic effect on ovarian weight observed by Kitaev et al. (1984) was not corroborated by Wang et al. (2013). The hormonal alterations observed by Kitaev et al. (1984) could have been related to increased preimplantation loss observed in that study or indicative of an adverse effect on female reproductive system integrity. Other evidence of hormonal disruption, such as 12% decreased estradiol (E2) levels observed by Wang et al. (2013), might have been related to the ovarian histopathology observed in that study.

Overall, as only *low* confidence animal studies of female reproductive toxicity were available, this points to the need for further evaluation of the female reproductive system following formaldehyde inhalation exposure, including an assessment of overall female reproductive function.

Table 1-56. Summary of female reproductive effects observed in animal studies following inhalation exposure to formaldehyde

Reference and study design[a]	Results[b] and exposure levels (mg/m^3)			
Low confidence (all animal studies of female reproductive toxicity)				
Reference: Kitaev et al. (1984) Rats (Wistar), 200 females total 4 hr/day, 5 days/wk, for 4 months 0, 0.5 or 1.5 mg/m^3 Test article: Not characterized **Main limitations**: Test article NC; limited description of methods.		**0**	**0.5**	**2.46**
	Mean relative ovary weight[c]	0	56	−33
	Mean blood LH (mg/mL)[c]	0	11	−17
	Mean blood FSH (mg/mL)[c]	0	36	191*
	Number (percentage) degenerated embryos GD 2 (*n* = 5–7)	2 (5.1)	3 (3.8)	5 (10.2)
	Number (percentage) degenerated embryos GD 3 (*n* = 5–9)	3 (4.4)	4 (9.1)	10 (14.9)
	*p<0.05			

Reference and study design[a]	Results[b] and exposure levels (mg/m^3)						
Reference: Maronpot et al. (1986) Mice (B6C3F1), 10/sex/group 6 hr/day, 5 days/wk, for 13 weeks 0, 2.46, 4.92, 12.3, 24.6 or 49.2 mg/m^3 Test article: formalin **Main limitations**: Formalin; limited reporting of methods and results.		**0**	**2.46**	**4.92**	**12.3**	**24.6**	**49.2**
	Ovarian hypoplasia	0/10	NE	NE	NE	0/10	10/10
	Uterine hypoplasia	0/10	NE	NE	NE	0/9	9/9
Reference: Wang et al. (2013) Rats (SD), 10 females/group 8 hr/day, 7 days/wk, for 60 days 0, 0.5, 2.46 mg/m^3 Test article: Not characterized **Main limitations**: Test article NC.		**0**	**0.5**	**2.46**			
	Mean serum E2 (ng/L)[c]	0	−2	−12			
	Mean ovarian weight (g)[c]	0	−2	−8			
	Ovarian histopathological findings at 2.46 mg/m^3 [d]: Number and size of mature follicles significantly decreased Number of atretic follicles increased Vascular congestion, interstitial edema, structure disorder						

Results from *low* confidence studies are shaded; these findings are considered less reliable.
Abbreviations: NE = not evaluated.
[a]Studies that evaluated female reproductive system toxicity are included in this table. Studies are organized by endpoint, species, and lowest dose tested.
[b]Response relative to control for mean data, or incidence data.
[c]Data digitized using Grab It!™, Datatrend Software.
[d]Incidence data not reported.
Study exposure levels converted from ppm to mg/m^3 are presented in italics (1 ppm = 1.23 mg/m^3).

Male reproductive toxicity

Fourteen studies in rodents assessed effects on the male reproductive system following inhalation formaldehyde exposure (see Table 1-57; Figure 1-34); although eight of the studies had substantial methodological limitations, 13 of the 14 studies demonstrated treatment-related effects. Of the available studies, only those by Vosoughi et al. (2013; 2012) (both of which reported data from the same cohort of mice; see footnote in Table 1-57), Özen et al. (2005; 2002), Appelman et al. (1988), Sapmaz et al. (2018), and Sarsilmaz et al. (1999) administered paraformaldehyde to the test animals and provided adequate characterization of the exposure paradigm. The results of these paraformaldehyde studies are interpreted with *high* (Vosoughi et al., 2013; Vosoughi et al., 2012; Ozen et al., 2005; Ozen et al., 2002) and *medium* (Sapmaz et al., 2018; Sarsilmaz et al., 1999) confidence; however, the results of the remaining studies in this section are considered much less reliable (i.e., *low* confidence), based in part upon deficient exposure criteria. Evaluations of male reproductive toxicity in the more reliable (e.g., *medium* and *high* confidence) studies are constrained by a complete lack of testing at lower formaldehyde concentrations. Specifically, one *medium* confidence study (Sapmaz et al., 2018) tested a single concentration of 6.15 mg/m^3 and one *medium* confidence study (Ozen et al., 2005) tested concentrations >6 mg/m^3, while the remainder of the *medium* (Sarsilmaz et al., 1999) and *high* (Vosoughi et al., 2013; Vosoughi et al., 2012; Ozen et

al., 2002) confidence studies only examined concentrations >12 mg/m^3. These high levels of formaldehyde could introduce additional complications to interpretation, including potential reflex bradypnea. In this regard, Özen et al. (2005), the only well-conducted study testing formaldehyde levels <12 mg/m^3, and Sarsilmaz et al. (1999) noted clinical signs of respiratory irritation or altered breathing rate, while Özen et al. (2002) and Vosoughi et al. (2013; 2012) did not report such observations. Sapmaz et al. (2018) did not report observations consistent with reflex bradypnea at 6.15 mg/m^3.

The evidence table is organized by outcomes of male reproductive toxicity, in order of the strength of the evidence: histopathology, sperm measures, gonadotropic hormone measures, organ weights, and reproductive function. Within each category, the studies are organized by *high* to *low* confidence, and then alphabetically within a confidence category. The available animal studies of male reproductive toxicity are illustrated in Figures 1-34 and 1-35, with Figure 1-34 presenting all of the studies and Figure 1-35 presenting in greater detail the studies interpreted with *medium* or *high* confidence.

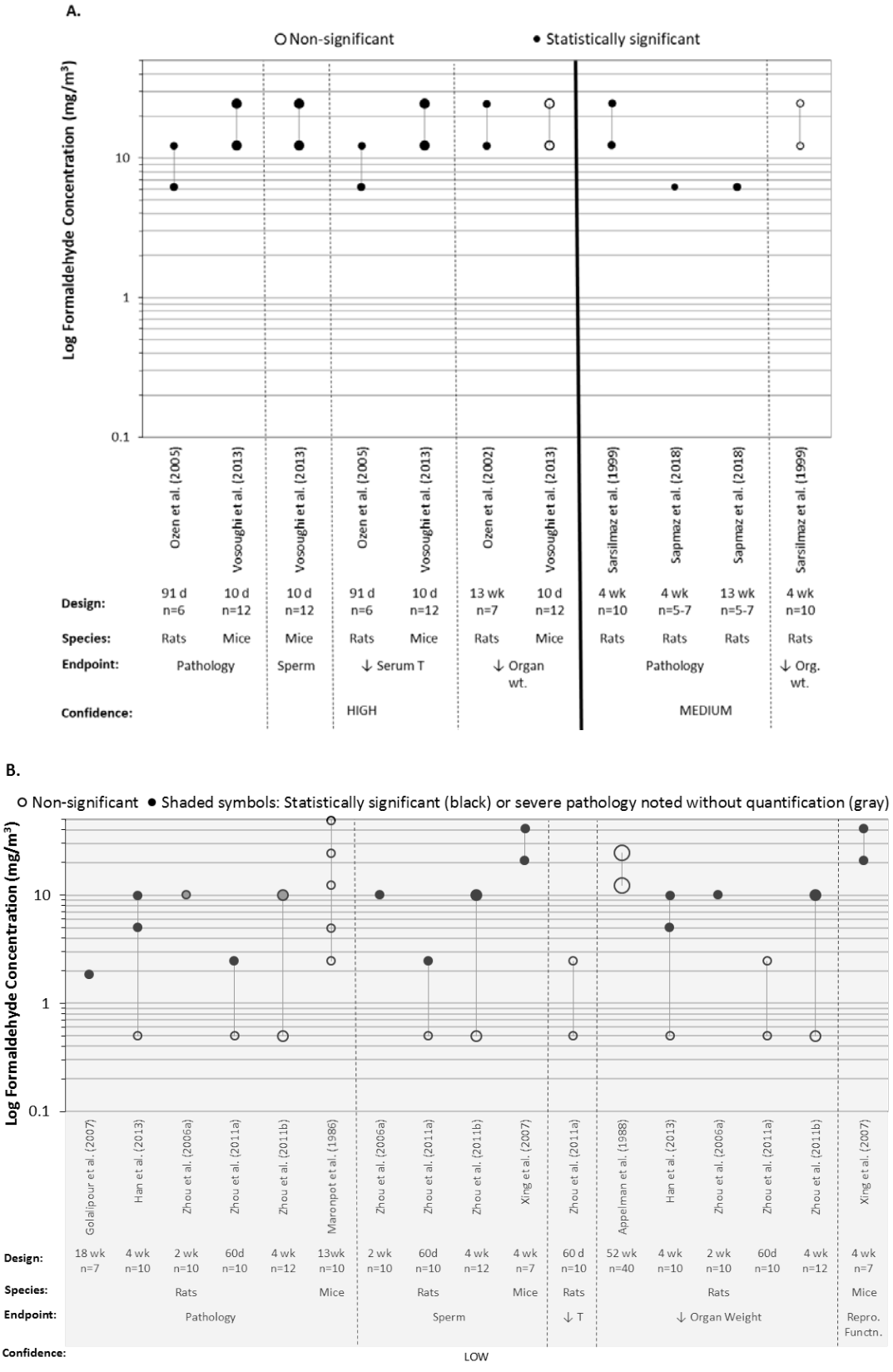


Figure 1-34. Animal studies evaluating male reproductive toxicity.

The available studies are organized into *high* or *medium* confidence (panel A) and *low* confidence (panel B) study evaluation interpretations (see Appendix A.5.8), then by endpoint, and then by species. Shaded symbols indicate statistically significant effects (unless otherwise noted), as reported by the study authors, and the size of the points reflects the sample size for that exposure group (larger size = larger *n*). The *low* confidence experiments (panel B) are shown on a gray background, as the identified study limitations substantially reduce confidence in the reliability of the results; these *low* confidence experiments contribute very little to the weight of evidence for male reproductive toxicity.

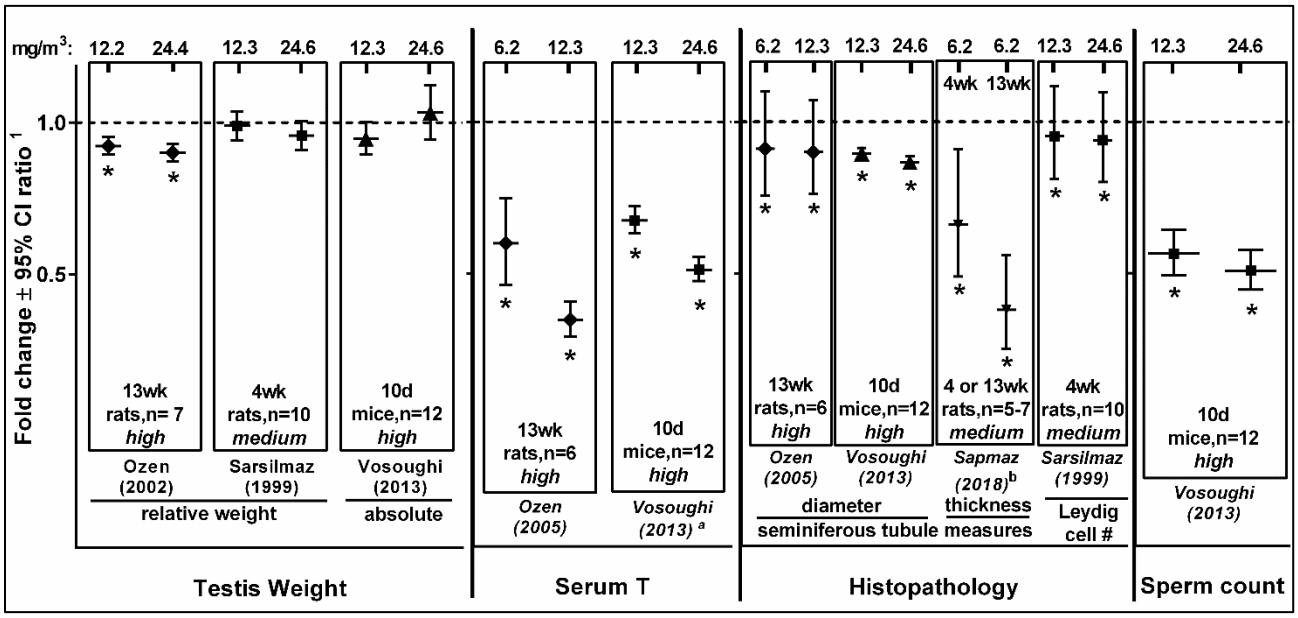


Figure 1-35. *Medium* and *high* confidence animal studies evaluating male reproductive toxicity.

The available *high* and *medium* confidence studies are arrayed and organized by endpoint. [1]Results are displayed as fold change from control animals (control responses at 1 are illustrated as a dashed line), with variability in both the controls and treatment groups represented by the quotient (ratio) of the 95% confidence intervals (CI), as calculated based on the method originally described by E.C. Fieller (Cox and Ruhl, 1966), which assumes Gaussian distributions. [a]The serum T measure at 24 hr is presented from Vosoughi et al. (2013). [b]Seminiferous tubule diameter was not significantly affected by formaldehyde exposure ($p > 0.05$) in Sapmaz et al. (2018), although in addition to the reduced thickness shown above, the authors also reported a significantly reduced percentage of intact tubules at both formaldehyde exposure timepoints (i.e., 71.1% in controls; 42.2% with 6.2mg/m^3 at 4 weeks; and 17.2% with 6.2 mg/m^3 at 13 weeks). Notes: * = author-reported statistical significance ($p \leq 0.05$). Vosoughi et al. (2013) reflects results from both the 2012 and 2013 studies (2013; 2012), which report data from the same cohort of mice; Özen et al. (2005; 2002) and Sarsilmaz et al. (1999) are studies from the same research group.

Testes and epididymides histopathology

Quantitative and qualitative histopathological findings in the testes of adult male rodents following from 10 days to 18 weeks of inhalation exposure were reported in two *high* confidence studies (Vosoughi et al., 2013; Vosoughi et al., 2012; Ozen et al., 2005) and two *medium* confidence studies (Sarsilmaz et al., 1999) that used paraformaldehyde, and in five *low* confidence studies that used formalin (Han et al., 2013; Zhou et al., 2011a; Zhou et al., 2011b; Golalipour et al., 2007; Zhou

et al., 2006). Alterations in germ cell number and integrity, statistically significant reductions in germinal epithelium thickness or seminiferous tubule diameter (5–30%), tubular atrophy, markers of disrupted spermatogenic process, and Leydig cell damage were observed. Epididymal findings (e.g., decreased tubule diameters or atrophy, epithelial alterations, or absence of sperm) in Zhou et al. (2011b) also indicated a disruption of spermatogenesis. One *low* confidence study in mice treated for 13 weeks (Maronpot et al., 1986) did not report any lesions of the male reproductive tract. Notably, while this study used formalin as the test article, this limitation would be expected to bias the study toward observing an effect; thus, there is no credible rationale for this negative outcome. However, evidence of treatment-related testicular pathology in the *high* confidence mouse study by Vosoughi et al. (2013; 2012) suggests that the absence of effects in Maronpot et al. (1986) is probably not attributable to a difference in species response, although any potential influence of animal strain on response is unknown.

Sperm measures

A significantly decreased sperm count of 44–49% was observed at 35 days posttreatment in a study of mice exposed to ≥12.2 mg/m^3 paraformaldehyde for 10 days (Vosoughi et al., 2013; Vosoughi et al., 2012). In rats, 10 mg/m^3 formalin exposure significantly decreased sperm count by 38% with a 2-week exposure (Zhou et al., 2011a) and 77% with a 4-week exposure (Zhou et al., 2011b), demonstrating an increase in the magnitude of the response as the duration of exposure increased, with the exposure concentration level remaining constant. Zhou et al. (2011a) reported a significant 13% reduction in sperm count at 2.46 mg/m^3 after 60 days of formalin exposure, consistent with the interrelationship among concentration, exposure duration, and magnitude of response. These data provide evidence of the downstream effects of disruptions to spermatogenesis that are observed histopathologically.

In the same studies, sperm motility was significantly decreased (by 40–46%) in mice (Vosoughi et al., 2013; Vosoughi et al., 2012) and by 13–17% in rats (Zhou et al., 2011a; Zhou et al., 2011b) at exposure levels ≥10 mg/m^3 paraformaldehyde or formalin, respectively, and significant abnormal sperm morphology was observed at the same exposure levels (Vosoughi et al., 2013; Vosoughi et al., 2012; Zhou et al., 2006). Statistically significant increases in abnormal sperm were also observed by Xing et al. (2007b) after 4 weeks of formalin exposure at exposure levels >20 mg/m^3. The alterations in sperm count, motility, and morphology reported by Vosoughi et al. (2013; 2012) achieved statistical significance at 35 days (but not at 24 hours) postexposure, demonstrating a biologically plausible temporal delay in the outcomes associated with disruption of spermatogenesis. Altered sperm measures are considered biomarkers of reduced fertility; however, with the exception of the high exposure study by Xing et al. (2007) that identified a male-mediated reduction in viable conceptuses, the formaldehyde database does not include any studies that specifically assessed fertility measures.

Hormone measures

Two *high* confidence studies that exposed rodents to paraformaldehyde (Vosoughi et al., 2013; Vosoughi et al., 2012; Ozen et al., 2005) found significant decreases in serum testosterone (T). Vosoughi et al. (2013; 2012) exposed mice to paraformaldehyde for 10 consecutive days and reported 32–49% decreases at 24 hours post-exposure and 10–15% decreases at 35 days postexposure. While this might suggest postexposure recovery or a compensatory process, there are no other studies that tested this possibility. Özen et al. (2005) noted significant 6–9% decreases in serum T after exposing rats for 91 days to paraformaldehyde. Zhou et al. (2011a), a *low* confidence formalin study in rats, demonstrated nonsignificant decreases (up to 6%) in serum T after 60 days of exposure. The decreased serum testosterone levels observed by Özen et al. (2005), Vosoughi et al. (2013; 2012), and Zhou et al. (2011a) are biologically consistent with the Leydig cell pathology observed by Vosoughi et al. (2013; 2012) and Sarsilmaz et al. (1999) because Leydig cells are the primary source of testosterone production in the testes. No other studies evaluated alterations in serum T levels following formaldehyde exposure.

Vosoughi et al. (2013; 2012) also reported a significant 15% decrease in serum LH at 24 hours postexposure but not at 35 days postexposure. In the same study, FSH levels were not affected at the 24-hour and 35-day assessment times.

Testes and epididymides weights

A treatment-related effect on testes weight is suggested by the available data. However, even though a number of studies examined testes and epididymides weights, the findings were neither consistent nor easily interpretable. Statistically significant decreased mean testes or epididymal weight of ≥20% magnitude was reported in three *low* confidence rat studies with inhalation exposures to 5–10 mg/m^3 formalin for 2 or 4 weeks duration (Han et al., 2013; Zhou et al., 2011b; Zhou et al., 2006). Conversely, testis or epididymal weights were not decreased in two studies: one *high* confidence study that exposed mice to paraformaldehyde for 10 days at up to 24.4 mg/m^3 (Vosoughi et al., 2013; Vosoughi et al., 2012) and one *low* confidence study that exposed rats for 60 days to 2.46 mg/m^3 formalin (Zhou et al., 2011a). It is possible that these two studies did not detect effects on testes weight due to either the short exposure duration or the low-exposure level used, respectively.

Slight decreases in relative (to body weight) testes weight data in rats resulting from 12.2 or 24.4 mg/m^3 paraformaldehyde exposures were reported by Özen et al. (2002) and Sarsilmaz et al. (1999), *high* and *medium* confidence studies in rats, respectively. Findings at 4 weeks of exposure in each study were similar, with ≤3% decreases in relative testes weights (although statistical significance was reported by Özen et al. (2002). Notably, following 13 weeks of exposure, Özen et al. (2002) reported significant relative testes weight decreases compared to control of up to 10%, suggesting that there was a duration-related component to the response. A significant increase in mean relative (to body weight) testes weight following 53 weeks of paraformaldehyde

exposure was reported for a *low* confidence study by Appelman et al. (1988); however, no quantitative data were presented in the study report. Appelman et al. (1988) attributed the relative testes weight increase to decreased body weights. Due to the absence of data on body weight, the veracity of this interpretation could not be assessed. The use of relative testes weights is typically not preferred for assessment of reproductive toxicity because testes weight has been shown to be generally conserved across 5–30% decreases in body weight (OECD, 2013). Insufficient information (on either the mean testes or body weights used in deriving the relative weight values) was provided in Özen et al. (2002), Sarsilmaz et al. (1999), and Appelman et al. (1988) to fully evaluate the magnitude of the absolute testes weight effects.

Overall, the database for the evaluation of male reproductive toxicity (histopathology, sperm measures, gonadotropic hormone measures, organ weights, and reproductive function) included multiple *high* or *medium* confidence studies that provided coherent evidence of toxicity spanning biochemical, cellular, tissue, and functional levels. These findings were supported by evidence of male reproductive system toxicity in seven of eight of the remaining *low* confidence studies, although the interpretability of these findings is questionable, primarily due to a lack of information about the test substance or the described use of formalin. Specifically, effects on testes and epididymides histopathology were observed in a *high* confidence study in mice (Vosoughi et al., 2013; Vosoughi et al., 2012) and another in rats (Ozen et al., 2005), a *medium* confidence study in rats (Sarsilmaz et al., 1999), and five *low* confidence studies in rats. The histopathological outcomes were supported by evidence of reduced serum testosterone in the two *high* confidence studies, alterations in sperm measures (count, motility, and morphology) in the *high* confidence study in mice (Vosoughi et al., 2013; Vosoughi et al., 2012) and four other *low* confidence studies in rodents, thus demonstrating downstream consequences of the testes and epididymides histopathological lesions. Data on testes and epididymides weights provided some limited supportive information from several *low* confidence studies, and from a *medium* and a *high* confidence study (Ozen et al. (2002) and Sarsilmaz et al. (1999), respectively), although the results were difficult to interpret. Uncertainties remain due to a complete lack of *high* or *medium* confidence studies testing exposure levels <6 mg/m^3, and observations potentially consistent with the occurrence of reflex bradypnea at >6 mg/m^3 in two of the studies. However, the observed responses to high levels of formaldehyde provided a coherent pattern of effects in well-conducted studies performed across two international laboratories, using two rodent species, and varied durations, and, in some cases, demonstrating clear concentration-dependent responses of exposure. None of the studies in the database conducted an in-depth assessment of male reproductive function (e.g., including mating or fertility) or evaluated outcomes attributable to early-life exposures (such as would be assessed in a multigeneration reproduction study).

Table 1-57. Summary of male reproductive effects observed in animal studies following inhalation exposure to formaldehyde

Reference and study design[a]	Results[b] and exposure levels (mg/m^3)			
Testes and epididymides histopathology				
High confidence				
Reference: Ozen et al. (2005) Rats (Wistar), 6 males/group 8 hr/day, 5 days/wk, for 91 days 0, 6.15, or 12.3 mg/m^3 Test article: Paraformaldehyde	Mean seminiferous tubule diameters (µm) (*n* = 100 randomly selected tubules/group)	**0**	**6.15**	**12.3**
		-	-23*	-26%*
Reference: Vosoughi et al. (2013); Vosoughi et al. (2012)[c] Mice (NMRI), 12 males/group 8 hr/day, 10 days 0, 12.3, or 24.6 mg/m^3 Test article: Paraformaldehyde	Histopathological findings in treated males at 35 days postexposure[d] Testes: seminiferous tubule atrophy Testes: increased space between germ cells Testes: degeneration of Leydig cells Testes: disintegration of seminiferous epithelial cells Testes: degeneration of a number of seminiferous tubules			
	Histopathological measurements:	**0**	**12.2**	**24.4**
	Mean seminiferous tubule diameter (µm)–24 hr postexposure	-	-6	-7%*
	Mean seminiferous tubule diameter (µm)–35 days postexposure	-	-11*	-13%*
Medium confidence				
Reference: Sapmaz et al. (2018) Rats (Sprague-Dawley), 7 males/group 8 hr/day, 5 days/wk, for 4 or 13 weeks 0 or 6.15 mg/m^3 Test article: Paraformaldehyde **Main limitations**: Lack of detailed reporting on quantitative analyses of histopathology.	Histopathological assessments:	**0**	**6.15 (4wk)**	**6.15 (13wk)**
	Mean germinal epithelial thickness	-	-33.7%*	-62%*
	Mean seminiferous tubule diameter	-	-5.2%	-2.2%
	Percent intact tubules	71.7%	42.2%*	17.2%*
Reference: Sarsilmaz et al. (1999) Rats (Wistar), 10 males/group 8 hr/day, 5 days/wk, for 4 weeks 0, 12.3, or 24.6 mg/m^3 Test article: Paraformaldehyde **Main limitations**: Inadequate information for quantitative analysis of histopathology data,	Mean Leydig cell quantity (100 sections total)	**0**	**12.3**	**24.6**
		-	-5*	-6%*
	Leydig cell nuclear damage (picnotic, karyoretic, karyolitic) (percentage normal)	-	-6	-22%

Reference and study design[a]	Results[b] and exposure levels (mg/m^3)
Low confidence	
Reference: Golalipour et al. (2007) Rats (Wistar), 7 males/group 18 weeks formaldehyde exposure (1) 4 hr/day, 4 days/wk (2) 2 hr/day, 4 days/wk (3) 2 hr/day, 2 days/wk 0 or 1.85 mg/m^3 Test article: Not characterized **Main limitations**: Test article NC; open air exposures; *N* = 4/group.	**Histopathological findings in formaldehyde exposure group (3)[d]:** Increased spaces between germ cells in seminiferous tubules Disrupted association between Sertoli and germinal cells **Histopathological findings in formaldehyde exposure group (2)[d]:** Decreased germ cells and increased thickness of basal membrane in 75% of seminiferous tubules **Histopathological findings in formaldehyde exposure group (1)[d]:** Severe decrease in germ cells in >85% of seminiferous tubules Arrested spermatogenesis **Histopathological measurements across study groups:** Control I and exposure paradigm (1–3) | (C) | (1) | (2) | (3) Mean seminiferous tubule diameter (µm) | - | -19* | -8* | -5%* Mean seminiferous tubule height (µm) | - | -21* | -16* | -12%*
Reference: Zhou et al. (2011b) Rats (Sprague Dawley), 10 males/group 8 hr/day, 7 days/wk, for 4 weeks 0, 0.5, 5, or 10 mg/m^3 Test article: Not characterized **Main limitations**: Test article NC; exposure generation NR; static chamber used; limited reporting of study results and group data.	Histopathological findings at 5 and 10 mg/m^3 d Testes: seminiferous tubule atrophy Testes: decreased spermatogenic cells Testes: oligospermic lumina Histopathological measurements: | **0** | **0.5** | **5** | **10** Mean seminiferous tubule diameter (µm) | - | -4 | -28* | -30%*
Reference: Zhou et al. (2006) Rats (Sprague Dawley), 10 males/group (1) 0 (gavage saline); (2) 10 mg/m^3, 12 hr/day, 2 weeks; (3) 10 mg/m^3, 12 hr/day, 2 weeks, plus 30 mg/kg-day oral vitamin E Test article: Not characterized **Main limitations**: Test article NC, exposure generation NR; static chamber used.	**Histopathological findings observed in formaldehyde exposure group (2)[d]:** Atrophy of seminiferous tubules Decreased spermatogenic cells Disintegrated and sloughed seminiferous epithelial cells Edematous interstitial tissue with vascular dilation and hyperemia Azoospermic seminiferous tubule lumina
Reference: Zhou et al. (2011a) Rats (Sprague Dawley), 10 males/group 8 hr/day, 7 days/wk, for 60 days 0, 0.5, or 2.46 mg/m^3 Test article: Not characterized **Main limitations**: Test article NC, exposure generation NR; static chamber used.	**Histopathological findings[d]** Testes: seminiferous tubule atrophy Testes: spermatogenic cells decreased Testes: oligozoospermic lumina Epididymis: oligozoospermic lumina **Histopathological measurements across exposure groups:**

Reference and study design[a]	Results[b] and exposure levels (mg/m^3)			
		0	**0.5**	**2.46**
	Mean seminiferous tubule diameter (µm)	-	-2	-7%*
	Mean epididymal tubular diameter (caput, µm)	-	-1	0%
	Mean epididymal tubular diameter (cauda, µm)	-	1	-2%
Reference: Zhou et al. (2011b) Rats (Sprague Dawley), 12 males/group 8 hr/day, 7 days/wk, for 4 weeks 0, 0.5, or 10 mg/m^3 Test article: Not characterized **Main limitations**: Test article NC, exposure generation NR; static chamber used.	**Histopathological findings**[d] Atrophy of epididymal tubules Disintegration of epididymal epithelium Disorganization and denaturalization of epididymal epithelial cells Epididymis: hyperemia of interstitial vasculature Epididymis: oligozoospermic lumina			
Reference: Maronpot et al. (1986) Mice (B6C3F1), 10/sex/group 6 hr/day, 5 days/wk, for 13 weeks 0, 2.46, 4.92, 12.3, 24.6 or 49.2 mg/m^3 Test article: Formalin **Main limitations**: Formalin; limited reporting of methods and results.	Testes histopathology	No observed effect of treatment		
Sperm measures				
High confidence				
Reference: Vosoughi et al. (2013); Vosoughi et al. (2012)[c] Mice (NMRI), 12 males/group 8 hr/day, 10 days 0, 12.3, or 24.6 mg/m^3 Test article: Paraformaldehyde	**Postexposure assessments, 24 hr:**	**0**	**12.2**	**24.4**
	Mean epididymal sperm count (106/mL)	-	-18	-22%
	Mean progressive motility (%)	-	-7	-18%
	Mean immotile sperm (%)	-	33	56%*
	Sperm viability (%)	-	-8	-14%*
	Mean normal morphology (%)	-	-7	-7%
	Postexposure assessments, 35 days:			
	Mean sperm count (106/mL)	-	-44*	-49%*
	Mean progressive motility (%)	-	-40*	-46%*
	Mean immotile sperm (%)	-	129*	170%*
	Sperm viability (%)	-	-26*	-34%*
	Mean normal morphology (%)	-	-13*	-16%*

Reference and study design[a]	Results[b] and exposure levels (mg/m^3)	
Low confidence		
Reference: Xing Sy (2007) Mice (unspecified strain), 7 males/group 2 hr/day, 6 days/wk, for 4 weeks 0, 20.79, 41.57, or 83.15 mg/m^3 Test article: Not characterized **Main limitations**: Test article NC; exposure generation, strain NR; high exposure levels.	Percentage abnormal sperm	**0** **20.8** **41.6** **83.2** 6.5 9.5* 14.3* 16.2*
Reference: Zhou et al. (2011a) Rats (Sprague Dawley), 10 males/group 8 hr/day, 7 days/wk, for 60 days 0, 0.5, or 2.46 mg/m^3 Test article: Not characterized **Main limitations**: Test article NC, exposure generation NR; static chamber used.	Mean epididymal sperm count (× 106) Mean percentage motile sperm Mean percentage abnormal sperm	**0** **0.5** **2.46** - -2 -13%* - -3 -4% - 1 4%*
Reference: Zhou et al. (2011b) Rats (Sprague Dawley), 12 males/group 8 hr/day, 7 days/wk, for 4 weeks 0, 0.5, or 10 mg/m^3 Test article: Not characterized **Main limitations**: Test article NC, exposure generation NR; static chamber used.	Mean epididymal sperm count (× 106)[e] Mean percentage motile sperm[e]	**0** **0.5** **10** - 3 -77%* - -1 -14%*
Reference: Zhou et al. (2006) Rats (Sprague Dawley), 10 males/group (1) 0 (gavage saline); (2) 10 mg/m^3, 12 hr/day, 2 weeks; (3) 10 mg/m^3, 12 hr/day, 2 weeks, plus 30 mg/kg-day oral vitamin E Test article: Not characterized **Main limitations**: Test article NC, exposure generation NR; static chamber used.	Mean epididymal sperm count (107/g epididymal wt) Mean percentage motile sperm Mean percentage abnormal sperm	**(1)** **(2)** **(3)** - -38* -16% - -17* -11% - 13* 6%
Hormone measures		
High confidence		
Reference: Ozen et al. (2005) Rats (Wistar), 6 males/group 8 hr/day, 5 days/wk, for 91 days 0, 6.15, or 12.3 mg/m^3 Test article: Paraformaldehyde	Mean (terminal) serum T (nmol/L) (n = 6)	**0** **6.15** **12.3** - -6* -9%*
Reference: Vosoughi et al. (2013); Vosoughi et al. (2012)[c] Mice (NMRI), 12 males/group 8 hr/day, 10 days 0, 12.3, or 24.6 mg/m^3 Test article: Paraformaldehyde	Postexposure assessments: Mean serum T (ng/mL), 24 hr Mean serum T (ng/mL), 35 days Mean serum LH (ng/mL), 24 hr Mean serum LH (ng/mL), 35 days Mean serum FSH (ng/mL), 24 hr Mean serum FSH (ng/mL), 35 days	**0** **12.2** **24.4** - -32* -49%* - -10* -15%* - -15%* - -5% - -5% - -5%

Reference and study design[a]	Results[b] and exposure levels (mg/m^3)	
Low confidence		
Reference: Zhou et al. (2011a) Rats (Sprague Dawley), 10 males/group 8 hr/day, 7 days/wk, for 60 days 0, 0.5, or 2.46 mg/m^3 Test article: Not characterized **Main limitations**: Test article NC, exposure generation NR; static chamber used.	Mean (terminal) serum T (nmol/L)[e]	**0** **0.5** **2.46** - -1 -6%
Testes and epididymides weights		
High confidence		
Reference: Ozen et al. (2002) Rats (Wistar), 7 males/group 8 hr/day, 5 days/wk, for 4 weeks or 13 weeks 0, 12.2, or 24.4 mg/m^3 Test article: Paraformaldehyde	Mean relative testes weight (4 wks) (n = 7) Mean relative testes weight (13 wks) (n = 7)	**0** **12.2** **24.4** - -2* -3%* - -8* -10%*
Reference: Vosoughi et al. (2013); Vosoughi et al. (2012)[c] Mice (NMRI), 12 males/group 8 hr/day, 10 days 0, 12.3, or 24.6 mg/m^3 Test article: Paraformaldehyde	Postexposure assessments: Mean testes weight (mg), 24 hr[e] Mean testes weight (mg), 35 days[e]	**0** **12.2** **24.4** - 2 7% - -1 0%
Medium Confidence		
Reference: Sarsilmaz et al. (1999) Rats (Wistar), 10 males/group 8 hr/day, 5 days/wk, for 4 weeks 0, 12.3, or 24.6 mg/m^3 Test article: Paraformaldehyde **Main limitations**: Inadequate information for quantitative analysis of histopathology data.	Mean relative testes weight	**0** **12.2** **24.4** - -1 -4%
Low confidence		
Reference: Appelman et al. (1988) Rats (Wistar), 40 males/group 6 hr/day, 5 days/wk, for 13 or 52 weeks 0, 0.123, or 12.3 mg/m^3 Test article: Paraformaldehyde **Main limitations**: No indication if histopathology performed on male reproductive organs; quantitative testes weights not presented.	Mean relative testes weight, 53 wks	Significant increase at 10 ppm (12.3 mg/m^3) reported (no data were presented); effect was attributed by study author to decreased body weight.
Reference: Zhou et al. (2011b) Rats (Sprague Dawley), 10 males/group 8 hr/day, 7 days/wk, for 4 weeks 0, 0.5, 5, or 10 mg/m^3 Test article: Not characterized **Main limitations**: Test article NC; exposure generation NR; static chamber used; limited reporting of study results and group data.	Mean testes weight (g)[e]	**0** **0.5** **5** **10** - -3 -24* -21%*

Reference and study design[a]	Results[b] and exposure levels (mg/m^3)	
Reference: Zhou et al. (2006) Rats (Sprague Dawley), 10 males/group (1) 0 (gavage saline); (2) 10 mg/m^3, 12 hr/day, 2 weeks; (3) 10 mg/m^3, 12 hr/day, 2 weeks, plus 30 mg/kg-day oral vitamin E Test article: Not characterized **Main limitations**: Test article NC, exposure generation NR; static chamber used.	Mean testes weight (g)[e]	**(1)** **(2)** **(3)** - -22* -3%
Reference: Zhou et al. (2011a) Rats (Sprague Dawley), 10 males/group 8 hr/day, 7 days/wk, for 60 days 0, 0.5, or 2.46 mg/m^3 Test article: Not characterized **Main limitations**: Test article NC, exposure generation NR; static chamber used.	Mean testes weight (g) Mean epididymis weight (g)	**0** **0.5** **2.46** - -1 -3% - 4 -2%
Reference: Zhou et al. (2011b) Rats (Sprague Dawley), 12 males/group 8 hr/day, 7 days/wk, for 4 weeks 0, 0.5, or 10 mg/m^3 Test article: Not characterized **Main limitations**: test article, exposure generation NR; static chamber used.	Epididymis weight (g)[e]	**0** **0.5** **10** - -2 -31%*
Reproductive function		
Low confidence		
Reference: Xing Sy (2007) Mice (unspecified strain), 7 males/group, mated with untreated females 2 hr/day, 6 days/wk, for 4 weeks 0, 20.79, 41.57, or 83.15 mg/m^3 Test article: Not characterized **Main limitations**: Test article NC; exposure generation, strain NR.	Mean live fetuses/litter Mean percentage resorptions[e]	**0** **20.8** **41.6** **83.2** - -3 -12 -18%* - 7* 8* 10%*

Results from *low* confidence studies are shaded; these findings are considered less reliable.
Abbreviations: NR = not reported; NC = not characterized; T = testosterone; LH = luteinizing hormone; FSH = follicle-stimulating hormone.
[a]Studies that evaluated male reproductive system toxicity are included in this table. Studies are organized by endpoint, species, and lowest dose tested.
[b]Response relative to control for mean data, or incidence data.
[c]Vosoughi et al. (2013; 2012) reported histopathology and sperm measure data for the same low-exposure group study animals. However, serum LH and FSH data were presented only in Vosoughi et al. (2012) and serum T and testes weight data were presented only in Vosoughi et al. (2013).
[d]Incidence data not reported.
[e]Data digitized using Grab It!™, Datatrend Software.
*Statistically significant difference from control value, as reported by the study author.
Study exposure levels converted from ppm to mg/m^3 are presented in italics (1 ppm = 1.23 mg/m^3).

Evidence on Mode of Action for Developmental and Reproductive Effects

Mode of action (MOA) information for potential developmental and reproductive toxicity associated with formaldehyde exposures is limited. No definitive data have been identified that fully support a specific MOA for developmental outcomes, or for alterations in male or female reproductive system conformation or function. Because it is considered unlikely that formaldehyde is distributed via systemic circulation to the reproductive organs, this section discusses potential mechanisms by which formaldehyde exposures might indirectly affect reproductive outcomes following toxic insult at the portal of entry. Mechanistic events associated with respiratory health effects (see Sections 1.2.1–1.2.4 and Appendix A.5.6) were considered. Biological mechanisms that could plausibly be associated with developmental and reproductive toxicity are discussed, based upon consideration of experimental animal data that included inhalation exposures to formaldehyde. These include: oxidative stress and neuroendocrine-mediated effects (alterations of adrenergic or gonadotropic hormones). Although additional study is needed to better define and verify these potential mechanisms, they could be operant in several primary outcomes that have been noted across toxicology or epidemiology studies with inhalation exposures to formaldehyde: developmental delays, fetal loss, and effects on sperm quality and quantity.

1) Effects on the reproductive system that are due to indirect oxidative stress, possibly linked to inflammatory responses following formaldehyde exposures (evidence from two *high* and two *low* confidence studies (Zhou et al., 2011b; Zhou et al., 2006; Ozen et al., 2005; Ozen et al., 2002)

Oxidative stress/damage by reactive oxygen species (ROS) has been hypothesized to play a role in reproductive and developmental toxicity (Wells and Winn, 1996; Juchau et al., 1992; Fantel and Macphail, 1982). Markers of increased oxidative stress have been identified in the blood following formaldehyde inhalation exposures (see Section 1.2.3), and thus, this could also be occurring in peripheral tissues. Plausibly, inflammatory mediators, ROS, or other factors observed in the blood could be operant in reproductive or developmental outcomes by indirectly eliciting responses in the reproductive system or in the developing fetus.

ROS-related outcomes have been detected in cells and tissues distal from the POE, notably in the male reproductive system, where testicular and epididymal toxicity and effects on sperm have been observed. In a *high* confidence study in rats, Ozen et al. (2002) investigated the mechanism of oxidative stress associated with testes toxicity by assessing testicular iron, copper, and zinc levels. Zinc and copper levels were reduced in the rat testes, consistent with an increase in testicular ROS. A *medium* confidence study in rats (Sapmaz et al., 2018) identified a statistically significant decrease in glutathione peroxidase (GSH-Px) activities and a statistically significant increase in malondialdehyde (MDA) levels, A *low* confidence study (Ozen et al., 2008; Zhou et al., 2006) investigated biomarkers of oxidative stress as a potential MOA for testicular toxicity following inhalation exposures of rats to formaldehyde. Significant effects on antioxidants and redox enzymes were observed: decreases in superoxide dismutase (SOD), GSH-Px, and glutathione

(GSH), as well as an increase in the oxidative stress biomarker, MDA. The authors also demonstrated the protective effect of coadministration with the antioxidant vitamin E (Zhou et al., 2006) on decreased testes weight, biochemical alterations, histopathological effects, or on sperm count, motility, and morphology. Zhou et al. (2011b), another *low* confidence study from the same research laboratory, demonstrated significantly decreased SOD and GSH-Px activities and significantly increased MDA levels in the epididymides of rats exposed to formaldehyde. No studies have been identified that specifically evaluated the generation of ROS in fetuses following maternal inhalation exposures to formaldehyde, which would be directly informative to this potential relationship.

Chemical or physical stress has been shown to increase the synthesis of heat shock protein 70 (Hsp70), which is involved in protein folding and repair (Craig and Schlesinger, 1985), regulation of apoptosis (Takayama et al., 2003), and it is synthesized during normal spermatogenesis (Dix et al., 1997; Dix, 1997). Additionally, testicular heat shock protein immunoreactivity has been associated with human infertility (Werner et al., 1997). Özen at al. (2005), a *high* confidence study, reported the detection of increased Hsp70 in spermatogenic cells from the seminiferous tubules of rats following 13 weeks of inhalation exposure to formaldehyde. The increase in testicular Hsp70 could reflect a response to chemical (formaldehyde) stress to the respiratory system, but no mechanisms exist to explain this potential association. Regardless, the role of heat shock proteins in mammalian fetal development is well-recognized (Walsh et al., 1997).

It has also been proposed that oxidative stress resulting from formaldehyde exposure could result in epigenetic consequences to the male reproductive system (Duong et al., 2011). Tunc and Tremellen (2009) reported that oxidative stress to sperm DNA has resulted in hypomethylation in infertile men. Abnormal methylation of a key spermatogenic gene is associated with defective sperm (Navarro-Costa et al., 2010). This represents a hypothetical indirect mechanism by which formaldehyde could influence methylation in sperm DNA and alter male fertility. None of the studies reporting sperm alterations or related measures (see previous sections) examined the potential role of sperm methylation in these outcomes.

2) Neuroendocrine-mediated mechanisms: disruption of the hypothalamus-pituitary-adrenal gland (HPA) axis or hypothalamic-pituitary-gonadal (HPG) axis (evidence from three *high*, one *medium*, and one *low* confidence studies—(Vosoughi et al., 2013; Vosoughi et al., 2012; Sari et al., 2004; Ozen et al., 2002; Sorg et al., 2001a; Kitaev et al., 1984)

A stress-induced mechanism might contribute to adverse outcomes on the reproductive system and development in the absence of systemic distribution of formaldehyde.

Disruption of the HPA axis: Stressors such as chemical exposure can cause increased secretion of CRH in the hypothalamus, ACTH in the anterior pituitary gland, and adrenal corticosteroids in the adrenal gland (Smith and Vale, 2006). In support of this hypothesis, a *high* confidence study, Sorg et al. (2001a), demonstrated an increase in blood corticosterone levels after inhalation exposure to formaldehyde. Additionally, Sari et al. (2004), a *medium* confidence study,

reported effects of inhalation formaldehyde exposures to mice on CRH neurons in the hypothalamus and ACTH cells in the pituitary gland. The effects of stress on disruptions to reproductive function and outcome in humans are well-recognized (Negro-Vilar, 1993; Barnea and Tal, 1991; Mcgrady, 1984). The preoptic area of the hypothalamus is considered a potential site of integration between the HPA axis and gonadal steroid hormones (Smith and Vale, 2006).

Disruption of the HPG axis: A steroidal endocrine-mediated mechanism would be consistent with outcomes observed in some of the reproductive and developmental epidemiology and toxicology studies. Developmental delays can result from effects on the maternal HPG axis. Hormone levels in pups were not measured in any identified studies; however, there are three studies in adult animals that have directly tested for changes in reproductive hormones after formaldehyde exposure. Kitaev et al. (1984), a *low* confidence study, observed serum FSH increases and LH decreases after inhaled formaldehyde in adult female rats. Alterations in hormone levels could compromise pregnancy maintenance. Another potentially endocrine-mediated outcome, lack of ovarian luteal tissue in females exposed to formaldehyde, was reported in a *low* confidence study by Maronpot et al. (1986). In males, alteration of the HPG axis by formaldehyde exposure could also be theoretically operant. Two *high* confidence inhalation studies with formaldehyde, Vosoughi et al. (2013; 2012) and Ozen et al. (2002), reported significant serum testosterone level decreases, accompanied by histopathological evidence of seminiferous tubule depletion. Vosoughi et al. (2013; 2012) also reported a significant decrease in serum LH at 24 hours after inhalation formaldehyde exposure. This is notable because the initiation and maintenance of spermatogenesis in rodents and primates require LH stimulation (Plant and Marshall, 2001). Reduced testosterone levels might also contribute to sperm quality and quantity decrements.

These two potential mechanisms are not necessarily mutually exclusive. If verified, they could be shown to be acting alone for certain endpoints (in which case the others may not be operant) or in concert for others. Nevertheless, as stated above, no definitive data have been identified that define an MOA(s) explaining how developmental or reproductive outcomes might occur following inhalation exposure to formaldehyde.

Integrated Summary of Evidence on Developmental and Reproductive Toxicity

Hazard conclusions integrating the evidence of developmental and reproductive hazards in humans and animals were drawn for two categories: female reproductive or developmental toxicity (TTP, spontaneous abortion, birth outcomes, fetal survival, growth, and malformations), and male reproductive toxicity (see Table 1-58). Specifically, for the purposes of this assessment and based on the outcomes reported in the epidemiological literature, female reproductive toxicity and developmental toxicity were considered as a group because it is difficult to distinguish the underlying events that may have resulted in either a delayed recognized pregnancy or fetal loss.

Female reproductive or developmental toxicity

While studies that evaluated physiological measures of reproductive health in females were not available, two *medium* confidence studies reported strong associations of occupational exposure to formaldehyde with decreased fecundability, increased TTP, and spontaneous abortion (Taskinen et al., 1999; John et al., 1994). A third study also reported an elevated risk of spontaneous abortion with higher exposure frequency of similar magnitude, but the effect estimate may have been biased to an unknown degree by confounding from coexposure to xylene (Taskinen et al., 1994). Excluding the study would not change the weight-of-evidence conclusion for the epidemiological evidence. It is recognized that the decreased fecundability and increased TTP might have resulted from early fetal loss, or be a consequence of alterations in maternal reproductive function (discussed below). Only one of the occupational studies (in woodworkers) reported the levels of formaldehyde that resulted in the observed associations (0.27 mg/m^3) (Taskinen et al., 1999). Studies of hospital, nursing, or medical employees generally did not report an association with formaldehyde exposure, although these *low* confidence studies tended to use less informative exposure-assessment methods, a major limitation that reduced the sensitivity of these studies. An association of uncharacterized birth defects with maternal exposure (Zhu et al., 2006; Saurel-Cubizolles et al., 1994; Hemminki et al., 1985) was suggested in some occupational epidemiological studies; the precision of the ORs was quite low, as indicated by the wide CIs, which limited the sensitivity of these analyses. Three studies of pregnancy cohorts indicate an association with fetal growth including biparietal diameter in the 2nd trimester and birthweight, although there are questions about the interpretation of the results overall given the strength of associations observed in a population with very low exposures (Franklin et al., 2019) and a relatively weak association with potential confounding by TVOCs in a population with higher exposure (Chang et al., 2017). Preterm birth and low birth weight were not associated with higher formaldehyde exposure among a cohort of male woodworkers in China (Wang et al., 2012).

Animal studies evaluated several endpoints relevant to developmental toxicity (i.e., decreased survival, decreased growth, or increased evidence of structural anomalies) or female reproductive toxicity (i.e., ovarian and uterine pathology, ovarian weight, or hormonal changes). All available studies were of *low* confidence, primarily due to exposure-quality concerns (i.e., the use of formalin, or an uncharacterized test substance). In addition, there was considerable heterogeneity in both of these data sets, and consistent evidence supporting manifestations of toxicity after formaldehyde exposure was not reported. However, as several of these studies did identify potential findings of concern, these outcomes are deserving of additional study. In addition, several studies examining effects on the nervous system after formaldehyde exposure in rats during development suggest that formaldehyde inhalation might have the potential to affect the developing nervous system (see Section 1.3.1), however, additional studies are needed to clarify these preliminary findings. Studies on developmental immunotoxicity were considered *not*

informative (see Section 1.2.3 and Appendix A.5.4) and no epidemiological studies of children were identified.

Overall, the **evidence indicates** that inhalation of formaldehyde likely causes increased risk of developmental or female reproductive toxicity in humans, given the appropriate exposure circumstances. This conclusion is based on *moderate* evidence in observational studies finding increases in TTP and spontaneous abortion risk among women exposed to occupational formaldehyde levels; the evidence in animals is *indeterminate*, and a plausible, experimentally verified MOA explaining such effects without systemic distribution of formaldehyde is lacking. The primary basis for this conclusion is from studies of women with occupational exposures to formaldehyde concentrations as high as 1.2 mg/m^3.

Male reproductive toxicity

Few epidemiological studies evaluated effects on the male reproductive system. Two studies of male woodworkers in China from one research group reported associations with lower total and progressive sperm motility, and delayed fertility and spontaneous abortion (Wang et al., 2015; Wang et al., 2012). The investigators used a well-designed exposure assessment to evaluate associations in this highly exposed occupational population (0.22–2.91 mg/m^3). Two other studies with low sensitivity to detect associations (due to concerns with low precision and exposure misclassification) did not observe effects on sperm counts and morphology or spontaneous abortion among exposed men (Lindbohm et al., 1991; Ward et al., 1984).

Animal studies were available that evaluated several effects from formaldehyde inhalation exposure on the male reproductive system. A coherent set of *high* and *medium* confidence studies in mice and rats that tested formaldehyde exposures >6 mg/m^3 reported effects on multiple endpoints, although interpretations could not be drawn regarding the potential for these effects in experimental animals at lower formaldehyde exposure levels. Qualitative and quantitative histopathological effects were observed in the testes and epididymides of a *high* confidence study in rats (Ozen et al., 2005) and another in mice (Vosoughi et al., 2013; Vosoughi et al., 2012) and in a *medium* confidence rat study (Sarsilmaz et al., 1999). Histopathological findings in testes were also observed by (Sapmaz et al., 2018), a *medium* confidence study in rats. These observations were supported by similar findings in a number of *low* confidence studies. Decreased serum testosterone (T) was also observed in the *high* confidence studies in rats and mice (Vosoughi et al., 2013; Vosoughi et al., 2012; Ozen et al., 2005), as well as in a *low* confidence rat study (Zhou et al., 2011b). The decreased serum T is biologically consistent with testicular Leydig cell damage observed in the histopathological evaluations reported in well-conducted studies (Vosoughi et al., 2013; Vosoughi et al., 2012; Sarsilmaz et al., 1999). Downstream effects of disruptions in spermatogenesis observed in the histopathology data included decreased sperm count and motility, and increased sperm morphological abnormalities in a *high* confidence study in mice (Vosoughi et al., 2013; Vosoughi et al., 2012) and several *low* confidence studies in rats. Testes and epididymides weight alterations are often correlated to some degree with histopathology in those organs; however,

while significantly decreased dose- and duration-dependent testes weights were observed in the *high* confidence study in rats by Özen et al. (2002), organ weight alterations were not observed in the *high* confidence study in mice by Vosoughi et al. (2013; 2012) or the *medium* confidence study in rats by Sarsilmaz et al. (1999), and results in *low* confidence studies were mixed, preventing interpretations.

Overall, the **evidence indicates** that inhalation of formaldehyde likely causes increased risk of reproductive toxicity in men, given the appropriate exposure circumstances, based on *robust* evidence in animals that presents a coherent array of adverse effects in two species, and *slight* evidence from observational studies of occupational formaldehyde exposure. No plausible, experimentally verified MOA exists to explain such effects without systemic distribution of formaldehyde; however, some support for indirect effects in rodents is provided by relevant mechanistic changes in male reproductive organs. The primary basis for this conclusion is based on bioassays in rodents testing formaldehyde concentrations above 6 mg/mg^3 (no *medium* or *high* confidence studies tested lower exposure levels).

Data gaps

While reduced fecundity observed in exposed women may be due to reproductive toxicity or toxicity to the developing fetus, no studies are available in exposed humans or animal experiments that provide more complete assessments of reproductive organ endpoints. This also is true for the evaluation of postnatal developmental toxicity. The anthropomorphic findings by a single study of low residential exposures are concerning and additional studies are needed of these endpoints. The findings by Wang et al. (2015) suggesting formaldehyde-related toxicity to sperm and possible resulting effects on fecundity and fetal survival, and which may be supported by a *low* confidence study in mice (Xing et al., 2007a), provide evidence of male-mediated decreases in fetal viability, and should be investigated further. Ideally, such investigations would include additional human studies of different populations using similarly detailed exposure assessments, as well as single or multigeneration reproductive toxicity studies in animals (which were not identified in the current database). Such studies would also assess female reproductive outcomes, which are not extensively evaluated in the current database. Ideally, any future toxicology experiments would generate formaldehyde exposures using paraformaldehyde to eliminate the uncertainties pertaining to potential confounding by methanol that limit the majority of currently available studies on developmental and reproductive toxicity.

Importantly, as the hazard conclusion for male reproductive toxicity is based largely on animal studies that only tested formaldehyde exposures ≥6 mg/m^3 (one study) or ≥12 mg/m^3, which introduces uncertainties regarding potential irritation-related effects (e.g., reflex bradypnea, which is not experienced by humans and is expected to be operant at these levels; see Appendix A.3), well-conducted, detailed animal studies testing these endpoints at lower formaldehyde concentrations are warranted.

Table 1-58. Evidence integration summary for effects of formaldehyde inhalation on reproduction and development

Evidence	Evidence judgment	Hazard determination
Female reproductive or developmental toxicity		
Human	*Moderate* for female reproductive or developmental toxicity, based on: *Human health effect studies*: • Two *medium* confidence studies in two independent populations (woodworkers, cosmetologists): decreased fecundability and increased spontaneous abortion risk. Supporting evidence of association with spontaneous abortion from one *low* confidence study among laboratory workers. All studies evaluated multiple exposure categories with highest risk at highest exposure level. • Two *low* confidence studies of maternal exposure among health workers with low precision: small increased risk of malformations (all combined). • Two medium confidence studies of pregnancy cohorts indicating decreased birth weight and head circumference. • Null evidence from five *low* confidence studies with low sensitivity: fecundability, spontaneous abortion. *Biological plausibility*: No direct evidence. However, evidence of elevated oxidative stress in the blood of exposed adults (see Section 1.2.3) might provide a potential indirect linkage (see explanation at right).	The **evidence indicates** that inhalation of formaldehyde likely causes increased risk of developmental or female reproductive toxicity in humans, given the appropriate exposure circumstances[a] Primarily based on studies of women with occupational exposures to formaldehyde concentrations as high as 1.2 mg/m^3. *Potential susceptibilities*: no specific data were available to inform potential differences in susceptibility.
Animal	*Indeterminate* for developmental toxicity, based on: *Animal health effect studies*: • Mixed findings for evidence of decreased fetal survival (pre- or postimplantation loss) across multiple *low* confidence studies • Mixed findings for evidence of altered fetal or postnatal growth across multiple *low* confidence studies. Variations in study design and reporting deficiencies inhibit interpretation. • Mixed findings for evidence of structural anomalies across multiple *low* confidence studies. *Biological plausibility*: No direct evidence. However, evidence of elevated oxidative stress and hormonal alterations in the blood of adult rodents (see Section 1.2.3) might provide a potential indirect linkage, as it is recognized that both oxidative stress and the HPG axis have potential roles in developmental toxicity. *Indeterminate* for female reproductive toxicity, based on: *Animal health effect studies*: • Two *low* confidence studies in rats: decreased ovarian weight, ovarian histopathology, and hormonal alterations • One *low* confidence study in mice: Ovarian and uterine histopathology (hypoplasia) *Biological plausibility*: Neuroendocrine-mediated mechanisms, particularly involving disruption of the hypothalamic-pituitary-gonadal axis, are consistent with alterations of female reproductive hormones observed in *low* confidence rodent studies following formaldehyde exposures.	
Other inferences	• *Relevance to humans*: Relevant health effects observed in humans are the primary basis for the hazard determination. • *MOA*: No experimentally established MOA exists, and any potential mechanisms have not been well studied.	
Male Reproductive Toxicity		

Humans	*Slight* for male reproductive toxicity, based on: *Human health effect studies*: • One *medium* confidence study of exposure among male woodworkers: inverse association with sperm motility measures, increased prevalence of time to pregnancy, spontaneous abortion and birth defects. • Null evidence for effects on sperm counts and morphology in one *low* confidence study (because of low power). *Biological plausibility*: No directly relevant studies were identified.	The **evidence indicates** that inhalation of formaldehyde likely causes increased risk of reproductive toxicity in men, given appropriate exposure circumstances[a] Primarily based on bioassays in rats and mice testing formaldehyde concentrations above 6 mg/m^3 (no *medium* or *high* confidence studies tested lower exposure levels). *Potential susceptibilities*: No specific data were available to inform potential differences in susceptibility.
Animals	*Robust* for male reproductive toxicity, based on: *Animal health effect studies*: • One *high* confidence study in mice, three *high* or *medium* confidence studies in rats, and five *low* confidence studies in rats: dose-related qualitative or quantitative histopathological lesions of the testes or epididymides. • Null evidence for testes histopathology in one *low* confidence study in mice. • One *high* confidence study in mice and *four* low confidence studies in rats: dose-related effects on epididymal sperm. • One *high* confidence study in mice, one *high* confidence study in rats, and one *low* confidence study in rats: dose-related decreased serum testosterone (and decreased serum luteinizing hormone in the *high* confidence study in mice). • Mixed results for organ weight changes (i.e., testes; epididymis) across multiple *high*, *medium*, and *low* confidence studies. • One *low* confidence study in mice with evidence of male-mediated decreases in fetal survival. • Note: No multigeneration study was conducted. *Biological plausibility*: Multiple biomarkers of oxidative stress, as well as heat shock protein induction, have been observed in the testes or epididymides of exposed rats in well-conducted studies. Heat shock protein immunoreactivity and oxidative stress resulting in hypomethylated sperm (no studies were identified that evaluated sperm methylation changes) were linked to human male infertility.	
Other inferences	• *Relevance to humans*: Some uncertainty regarding the relevance of the animal evidence exists, as the studies only tested extremely high concentrations expected to cause strong irritant effects that may not occur in humans; however, in light of the concordant findings in a well-conducted study of humans and an absence of other evidence to the contrary, the relevance of animal male reproductive toxicity outcomes to humans is presumed. • *MOA*: No experimentally established MOA exists, and any potential mechanisms have not been well-studied; however, mechanistic data provide some support for indirect effects on the male reproductive system.	

[a]The "appropriate exposure circumstances" are more fully evaluated and defined through dose-response analysis in Section 2.

1.3.3. Lymphohematopoietic Cancers

The specific endpoints considered in this section include diagnoses of Hodgkin lymphoma, multiple myeloma, myeloid leukemia, or lymphatic leukemia in exposed humans (note: diagnosis of non-Hodgkin lymphoma, a nonspecific grouping of dozens of different lymphomas, was not formally evaluated; see Appendix A.5.9), as well as experimental animal and mechanistic studies

relevant to the interpretation of potential effects on the lymphohematopoietic (LHP) system. For these subtypes, there have been different interpretations of the weight of evidence for whether formaldehyde inhalation causes LHP cancers. Expert review panels have determined that there is sufficient evidence to conclude that formaldehyde inhalation increases the risk for myeloid leukemia based on the results of epidemiological studies alone (NTP, 2011), or additionally supported by mechanistic research (NRC, 2014b; IARC, 2012). Two European Union scientific bodies were not in agreement with those conclusions, noting that although there is evidence of associations between formaldehyde exposure and LHP cancers in the epidemiological literature, the observations are not biologically plausible since formaldehyde is not distributed to distal tissues preventing direct interactions in the bone marrow (SCOEL, 2017; ECHA, 2012). Health Canada did not draw a hazard conclusion for LHP cancer subtypes in their assessment of carcinogenesis and other health effects for formaldehyde, which was finalized prior to the publication of several epidemiological studies that reported associations (Health Canada, 2006, 2001). An independent review of the evidence was conducted and is presented in this section.

Human studies provided *robust* evidence for myeloid leukemia and *slight* evidence for multiple myeloma based on epidemiology studies of occupational formaldehyde levels either in specific work settings (e.g., cohort studies) or in case-control studies. Aneuploidy in chromosomes 1, 5, and 7 in circulating myeloid progenitor cells, considered a potential primary target for LHP carcinogenesis, was associated with occupational formaldehyde exposure. The type of aneuploidies observed in the formaldehyde-exposed asymptomatic human workers are also found in patients with leukemia, as well as in other worker cohorts at increased risk of developing leukemias, which provides support for the plausibility of an association between chronic formaldehyde exposure and leukemogenesis. Moreover, the strong and consistent evidence from a large set of studies that observed mutagenicity in circulating leukocytes of formaldehyde-exposed humans, specifically chromosomal aberrations (CA), and micronucleus (MN) formation, provides additional evidence of biological plausibility for these cancer types. Further support is provided by studies that observed perturbations to immune cell populations in peripheral blood associated with formaldehyde exposure. In particular, decreases in red blood cells (RBCs), white blood cells (WBCs), and platelets, along with a 20% decrease in colony-forming units that arose in vitro as descendants from dedicated progenitors of granulocytes and macrophages (CFU-GMs) were observed in the same exposed group, suggesting both a decrease in the circulating numbers of mature RBCs and WBCs as well as possible decreases in the replicative capacity of myeloblasts.

Increased LHP cancers have not been observed in a well-reported chronic rodent bioassay involving inhalation exposure of both rats and mice to formaldehyde, nor in another rat bioassay that failed to report the incidence of non-nasal neoplastic lesions. Further, positive associations with leukemia have not been reported in rodent studies. Thus, there appears to be a lack of concordance between evidence from chronic rodent bioassays and human epidemiological evidence, although such concordance is not necessarily expected (U.S. EPA, 2005a).

Taken together, based on the *robust* human evidence for these cancers from studies that reported increased risk in groups exposed to occupational formaldehyde levels, the **evidence demonstrates** that formaldehyde inhalation causes myeloid leukemia in humans, given appropriate exposure circumstances. Separately, based on a limited number of epidemiological studies and potentially relevant mechanistic evidence in exposed humans, the **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation might cause multiple myeloma and Hodgkin lymphoma, given appropriate exposure circumstances. While mechanisms for the induction of myeloid leukemia are yet to be elucidated, they do not appear to require direct interactions between formaldehyde and bone marrow constituents, and either are different in animals or the existing animal models tested thus far do not characterize the complex process leading to cancers in exposed humans.

Literature Search and Screening Strategy

The primary databases used for the literature searches were PubMed, Web of Science, and Toxline, with the last update of the search completed in September 2016 (see Appendix A.4.7, A.5.9 and A.5.6), and a systematic evidence map updating the literature through 2021 (see Appendix F). The occurrences of lymphohematopoietic cancers in humans have been described and grouped according to the International Classification of Disease (ICD) coding rubrics. Epidemiological reviews were restricted to those specific cancer diagnoses available in the epidemiological literature. The primary focus of this review was the specific lymphohematopoietic cancers that are most commonly reported, myeloid leukemia, lymphatic leukemia, multiple myeloma, and Hodgkin lymphoma. Published results for nonspecific aggregations of lymphomas, "all leukemias," and "all lymphohematopoietic cancers" were not reviewed. Only primary epidemiological studies of specific cancer endpoints with identified or inferred formaldehyde exposure were included. Additional studies were identified from review articles and government documents. Studies of non-Hodgkin lymphoma were not formally reviewed (see Appendix A.5.9). In addition, three pertinent primary research articles and an unpublished Battelle-Columbus report (Battelle, 1982) were considered relevant to investigations of leukemias following formaldehyde exposure in experimental animals; these four studies were evaluated. Literature searches pertaining to potential mechanisms relevant to LHP carcinogenicity, including genotoxicity (Appendix A.4) and inflammation- and immune-related changes (Appendix A.5.6) also were conducted.

The bibliographic databases, search terms, and specific strategies used to search them are provided in Appendix A.4, A.5.6, and A.5.9, as are the specific PECO criteria. Literature flow diagrams summarize the results of the sorting process using these criteria and indicate the number of studies that were selected for consideration in the assessment through 2016 (see Appendix F for the identification of newer studies through 2021). The relevant human and animal health effect studies (i.e., meeting the requirements outlined above), and mechanistic data informative to LHP cancers were evaluated to ascertain the level of confidence in the study results for hazard identification (see Appendix A.4.7, A.5.6 and A.5.9).

Overview of Lymphohematopoietic Cancer Biology

LHP neoplasias describe a broad group of cancers of the blood, bone marrow, and lymph nodes, which includes leukemia, lymphoma, and myeloma. The various LHPs originate through a multistep process in different stages of the hematopoietic pathway (the process through which blood cells are formed). In normal human adults, this process occurs primarily in the bone marrow, with the exception of lymphocytes, which continue to mature in the thymus, spleen, and peripheral tissues. Therefore, LHPs may derive from discrete precursor or stem cells, as well as mature lymphoid cells. Figure 1-36 illustrates the hematopoietic pathway, the location of each differentiation (bone marrow or peripheral tissues), and the likely site of occurrence for transformation in each subtype of LHP. Briefly, normal hematopoietic stem cells differentiate into one of two lineages: myeloid or lymphoid progenitor cells. Normal myeloid progenitor cells may then differentiate into mature RBCs, platelets, or granulocytes; lymphoid progenitor cells derive T and B lymphocytes as well as natural killer (NK) cells and dendritic cells (see Figure 1-36).

LHP neoplasias arise from abnormal hematopoietic and lymphoid cells that are unable to differentiate normally to form mature blood cells. Neoplasias following the myeloid lineage are designated as chronic or acute leukemias, depending on the rate of expansion and the dominant stage of cell differentiation. Acute leukemias are characterized by a rapid onset, whereas chronic leukemias develop slower and progress over a period of months or years. Lymphoid neoplasias may either reside in the blood as chronic or acute lymphoblastic leukemias or develop within peripheral lymphoid sites such as the lymph nodes, spleen, or thymus—these are designated as lymphomas. Some rare leukemias exhibit both myeloid and lymphoid characteristics and are known as biphenotypic leukemias (Russell, 1997).

The majority of leukemias originate in the bone marrow at the hematopoietic stem cell stage or at a later, lineage-restricted stage. Specifically, adult leukemias of myeloid origin such as acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), and chronic myeloid leukemia (CML) as well as adult acute lymphoblastic leukemia (ALL) are thought to originate at the stem or progenitor cell stage (Warner et al., 2004).

Lymphomas primarily derive from mature lymphoid cells in peripheral tissues such as the spleen, lymph nodes, and thymus, and are generally classified as either Hodgkin or non-Hodgkin lymphomas (NHLs) depending on the appearance of a specific cancer cell type found in Hodgkin lymphomas. Within the larger groupings of NHLs are numerous subtypes with unique characteristics and origins. Myeloma (also called multiple myeloma) is a cancer of the plasma cells that forms a mass or tumor located in the bone marrow. Most lymphomas and all myelomas, as well as some rare leukemias/lymphomas (adult T cell leukemia [TCL], adult chronic lymphocytic leukemia [CLL], prolymphocytic leukemia [PLL], and hairy cell leukemia [HCL]) originate in mature lymphoid cells (Harris et al., 2001; Greaves, 1999).

While hematopoietic stem cells are normally located in the bone marrow, they do spontaneously mobilize into the peripheral blood at low levels, or in response to chemical insult,

mobilize in large numbers (Schulz et al., 2009; Lévesque et al., 2007). These mobilized cells remain in circulation for very short periods of time (minutes to hours) and then localize to peripheral tissues or in some cases, return to the bone marrow. Consequently, there may be a recirculation of hematopoietic stem cells between the bone marrow and other peripheral tissues. Therefore, the potential exists for DNA damage or other types of leukemogenic alteration during this mobilization between tissues. Cells confined to the bone marrow are less vulnerable to environmental insult than cells that enter the general circulation. Therefore, knowledge of the location of origin of discrete LHPs is important to understanding the potential targets of carcinogenic compounds.

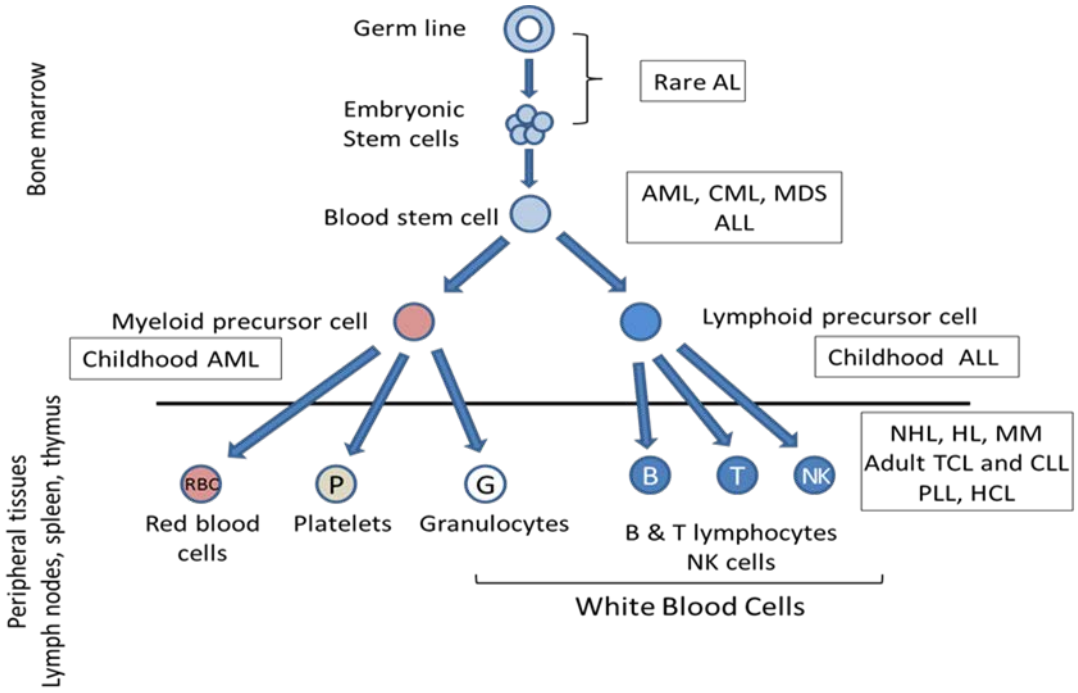


Figure 1-36. The hematopoietic pathway and likely sites of neoplastic transformation for LHPs.

Abbreviations: AML = acute myeloid leukemia; CML = chronic myeloid leukemia; MDS = myelodysplastic syndrome; ALL = acute lymphoblastic leukemia; NHL = non-Hodgkin lymphoma; HL = Hodgkin lymphoma; MM = multiple myeloma; TCL = T cell lymphoma; CLL = chronic lymphocytic leukemia; PLL = prolymphocytic leukemia; HCL = hairy cell leukemia (adapted from: https://www.seattlecca.org/diseases/chronic-myeloid-leukemia-cml/cml-facts-0).

Lymphohematopoietic Cancers in Human Studies

Each specific type of LHP cancer (myeloid leukemia, lymphatic leukemia, multiple myeloma, and Hodgkin lymphoma) is reviewed and evaluated independently in the sections below. For each type of LHP cancer, the evidence is organized by considerations that inform the strength of evidence (e.g., consistency, exposure-response) and evaluation of the potential for bias and insensitivity in individual studies to affect the estimates of relative risk (RR). Evidence tables for

each type of LHP cancer (Tables 1-59 through 1-62) are included that are organized first by the study evaluation conclusions (i.e., *high, medium, low*) and then by publication year.

Methodological issues and approaches for evaluation

The epidemiology studies generally examined occupational exposure to formaldehyde either in specific work settings (e.g., cohort studies) or in case-control studies. The considerations with respect to design, exposure assessment, outcome assessment, potential bias and confounding, and analysis differ for these different types of studies, and are discussed in more detail in Appendix A.5.9. Because a single epidemiology study may report on several different cancer endpoints, the confidence classifications are for the specific cancer results and are not judgments on the study as a whole except when a study has only a single cancer endpoint. The distinction here is important in that a study of adequate quality overall may still report an effect estimate judged to be of *low* confidence due to the rarity of the cancer outcome, the rarity of the exposure, or noncritical biases that are expected to yield effect estimates that underestimate any true effect.

The diagnosis of cancers in epidemiological studies has historically been ascertained from death certificates according to the version of the International Classification of Diseases (ICD) in effect at the time of study subjects' deaths [i.e., ICD-8 and ICD-9: (WHO, 1977, 1967)]. The most specific classification of diagnoses commonly reported across the epidemiological literature was based on the first three digits of the ICD code (i.e., myeloid leukemia ICD-8/9: 205) without further differentiation—although a few studies reported results at finer levels (i.e., Acute Myeloid Leukemia ICD-8/9: 205.0), and these are discussed.

For some cancers, the reliance of cohort studies on death certificates to detect cancers with relatively high survival may have underestimated the actual incidence of those cancers, especially when the follow-up time may have been insufficient to capture all cancers that may have been related to exposure. The potential for bias may depend upon the specific survival rates for each cancer. Five-year survival rates vary among the selected cancers, from 86% for Hodgkin lymphoma to less than 50% for multiple myeloma (MM) and myeloid leukemia (ML). EPA considered the likelihood of underreporting of incident cases to be higher for mortality-based studies of Hodgkin lymphoma and LL, which may result in undercounting of incident cases and underestimates of effect estimates compared to general populations (e.g., Mayr et al., 2010; Hansen and Olsen, 1995; Hansen et al., 1994; Hayes et al., 1990; Solet et al., 1989).

The overwhelming majority of information bias in epidemiological studies of formaldehyde stems from the use of occupational records to gauge exposures with some degree of random exposure misclassification or exposure measurement error considered to be commonplace. A primary consideration in the evaluation of these studies is the ability of the exposure assessment to reliably distinguish among levels of exposure within the study population, or between the study population and the referent population. A large variety of occupations were included within the studies; some represented work settings with a high likelihood of exposure to high levels of formaldehyde, and some represented work settings with variable exposures and in which the

proportion of people exposed was quite small. In the latter case, the potential effect of formaldehyde would be "diluted" by the random exposure measurement error within the larger study population, limiting the sensitivity of the study. The exposure-assessment methods of the identified studies were classified into four groups (A through D), reflecting greater or lesser degree of reliability and sensitivity of the measures (see Appendix A.5.9). Outcome-specific associations based on Group A exposures were considered to be without appreciable information bias due to exposure measurement error while those based on Groups B–D were considered to be somewhat biased toward the null.

Additional exposure measurement error may arise in circumstances when the time period of exposure assessment is not well aligned with the time period when formaldehyde exposure could induce carcinogenesis that develops to a detectable stage (incident cancer) or result in death from a specific cancer. The cohort studies were evaluated to assure that they analyzed the analytic impact of different lengths of "latency periods" (i.e., excluded from the analyses the formaldehyde exposure most proximal to each individual's cancer incidence or cancer mortality). Analyses that did not evaluate latency were considered to be somewhat biased toward the null because irrelevant exposure periods were included.

Studies with small case counts may have little statistical power to detect divergences from the null but are not necessarily expected to be biased and no study was excluded solely on the basis of case counts as this methodology would exclude any study that saw no effect of exposure. Therefore, cohort studies with extensive follow-up that reported outcome-specific results on a number of different cancers, including very rare cancers, were evaluated even when few or even no cases were observed—if information on the expected number of cases in the study population was provided so that CIs could be presented to show the statistical uncertainty in the associated effect estimated.

In addition to potential bias, study sensitivity was specifically evaluated; study results with low sensitivity could result in effect estimates that underestimated a "true" association if it existed. For example, an outcome-specific effect estimate based on fewer than five observed cases of a particular cancer would be classified as *low* confidence based on a lack of sensitivity—even if there were no appreciable biases. Another example would be a study that might have relied on exposure-assessment methodologies that were unbiased, but were nonspecific in nature, so as to yield effect estimates that were likely biased toward the null and thus underestimated any true effect. Finally, cohort studies should have a sufficiently long follow-up period to allow for any exposure-related cancer cases to develop and be detected and, ideally, allow for analyses of potential cancer latency. Outcome-specific effect estimates from cohort studies with short follow-up could be considered uninformative depending on the size of the study population and the baseline frequency of the cancer.

Myeloid leukemia

Epidemiological evidence

The most specific classification of myeloid leukemia diagnosis that is commonly reported across the epidemiological literature has been based on the first three digits of the Eighth or Ninth Revision of the ICD code (i.e., myeloid leukemia ICD-8/9: 205) —although the smaller sets of studies that reported specific results for AML (ICD-8/9: 205.0) and CML (ICD-8/9: 205.1) are discussed. For the purposes of this evaluation, cancer cases reported as monocytic leukemia or nonlymphocytic leukemia were included as myeloid leukemia. Evidence describing the association between formaldehyde exposure and the risk of myeloid leukemia was available from 13 epidemiological papers reporting on 10 different study populations—three case-control studies (Talibov et al., 2014; Hauptmann et al., 2009; Blair et al., 2001) and nine cohort studies (Coggon et al., 2014; Pira et al., 2014; Meyers et al., 2013; Saberi Hosnijeh et al., 2013; Beane Freeman et al., 2009; Hayes et al., 1990; Ott et al., 1989; Stroup et al., 1986; Walrath and Fraumeni, 1984, 1983). Hauptmann et al. (2009) combined the study populations from Hayes et al. (1990) with those from Walrath and Fraumeni (1984, 1983) and reconstructed individual exposure estimates. Checkoway et al. (2015) reanalyzed Beane Freeman et al. (2009) with a different definition of the exposure categories and presented results for specific subtypes of myeloid leukemia. These are the only formaldehyde studies that specifically evaluated the risk of myeloid leukemia. The outcome-specific evaluations of confidence in the reported effect estimate of an association from each study are provided in Appendix A.5.9, and the confidence conclusions are provided in the evidence table for myeloid leukemia (see Table 1-60) following the causal evaluation.

Consistency of the observed association

The majority of studies of the 10 populations reported elevated risks of myeloid leukemia (or a specific subtype) associated with exposure to formaldehyde for at least one metric of exposure, although four *low* confidence studies reported results based on fewer than 10 cases and two other *low* confidence studies reported relative effect estimates of RR = 1.02 and OR = 1.17. These studies examined different populations, in different locations and exposure settings, and using different study designs. The study results presented in Table 1-60 (by confidence level and publication date) detail all of the reported associations between exposures to formaldehyde and the risks of developing or dying from myeloid leukemia along with a summary graphic of any limitation and the confidence classification of the available effect estimates. Results for all studies are plotted in Figure 1-37 and grouped by the exposure-assessment methodology (e.g., population-level versus individual-level) and by the type of occupation of the exposed workers (e.g., anatomist/embalmers, industrial workers, garment workers). The same results for the *high* and *medium* confidence studies are plotted in Figure 1-38, and exposure-response trends describing the effect estimates of association between formaldehyde exposure and risk of myeloid leukemia in high confidence studies are shown in Table 1-59.

The first five studies in Figure 1-37 (Pira et al., 2014; Hayes et al., 1990; Stroup et al., 1986; Walrath and Fraumeni, 1984, 1983) shown at the left, under the header "Population-level exposure assessment" followed the health of a group of workers exposed to formaldehyde in a plastics manufacturing facility and four sets of anatomists and embalmers—professions known to be exposed to formaldehyde. These studies compared the risk of death from myeloid leukemia among those workers to the risk of death from myeloid leukemia among the general population. All five studies showed elevated RRs of myeloid leukemia mortality as measured by the mortality ratios, including two studies with 95% CIs that excluded the null, thereby decreasing the likelihood of chance as an alternative explanation for these findings. One study (Stroup et al., 1986) observed a much higher RR (standardized mortality ratio [SMR] 8.8) compared with the others (SMR ~1.4 to 2.0); this higher estimate was based on one subtype (CML), and was relatively imprecise (95% CI: 1.8, 22.5). The results from Pira et al. (2014) and Stroup et al. (1986) were classified with *low* confidence. The results from the other three studies (Hayes et al., 1990; Walrath and Fraumeni, 1984, 1983) were classified with *medium* confidence and are shown in Figure 1-37 to document their findings while acknowledging that these three studies populations were combined in (Hauptmann et al., 2009).

The second set of eight studies (Coggon et al., 2014; Talibov et al., 2014; Meyers et al., 2013; Saberi Hosnijeh et al., 2013; Beane Freeman et al., 2009; Hauptmann et al., 2009; Blair et al., 2001; Ott et al., 1989) is displayed in Figure 1-37 beneath the header of "Individual-level exposure assessment." A general strength of this second set of eight studies was their use of individualized exposure data, which, for six of the studies, allowed for the evaluation of exposure-response relationships with increased formaldehyde exposures using multiple metrics of exposure; additional detail of this consideration is included below under the *exposure-response relationships* section below. A further strength is that three of these studies had their effect estimates classified with *high* confidence (Meyers et al., 2013; Beane Freeman et al., 2009; Hauptmann et al., 2009) and were able to evaluate the impact of the timing of initial exposure relative to mortality; further detail of this consideration is included below under the *temporal relationship* section below. One study's results that were classified with *medium* confidence due to exposure measurement error (Coggon et al., 2014) showed a slightly elevated risk for those workers with the highest job exposures, but also slightly decreased risk for those with the highest duration of exposure. The results from the other four studies with individual-level exposure assessment were classified with *low* confidence due to the lower quality exposure assessment methods (Talibov et al., 2014; Saberi Hosnijeh et al., 2013; Blair et al., 2001; Ott et al., 1989). Additional findings from each of the studies are provided in Table 1-60. Different measures of exposure reflected different risks and this was true within studies and across studies but all provided some evidence of increased risk of dying from myeloid leukemia associated with formaldehyde exposure. One study showed the strongest relationship of myeloid leukemia mortality with duration of formaldehyde exposure (Hauptmann et al., 2009). Another showed increased risks for peak exposure and average exposure but not for cumulative

exposure or "any" exposure (Beane Freeman et al., 2009). The Checkoway et al. (2015) reanalysis of Beane Freeman et al. (2009) reported nonsignificant increased risks of AML and CML after redefining the referent group to include all workers with peak exposures of less than 2 ppm as well as some originally classified as having peak exposures of greater than 4 ppm because those worker's peak exposures were thought to be either too frequent or too rare (Beane Freeman et al., 2009). The result of this change in exposure assessment shifted nine cases of myeloid leukemia from the highest exposure category to the lowest exposure category (Checkoway et al., 2015).[28] Because this change in methodology for exposure assessment blends the highly exposed people with the low and unexposed people and thereby induces bias toward the null reducing study sensitivity, these results were classified with *low* confidence. A third study showed increased risk in the study population as a whole that was stronger among workers with the longest duration of exposure and workers with the greatest length of time since first occupational exposure to formaldehyde (Meyers et al., 2013).

The pattern of increased risk of myeloid leukemia (ICD-8/9: '204') associated with exposure to formaldehyde reflects the associations seen within two subtypes, AML and CML. Among the studies with separate estimates by subtype, risks were elevated for both AML and CML, with the associations for CML appearing to be as strong as or stronger than the associations with AML. Four studies reported specific results for CML (Checkoway et al., 2015; Saberi Hosnijeh et al., 2013; Blair et al., 2001; Stroup et al., 1986). All four studies reported elevated risks of CML. Six studies reported specific results for AML; two were classified with *high* confidence (Meyers et al., 2013; Hauptmann et al., 2009), and four with *low* confidence (Checkoway et al., 2015; Talibov et al., 2014; Saberi Hosnijeh et al., 2013; Blair et al., 2001). Both of the high confidence results showed nonsignificantly elevated risks of AML associated with formaldehyde, as did three of four of the *low* confidence results—although substantially higher risks were reported in the *high* confidence results. One *low* confidence result showed a slight decrease in risk of AML (Blair et al., 2001). Results specific to AML are plotted in Figure 1-39. Four of these six studies reported effect estimates for both ML and AML (Checkoway et al., 2015; Meyers et al., 2013; Saberi Hosnijeh et al., 2013; Hauptmann et al., 2009) on a total of 14 specific metrics of exposure. To assess whether the results for AML were comparable to those for ML, the pair-wise effect estimates were evaluated.[29] The correlation between the AML results and the ML results was 0.72 ($p < 0.0001$) and the slope

[28]In Beane Freeman et al. (2009), for peak exposure there were four cases of ML who were unexposed, 14 cases with peak exposure from >0 to <2 ppm, 11 cases with peak exposure from 2 to <4 ppm, and 19 cases with peak exposure ≥4 ppm. In Checkoway et al. (2015), the new definition of peak exposure and the recategorization resulted in 27 cases of ML with peak exposures from 0 to <2 ppm, 11 cases with peak exposure from 2 to <4 ppm, and 10 cases with peak exposure ≥4 ppm. The Checkoway et al. (2015) results were classified with *low* confidence due to information bias and low sensitivity.

[29] Based on six paired effect estimates from Hauptmann et al. (2009), five paired estimates from Meyers et al. (2013), two paired effect estimates from Checkoway et al. (2015) and one pair of effect estimates from Saberi Hosnijeh et al. (2013).

was 0.97 indicating a very strong alignment among these studies and strongly suggesting that the collective results for the broader group of ML cases may be inferred to represent AML as well.

Strength of the observed association

While reported relative effect estimates were consistently elevated above the null value of one across the 10 study populations, the magnitude of the relative effect estimates varied with the quality of the exposure assessment. Studies with higher quality exposure data based on individual-level exposure assessment generally reported higher relative effect estimates (stronger associations). The Hauptmann (2009) study reported the strongest association based on 34 cases of myeloid leukemia of whom 33 had ever performed an embalming (OR = 11.2, 95% CI 1.3, 95.6; p = .027); however, with just 1 case subject who had never embalmed in the reference group, the effect estimate, while statistically significant, is imprecise. The investigators conducted additional analyses that defined the reference group as having performed fewer than 500 embalmings so as to include five cases of myeloid leukemia in the reference group and those results are discussed below.

The results at the highest levels of formaldehyde exposure showed an approximately two- to three-fold relative increase in risk of mortality from myeloid leukemia (Meyers et al., 2013; Beane Freeman et al., 2009; Hauptmann et al., 2009; Blair et al., 2001) with one exception, which reported no increase in risk among those who had ever had a job in the highest category of exposure (Coggon et al., 2014). This may have been due to the choice in (Coggon et al., 2014) to classify as highly exposed all workers who ever worked in a highly exposed job, even if just for one year out of 20, a methodology that mixes workers with many years of high exposure together with workers with just a single year of high exposure, thereby potentially diluting the strength of the association. Results from other studies using a cruder exposure classification (i.e., exposed versus not exposed), and low to medium confidence, generally showed elevated risks in the 1.02– to 2–fold range (Pira et al., 2014; Talibov et al., 2014; Saberi Hosnijeh et al., 2013; Ott et al., 1989). Results from the studies with higher quality exposure data were judged with greater confidence.

Temporal relationship of the observed association

Two related aspects of time are encompassed in the consideration of temporality. One aspect is the necessity for the exposure to precede the onset of the disease. In each of the studies, the formaldehyde exposures among the study participants started prior to their diagnoses of myeloid leukemia or deaths from myeloid leukemia and in the studies that ascertained individual-level exposures, the estimation of formaldehyde exposures was based on job titles and was done in a blinded fashion with respect to outcome status. The second aspect involves the time course of formaldehyde exposures in relation to the incidence of myeloid leukemia and death from myeloid leukemia; this aspect of time is defined as the etiologically relevant window of time when exposure to a causal factor is relevant to the causation of disease. From the epidemiological literature of benzene-related leukemia, it is known that there can be an induction/latency period for some

environmental agents and that the induction period may exceed 10 years (Rinsky et al., 1987). The epidemiological literature for formaldehyde and myeloid leukemia describes three studies that evaluated the impact of the TSFE (Meyers et al., 2013; Beane Freeman et al., 2009; Hauptmann et al., 2009). All three studies show some indication of an increase in risk at about 15–20 years of time since first exposure (TSFE) to formaldehyde that is consistent with a biologically relevant induction/latency period. However, the Hauptmann et al. (2009) study clearly shows increased risk at 20+ years of time since first exposure. (Beane Freeman et al., 2009) reported that the best fitting exposure lag length of time to potentially account for cancer latency was 18 years. While those three studies support the estimation of the beginning of the potentially relevant window of time, the window may also have an ending when exposures that have occurred a very long time before may no longer be relevant to the causation of disease.

In the mortality follow-up of this cohort through 1980, the High peak exposure had RR = 3.92 (95% CI 0.78, 19.67; *p*-trend = 0.12) (Blair et al., 1986); in the follow-up through 1994, the High peak exposure had RR = 2.79 (95% CI 1.08, 7.21; *p*-trend = 0.02) (Hauptmann et al., 2003); and in the follow-up through 2004 the RR = 1.78 (95% CI 0.87, 3.64; *p*-trend = 0.07). Beane Freeman (2009) reported the effect estimates for follow-up through every individual calendar year starting with 1965 and ending with 2004. Figure 1 of (Beane Freeman et al., 2009) shows the association between peak formaldehyde exposure and the risk of myeloid leukemia; risks of High exposures were compared against the lowest exposed category. Risks were significantly elevated in each year of follow-up during the 1990's before losing significance in the 2000's. Such a pattern may reflect the closing of the potentially relevant window of time when exposures are relevant to disease causation. With very long follow-up of a cohort, those workers who were highly exposed may have experienced a window of increased risks of myeloid leukemia associated with exposure to formaldehyde that tapered off or closed. This phenomenon may occur as additional background cases of myeloid leukemia − unrelated to formaldehyde exposure, were added to both the High and the Low exposures groups thereby bringing the relative risks of these groups toward the null value of 1.00.

As formaldehyde exposure had ceased by 1980 for all but 3.5% of person-time and latency analyses showed higher risks in the period 15 to 25 years after first exposure with the best fitting exposure lag of 18 years (Beane Freeman et al., 2009), the 1994 follow-up of the NCI formaldehyde cohort (Hauptmann et al., 2003) which reported that High peak exposure had RR = 2.79 (95% CI 1.08, 7.21; *p*-trend = 0.02) may be a more informative estimate of the association between formaldehyde exposure and risks of myeloid leukemia. There is some indication that a similar phenomenon may have occurred in the study of garment worker and the mortality follow-up through 1988 (Pinkerton et al., 2004) which reports somewhat stronger results for workers with 20+ years TSFE than was reported in the 2008 follow-up (Meyers et al., 2013)(SMR = 1.91; $p < 0.05$ vs. SMR = 1.49 (95% CI 0.90, 2.32); and for duration longer than 10 years (SMR = 2.19 vs. SMR =1.84). If the follow-up of these two cohorts has exceeded the window of time when exposures are

relevant to disease causation, then the evidence may be somewhat stronger than is evident in the reports from the most recent follow-ups.

Exposure-response relationship

Of the studies that provided evidence to evaluate the association between exposure to formaldehyde and the risk of myeloid leukemia, four studies (Hayes et al., 1990; Stroup et al., 1986; Walrath and Fraumeni, 1984, 1983) followed the health of anatomists and embalmers and did not have specific individual-level exposure data to assess an exposure-response relationship. One study (Ott et al., 1989) did assess individual-level exposures but did not report differentiated risks by exposure levels of formaldehyde. One study, Saberi Hosnijeh et al. (2013), which had risk analyses on three levels of exposure for other health endpoints, did not identify any people with high exposures to formaldehyde and thus could only compare risks of low exposures with risks of no exposures.

The remaining studies did present distinct risk estimates differentiated by formaldehyde exposure levels. Meyers et al. (2013) reported results by workers' year of first exposure, their time since first occupational exposure, and by their duration of exposure. Data on cumulative exposure was not available. The investigators considered that the initial study years (prior to 1963) had the highest formaldehyde exposures as ongoing industrial hygiene practices were thought to have decreased exposures over time. For first employment in the earliest period (before 1963), the overall SMR was 1.37 (95% CI 0.75, 2.30) while first employment in the middle (1963–1970) and late time periods (after 1970) had ORs of 1.13 and 1.15. There was an extensive investigation of exposure-response by duration of exposure with external and internal comparisons by strata of duration as well as multivariate Poisson modeling of exposure duration, all of which showed increasing risk with longer duration (see Table 1-60). Multiple models all showed positive trends of increasing rate ratios with increasing exposure duration (see Figure 1B in (Meyers et al., 2013 but the continuous model with duration was not statistically significant with rate ratio of 1.04 per one year increase in duration (95% CI 0.097, 1.12) provides only modest evidence of an exposure-response relationship based on duration of exposure.

Beane Freeman et al. (2009) evaluated results by each worker's highest formaldehyde concentration during a "peak" exposure event, by average intensity of exposure, by cumulative exposure, and by duration of exposure. "Peak" exposure events were defined as short-term exposures (<15 minutes) that exceed the TWA formaldehyde intensity (Beane Freeman et al., 2009). Workers' "peak" exposures were defined as the highest concentration among their "peak" exposure events. Among only those workers with some "peak" exposure, the RR in the highest category compared to the lowest category was 1.78 (95% CI 0.87, 3.64) with a trend *p*-value of 0.13 for the continuous values of the peak exposure data. While the investigators considered the lowest group of exposed workers to be the most appropriate reference group (possibly due to a potential for selection bias between exposed and unexposed workers), had the unexposed group been used as the referent group, the RR would have been higher (~ RR of 2.17). This relationship between

myeloid leukemia and high peak formaldehyde exposure is not only seen for the complete 2004 follow-up when the average length of follow-up was 42 years, but throughout the cohort experience (see Beane Freeman et al., 2009, Figure 1). These plots show that during the 1970s and 1980s, the RR > 10 until about 1970 and then remained elevated between RR = 4 and RR = 6 until about 1980 and then between about RR = 2 and RR = 3 through the end of follow-up in 2004. Such a consistent finding of a strong effect over many years of follow-up reduces the possibility that the results for the full follow-up period could be due to chance. Beane Freeman et al. (2009) reported that among all workers there was an exposure-response trend through follow-up in 2004 with *p*-value of 0.07 for the continuous values of the peak exposure data; and there was an exposure-response trend through follow-up in 1994 with *p*-value of 0.0087.

Beane Freeman et al. (2009) also reported that among those with any formaldehyde exposure in the 2004 follow-up, the RR in the highest category of average intensity of exposure was 1.61 (95% CI 0.76, 3.39) with little evidence of any trend for the continuous exposure data at nearly 40 years of follow-up ($p = 0.40$). However, the supplementary tables from Beane Freeman et al. (2009) reported that for follow-up through 1994, the exposure-response trend value for all workers was $p = 0.11$. No trend in RR was found for cumulative exposure (see Table 1-60). Overall, the evidence from Beane Freeman et al. (2009) provides limited evidence of an exposure-response relationship based on "peak" exposures.

Hauptmann et al. (2009) evaluated results by multiple metrics of exposure including exposure duration, number of embalmings, cumulative exposure, average formaldehyde intensity while embalming, time-weighted formaldehyde intensity, and peak exposure. Peak exposure levels were defined as the maximum of moving averages of any series of measurements covering 15 minutes. Results for two different reference groups were reported, the first set from the authors' Table 3 used unexposed people as the "a priori" reference group but as there was only one case of myeloid leukemia in this group, the results were statistically unstable with wide Cis. Those results showed an OR of 13.6 (95% CI 1.6, 119.7) for the highest category of duration with a statistically significant trend *p*-value of 0.020; and an OR of 9.5 (95% CI 1.1, 86.0) for the highest category of average exposure; and an OR of 13.0 (95% CI 1.4, 116.9) for the highest category of peak exposure. The second set of results redefined the reference category as those people with fewer than 500 lifetime embalmings. Thus, this referent group includes some exposed individuals, which mutes the categorical comparisons (i.e., this methodology causes bias toward the null and underestimates the effect estimates) but allows for more statistically stable effect estimates as there were five cases of myeloid leukemia in this reference group. Those results showed an OR of 3.9 (95% CI 1.2, 12.5) for the highest category of exposure duration, an OR of 2.3 (95% CI 0.7, 7.5) for the highest category of average exposure, and an OR of 2.9 (95% CI 0.9, 9.5) for the highest category of peak exposure.

Hauptmann et al. (2009) assessed two methodologies to measure potential exposure-response trends: (1) trends based on the complete range of continuous exposure metric data and (2) trends based on the ordinal levels of the categories of the difference exposure metrics, with the

former method selected a priori. There was a statistically significant positive exposure-response trend for duration of formaldehyde exposure (p = 0.020) as well as a statistically significant positive trend for peak exposures (p = 0.036) and the trend p-value for average formaldehyde exposure was 0.058. For the other metrics of exposure, the continuous exposure metric data trend p-values were greater than 0.10. However, analyses using the ordinal levels of the exposure metrics also showed trends for the TWA8 intensity (p = 0.021), the number of embalmings (p = 0.012) and for cumulative exposure (p = 0.023). Table 1-59 provides a summary of the exposure-response trends reported by Hauptmann et al. (2009), Beane Freeman et al. (2009), and Meyers et al. (2013)—all three of which reported results that were judged to be of *high* confidence (see Table 1-60 and Appendix A.5.9).

Table 1-59. Summary high confidence studies of reported exposure-response trends describing the effect estimates of association between formaldehyde exposure and risk of myeloid leukemia

***High* confidence studies reporting exposure-response trend assessments**						
	Hauptmann et al. (2009)[a]		Beane Freeman et al. (2009)[a]		Meyers et al. (2013)[a]	
Exposure metric	Continuous	Categorical	Continuous 2004 follow-up	Continuous 1994 follow-up	Continuous	Categorical
Duration	p = **0.020**	NR	NR	NR	p = 0.30	NR
# of Embalmings	p = 0.314	p = **0.012**	NR	NR	NR	NR
Cumulative	p = 0.192	p = **0.023**	p = 0.44	p = 0.171	NR	NR
Average	p = 0.058	NR	p = 0.40	p = 0.110	NR	NR
TWA8	p = 0.396	p = **0.021**	NR	NR	NR	NR
Peak	p = **0.036**	NR	p = 0.07	p = **0.0087**	NR	NR

Abbreviations: TWA8 = 8-hour time-weighted average; NR = not reported.
[a]Formaldehyde exposure measured as a continuous variable among unexposed and exposed persons.

Coggon et al. (2014) classified workers' exposures according to the highest level of exposure ever experienced, which can be interpreted as an indicator of peak occupational exposure because each worker was assigned the highest exposure classification ever experienced, and reported exposure-level specific results with an OR of 1.10 (95% CI 0.51, 2.38) for workers with peak occupational exposure of low/moderate and an OR of 1.26 (95% CI 0.39, 4.08) for those workers who had ever worked in a job with high exposures. Among the group with high exposures, those with less than one year of employment at high exposure had an OR of 1.77 (95% CI 0.45, 7.03; 9 exposed cases) while those with 1 year or more at high exposure had an OR of 0.96 (95: CI: 0.24, 3.82; 4 exposed cases). The limitation of this study was the likelihood of nondifferential exposure misclassification due to the quality of the exposure assessment and the lack of any latency analysis. The expected impact is of a downward bias toward the null thereby muting any potential exposure-

response. The evidence from Coggon et al. (2014), while potentially biased toward the null and statistically unstable within the "high" exposure category (nine exposed cases), provided only weak evidence of an exposure-response relationship with "peak exposure."

Blair et al. (2001) reported separate results for AML and CML by *low* and *high* intensity of exposure although data were only available to examine exposure-response for CML. Blair et al. (2001) reported an OR = 1.3 (95% CI 0.6, 3.1) for low exposure based on seven cases and an OR = 2.9 (95% CI 0.3, 24.5) for high exposure based on one case. Given that that the OR in the high exposure group was based on only one case, these results provided only weak evidence of an exposure-response relationship.

Talibov et al. (2014) reported results across three levels of cumulative formaldehyde exposure and showed some increasing risk with each increasing level of exposure from HR = 0.89 (95% CI: 0.81, 0.97) in the lowest group to HR = 0.92 (95% CI: 0.83, 1.03) in the middle group and HR = 1.17 (95% CI: 0.91, 1.51) in the highest exposure group. The test for trend showing an exposure-response had a *p*-value of 0.07. As with the other results classified with *low* confidence, the limitation of this study was the likelihood of nondifferential exposure misclassification due to the quality of the exposure assessment, which was based on decennial census records. The expected impact is of a downward bias toward the null thereby muting any potential exposure-response.

The evidence for an exposure-response relationship is most strongly supported by the study of embalmers by Hauptmann et al. (2009), which reported statistically significant trends for five of the six exposure metrics evaluated including duration of exposure, the number of embalmings, cumulative exposure, average intensity of exposure, TWA8 exposure, and "peak" exposure; and a borderline significant trend for the sixth exposure metric (average intensity of exposure). Beane Freeman et al. (2009) reported a borderline significant exposure-response trend for the measure of "peak" exposure that was shown to be statistically significant over the course of more than 30 years of annual follow-up but which faded somewhat as the maturity of the cohort approached 40 years of follow-up—a span of time that far exceeds the latency of all but a few cancers such as mesothelioma. Meyers et al. (2013) also provided solid evidence of an exposure-response relationship based on duration of exposure. Coggon et al. (2014), a *medium* confidence study, found little evidence for an exposure-response relationship.

While it is not known which of these exposure metrics is of greatest biological relevance for myeloid leukemia, all of the exposure metrics reflect different aspects of increased exposure to formaldehyde and associations with increased risks of myeloid leukemia. As the different measures of exposure are all likely to be correlated with each other, it may not be possible at this time to single out one exposure metric as more biologically meaningful than another. It appears that these various trend results reflect some true underlying exposure-response relationship.

Observations of exposure-response relationships are strong evidence in support of an association consistent with causation (Hill, 1965) and against a spurious association because it

would necessitate a third (uncontrolled) factor, which changes in the same manner (direction and magnitude) as the exposure of interest (CDC, 2004) to explain away each of the reported exposure-response relationships.

Potential impact of selection bias, information bias, confounding bias, and chance

Selection bias is an unlikely alternative explanation for the consistent evidence of increased risk of myeloid leukemia in people exposed to formaldehyde. Selection bias is unlikely in the case-control studies of myeloid leukemia as the case-control (Blair et al., 2001) and nested case-control studies (Coggon et al., 2014; Hauptmann et al., 2009) evaluated exposure status without regard to outcome status and had participation levels of 77-99%. Each of the cohort studies (Coggon et al., 2014; Pira et al., 2014; Talibov et al., 2014; Meyers et al., 2013; Saberi Hosnijeh et al., 2013; Beane Freeman et al., 2009; Hayes et al., 1990; Ott et al., 1989; Stroup et al., 1986; Walrath and Fraumeni, 1984, 1983) included at least 75% of eligible participants and lost fewer than 3% of participants over the course of mortality follow-up.

Selection bias due to the comparison of a generally healthier group of workers to those in the general population (called the healthy worker effect) could have obscured a truly larger effect of formaldehyde exposure in analyses based on "external" comparisons with mortality in the general population in one study with an SMR = 0.64 for "all cancers" (Stroup et al., 1986), but would not influence analyses using "internal" or matched comparison groups (Coggon et al., 2014; Meyers et al., 2013; Beane Freeman et al., 2009; Hauptmann et al., 2009; Blair et al., 2001). The clearest example of the potential influence of the healthy worker effect is shown in the comparison on results from the study of garment workers (Meyers et al., 2013). That study compared SMRs using an external referent group based on the general population alongside standardized rate ratios (SRR) using an internal referent group of workers in the lowest category of duration of exposure. Compared to the general population (matched on sex, race, age, and calendar time), garment workers with less than a 3-year duration of exposure had an SMR of 0.65 (95% CI 0.18,1.65), which is a 35% lower risk of dying from myeloid leukemia than people in the general population. For workers with a 3- to 9-year duration, the SMR was 1.46, and for workers with 10 or more years of exposure, the SMR was 1.84. Internal comparisons were made by comparing the risk of dying from myeloid leukemia in workers with 3–9 years of exposure to the risk among those with less than 3 years of exposure for an SRR of 2.12. The SRR for workers with 10 or more years of exposure was 3.25. Selection bias may explain why results based on comparisons of mortality of workers with the general population are lower than comparisons of workers to workers. Selection bias does not explain increased risks in exposed workers.

Information bias is an unlikely alternative explanation for the consistent evidence of increased risk of myeloid leukemia in people exposed to formaldehyde. Information bias may distort epidemiological findings when subjects' true exposures are inaccurately assigned at the individual or group level. A differential misclassification, in which exposure status influences disease classification by the investigator (or disease status influences exposure classification), can

lead to spurious (i.e., "false positive") associations. However, information bias is considered unlikely among these studies of myeloid leukemia mortality because the likelihood of differential misclassification based on these study designs is low. The assignment of exposure status or calculation of exposure measures in the cohort studies was done independent of knowledge of the cause of death. In the nested case-control studies by Coggon et al. (2014) and Hauptmann et al. (2009) the ascertainment of individual-level exposure levels was independent of the cause of death. In the case-control study by Blair et al. (2001), many different occupational exposures were evaluated based on interview data and subjects were unlikely to be aware of specific chemical exposure of interest in the study. Therefore, an exposure-related recall bias of their occupational histories is unlikely. The exposure assignments in Blair et al. (2001) were based on typical exposure characteristics of the individual's job and were made blinded to case/control status.

There does not appear to be any evidence of confounding that would provide an alternative explanation for the observed association of formaldehyde exposure with increased risk of myeloid leukemia seen in these studies. Chemicals and other coexposures that have not been independently associated with myeloid leukemia are not expected to confound results. However, other known risk factors for myeloid leukemia include exposure to benzene, ionizing radiation, and smoking. Benzene is not used in the embalming process (Stewart et al., 1992; Hayes et al., 1990) and was not a chemical coexposure in the garment plants (Stayner et al., 1985), and consequently, could not be a confounder of those results. Benzene was evaluated by Ott et al. (1989) and not found to be a risk factor (OR = 1.0), and thus, could not be a confounder. Benzene was specifically assessed as a potential confounder among the U.S. industrial workers (Beane Freeman et al., 2009) and found not to be a confounder. Ionizing radiation can be a coexposure for embalmers but the limited extent of such radiation exposure is unlikely to explain the observed association in embalmers (Hauptmann et al., 2009). Exposures to ionizing radiation were not mentioned as coexposures for the industrial workers or the garment workers, and would not be expected to be correlated with their formaldehyde exposures. Smoking was controlled for in the analyses of the embalmers (Hauptmann et al., 2009), which demonstrated a statistically significant exposure-response relation between both duration of formaldehyde exposure and peak exposures with increased risk of death from myeloid leukemia. Blair et al. (2001) also controlled for smoking in their analyses thereby reducing the likelihood of confounding by smoking. Smoking was not evaluated as a potential confounder in the industrial or garment worker cohorts (Coggon et al., 2014; Meyers et al., 2013; Beane Freeman et al., 2009). However, there is no evidence that smoking rates in the industrial or garment worker cohorts (Meyers et al., 2013; Beane Freeman et al., 2009) were correlated with formaldehyde exposures—a necessary condition for potential confounding. Moreover, the internal comparisons used in the analyses of the industrial cohort should mitigate any potential confounding effects of smoking because smoking rates within a cohort are likely to be more similar than compared to the general population.

Consistency across multiple studies is demonstrated by a pattern of increased risk in different populations, exposure scenarios, and time periods. Such consistency makes unmeasured confounding an unlikely alternative explanation for the observed associations. This consistency also reduces the likelihood of chance as an alternative explanation. The observations of exposure-response trends similarly reduce the likelihood that chance, confounding, or other biases can explain the observed association.

Causal evaluation

The causal evaluation for formaldehyde exposure and the risk of developing or dying from myeloid leukemia placed the greatest weight on five particular considerations: (1) the generally consistent increases in risk observed across a set of *high* and *medium* confidence independent results from epidemiology studies of occupational formaldehyde levels using varied study designs and populations; (2) the strength of the association showing a 1.5- to 3-fold increase in risk in studies with higher quality exposure assessment; (3) the reported exposure-response relationships showing that increased exposure to formaldehyde were associated with increased risk of dying from myeloid leukemia; (4) a biologically coherent temporal relationship consistent with a pattern of exposure to formaldehyde and subsequent death from myeloid leukemia allowing time for cancer induction, latency, and mortality; and (5) reasonable confidence that alternative explanations are ruled out, including chance, bias, and confounding within individual studies or across studies. Consistent observations of genotoxicity in peripheral blood lymphocytes across several occupational studies involving diverse exposure settings further supports the evidence in humans, as does evidence of perturbations to immune cell populations in peripheral blood with formaldehyde exposure.

Conclusion

- The available epidemiological studies provide *robust* evidence of an association consistent with causation between formaldehyde exposure and increased risk of myeloid leukemia.

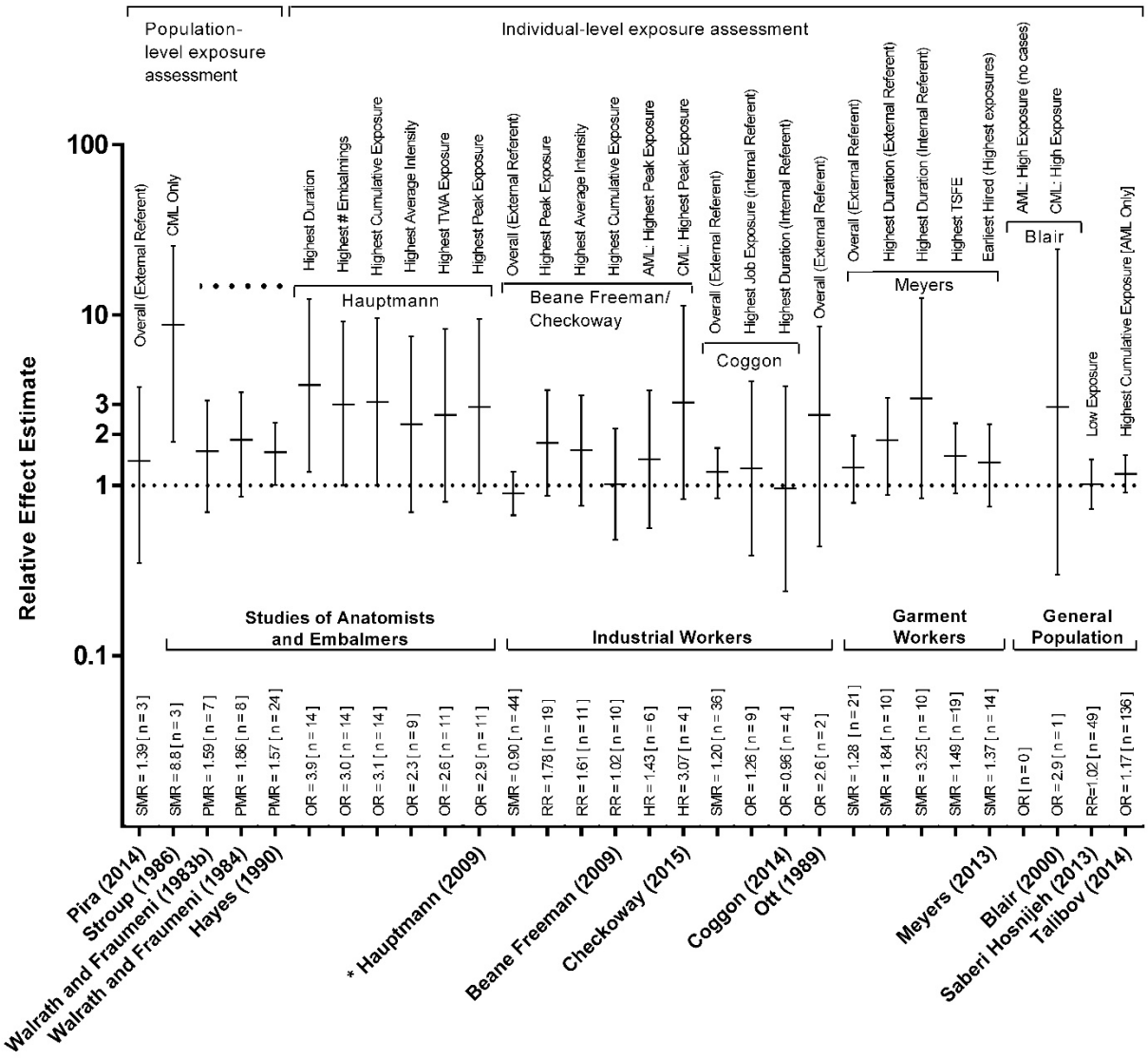


Figure 1-37. All epidemiological studies reporting myeloid leukemia risk estimates.

Results specifically for acute myeloid leukemia (AML) or chronic myeloid leukemia (CML) are noted by these abbreviations: SMR = standardized mortality ratio; PMR = proportionate mortality ratio; RR = relative risk; OR = odds ratio. For each measure of association, the number of exposed cases is provided in brackets (e.g., [*n* = 3]). For studies reporting results on multiple metrics of exposure, each metric is included; however, only the highest category of each exposure metric is presented in the figure. *The dotted line extending from Hauptmann et al. (2009) reflects that study's inclusion of the original cohorts from Walrath and Fraumeni (1984, 1983) and Hayes et al. (1990), which were combined with extended follow-up in Hauptmann et al. (2009) in a nested case-control study with internal referents.

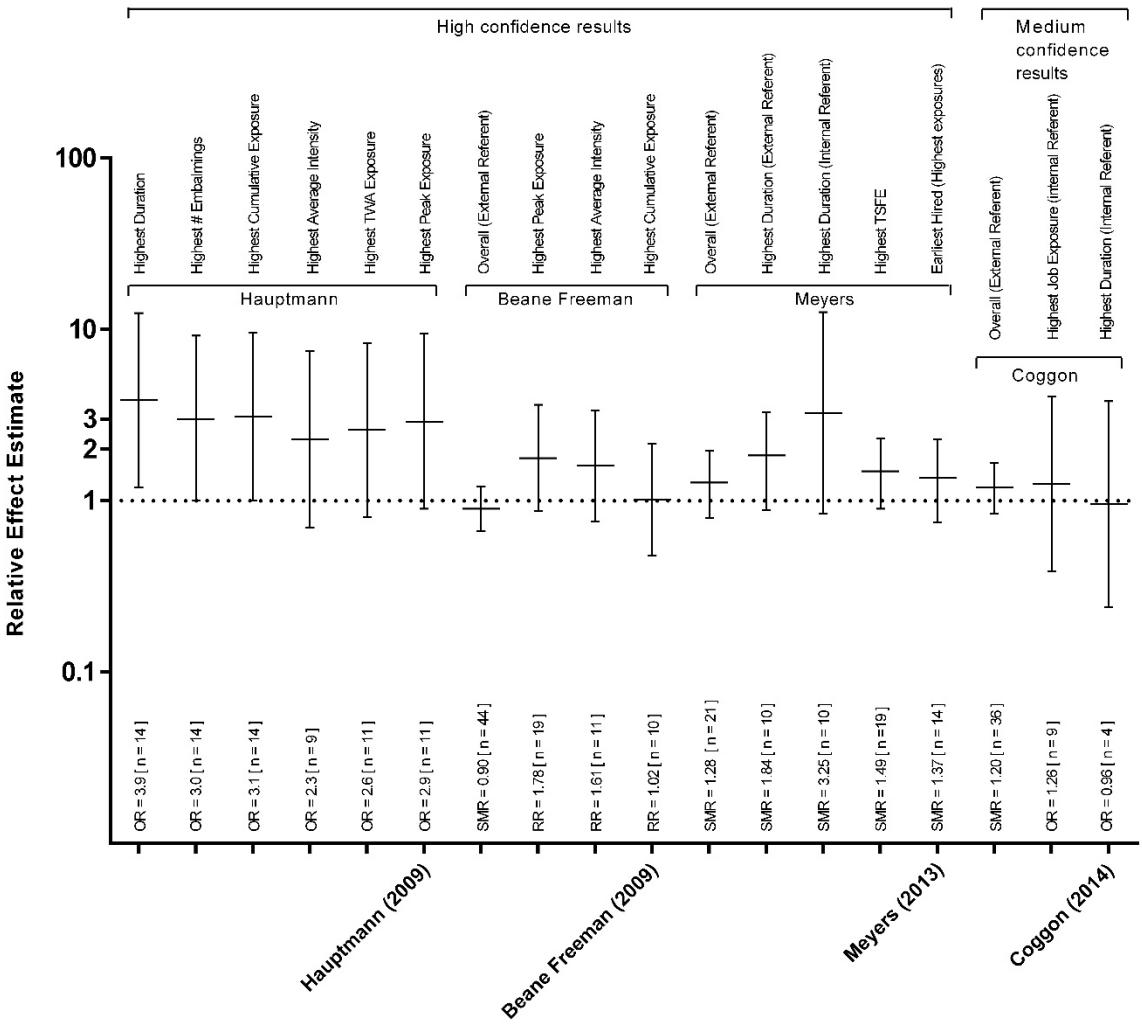


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Figure 1-38. High and medium confidence epidemiological studies reporting myeloid leukemia risk estimates.

For each measure of association, the number of exposed cases is provided in brackets (e.g., [*n* = 14]). For studies reporting results on multiple metrics of exposure, each metric is included; however, only the highest category of each exposure metric is presented in the figure. Abbreviations: OR = odds ratio; RR = relative risk; SMR = standardized mortality ratio; HR = hazard ratio.

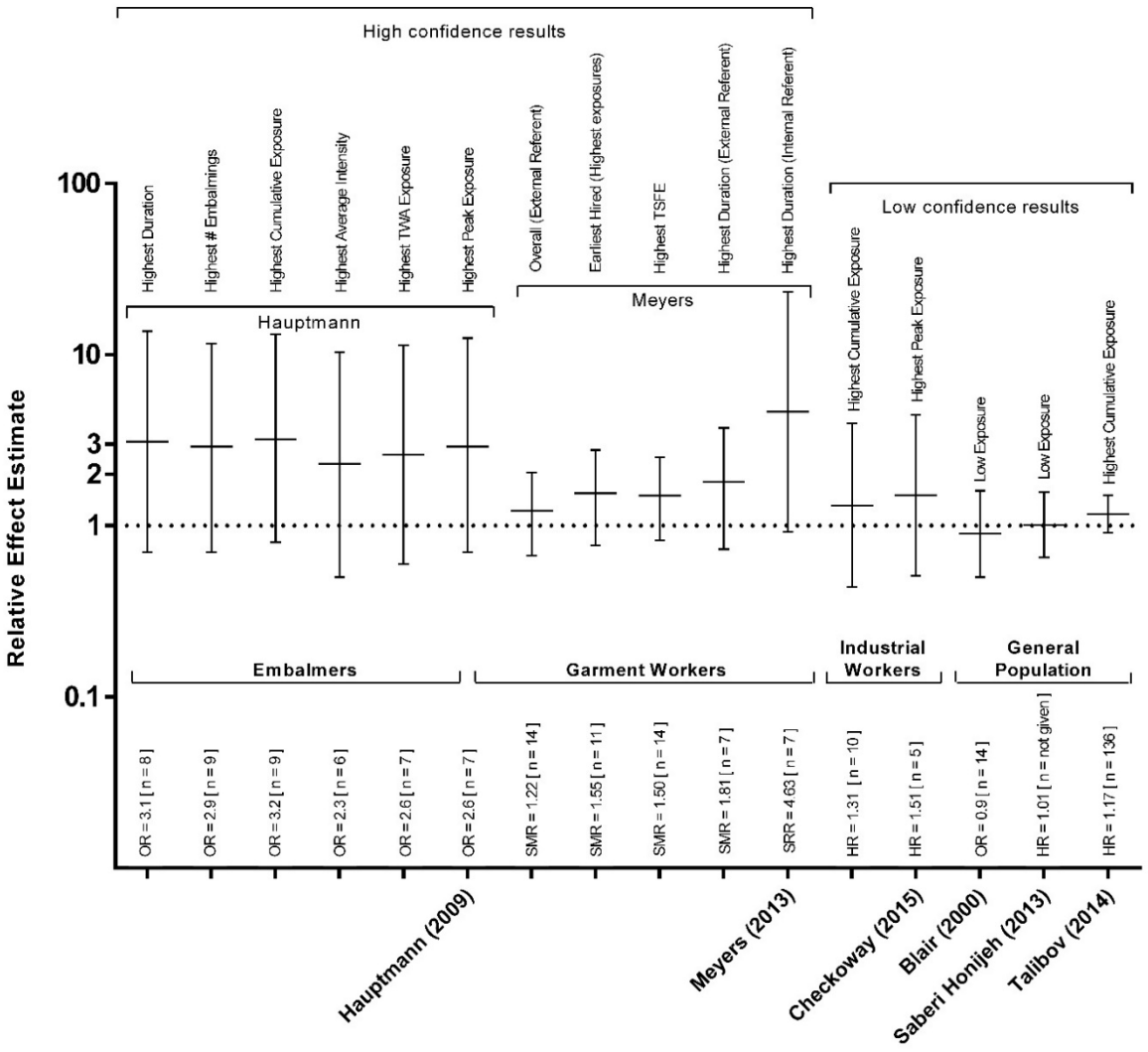


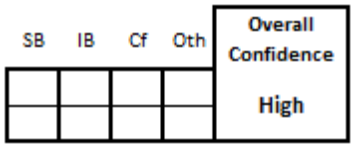
Figure 1-39. Epidemiological studies reporting acute myeloid leukemia risk estimates.

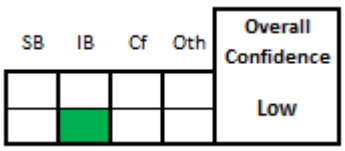
For each measure of association, the number of exposed cases is provided in brackets (e.g., [*n* = 8]). For studies reporting results on multiple metrics of exposure, each metric is included; however, only the highest category of each exposure metric is presented in the figure. Abbreviations: OR = odds ratio; RR = relative risk; SMR = standardized mortality ratio; HR = hazard ratio.

Table 1-60. Epidemiological studies of formaldehyde exposure and risk of myeloid leukemia

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Reference: Beane Freeman et al. (2009) with supplemental online tables.	**Exposure assessment:** Individual-level exposure estimates based on job titles, tasks, visits to plants by study	**Internal comparisons:** Peak exposure: 1980 follow-up:

Study	Exposures	Results: effect estimate (95% CI) [# of cases]

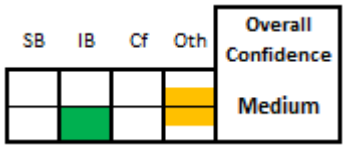
Population: 25,619 workers employed at 10 formaldehyde-using or formaldehyde-producing plants in the U.S., followed from either the plant start-up or first employment through 2004. Deaths were identified from the National Death Index with remainder assumed to be living. Vital status was 97.4% complete and only 2.6% lost to follow-up.
 	
Outcome definition: Death certificates used to determine UCOD from myeloid leukemia (ICD-8: 205).
 	
Design: Prospective cohort mortality study with external and internal comparison groups.
 	
Analysis: RRs estimated using Poisson regression stratified by calendar year, age, sex, and race; adjusted for pay category compared to workers in lowest exposed category. Lagged exposures were evaluated to account for cancer latency.
 	
SMRs calculated using sex, age, race, and calendar-year-specific U.S. mortality rates.
 	
Related studies:
Blair et al. (1986)
Hauptmann et al. (2003)
 	
Confidence in effect estimates:[a]
 
 	
HIGH ● (No appreciable bias)
IB: Exposure Group A
	industrial hygienists who took 2,000 air samples from representative jobs, and monitoring data from 1960 through 1980.
	
	Median TWA (over 8 hours) = 0.3 ppm (range 0.01–4.3).
	
	Median cumulative exposure = 0.6 ppm-years (range 0–107.4).
	
	Multiple exposure metrics including peak, average, and cumulative exposures were evaluated using categorical and continuous data.
	
	Duration and timing: Exposure period from before 1946 through 1980. Median length of follow-up: 42 years. Duration and timing since first exposure were evaluated.
	
	Variation in exposure:
	For all variations in exposure:
	Level 1 (unexposed)
	
	Peak exposure:
	Level 2 (>0 to <2.0 ppm)
	Level 3 (2.0 to <4.0 ppm)
	Level 4 (≥4.0 ppm)
	Average intensity:
	Level 2 (>0 to <0.5 ppm)
	Level 3 (0.5 to <1.0 ppm)
	Level 4 (≥1.0 ppm)
	Cumulative exposure:
	Level 2 (>0 to <1.5 ppm-yrs)
	Level 3 (1.5 to <5.5 ppm-yrs)
	Level 4 (≥5.5 ppm-yrs)
	
	Coexposures: Exposures to 11 other compounds were identified and evaluated as potential confounders and found not be confounders.
	
	[As noted in Appendix A.5.9: There was no information on smoking; however, according to Blair et al. (1986), "The lack of a consistent elevation for tobacco-related causes of death, however, suggests that the smoking habits among this cohort did not differ substantially from those of the general population."
		Highest peak RR = 3.92 (0.78–19.67) (*p*-trend = 0.12)
		1994 follow-up:
		Highest peak RR = 2.79 (1.08–7.21) (*p*-trend = 0.02)
		2004 follow-up:
		Level 1 RR = 0.82 (0.25-2.67) [4]
		Level 2 RR = 1.00 (Ref. value) [14]
		Level 3 RR = 1.30 (0.58–2.92) [11]
		Level 4 RR = 1.78 (0.87–3.64) [19]
		p-trend (exposed) = 0.13;
		p-trend (all) = 0.07
		
		Average intensity:
		Level 1 RR = 0.70 (0.23–2.16) [4]
		Level 2 RR = 1.00 (Ref. value) [24]
		Level 3 RR = 1.21 (0.56–2.62) [9]
		Level 4 RR = 1.61 (0.76–3.39) [11]
		p-trend (exposed) = 0.43;
		p-trend (all) = 0.40
		
		Cumulative exposure:
		Level 1 RR = 0.61 (0.20–1.91) [4]
		Level 2 RR = 1.00 (Ref. value) [26]
		Level 3 RR = 0.82 (0.36–1.83) [8]
		Level 4 RR = 1.02 (0.48–2.16) [10]
		p-trend (exposed) > 0.50;
		p-trend (all) = 0.44
		
		Duration of exposure:
		No evidence of association (data not shown).
		
		Time since first exposure:
		>0–15 yrs RR = 1.00 (Ref. value) [3]
		>15–25 yrs RR = 2.44 (0.45–13.25) [11]
		>25–35 yrs RR = 0.77 (0.11–5.24) [8]
		>35 yrs RR = 0.67 (0.09–4.88) [24]
		
		External comparisons:
		$SMR_{Unexposed}$ = 0.65 (0.25–1.74) [4]
		$SMR_{Exposed}$ = 0.90 (0.67–1.21) [44]

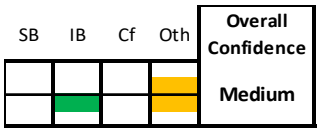
Study	Exposures	Results: effect estimate (95% CI) [# of cases]
	Beane Freeman et al. (2013) reported that among a sample of 379 cohort members, they "found no differences in prevalence of smoking by level of formaldehyde exposure."]	
Reference: Beane Freeman et al. (2009) as re-analyzed by Checkoway et al. (2015) with differences noted. **Population:** No differences. **Outcome definition:** Death certificates used to determine UCOD from acute and chronic myeloid leukemia (ICD-8: 205.0 and 205.1). **Design:** No differences. **Analysis:** HRs estimated using Cox proportional hazards models controlling for age, sex, and race; adjusted for pay category compared to workers in the redefined lowest exposed category. Did not control for calendar year as did Beane Freeman et al. (2009). Lagged exposures were evaluated to account for cancer latency. SMRs calculated using sex, age, race, and calendar-year-specific U.S. mortality rates. **Related studies:** Blair et al. (1986) Hauptmann et al. (2003) Checkoway et al. (2015) [reviewed here] **Confidence in effect estimates:**[a]  **LOW** ● (Potential bias ↓) **IB**: Exposure Group A (from Beane Freeman et al., 2009) downgraded to Group D based on authors' decision to reclassify all peak exposures <2 ppm as unexposed and to reclassify peak	**Exposure assessment:** No differences in measurements; however, the exposure metrics we redefined. Redefined peak exposures as having "at least one continuous month of employment in jobs identified in the original exposure characterization as likely having short-term exposure excursions of 2 ppm or more to less than 4 ppm or 4 ppm or more on a weekly or daily basis." Redefinition of peak exposures excluded "employment in jobs likely experiencing (1) short-term excursions more than 0 ppm and less than 2 ppm; (2) short-term excursions identified as occurring as frequently as hourly; and (3) short-term excursions identified as occurring as infrequently as monthly." **Duration and timing:** No differences. **Variation in exposure:** For all variations in exposure: Peak exposure: Level 1 (exposed to <2.0 ppm) Level 2 (2.0 to <4.0 ppm) Level 3 (≥4.0 ppm) Average intensity: Did not evaluate Cumulative exposure: Level 1 (exposed to <0.5 ppm-yrs) Level 2 (>0.5 to <2.5 ppm-yrs) Level 3 (≥2.5 to <5.5 ppm-yrs) **Coexposures:** Exposures to 11 other compounds were identified and evaluated as potential confounders by Beane Freeman et al. (2009) and found not be confounders. Checkoway et al. (2015) did not re-evaluate potential confounding.	**Internal comparisons:** **Myeloid Leukemia** Peak exposure: Level 1 HR=1.00 (Ref. value) [27] Level 2 HR=2.09 (1.03–4.26) [11] Level 3 HR=1.80 (0.85–3.79) [10] *p*-trend = 0.06 Cumulative exposure: Level 1 HR=1.00 (Ref. value) [23] Level 2 HR=0.98 (0.47–2.03) [11] Level 3 HR=0.94 (0.47–1.86) [14] *p*-trend = 0.90 **AML** Peak exposure: Level 1 HR=1.00 (Ref. value) [21] Level 2 HR=1.71 (0.72–4.07) [7] Level 3 HR=1.43 (0.56–3.63) [6] *p*-trend = 0.31 Cumulative exposure: Level 1 HR=1.00 (Ref. value) [17] Level 2 HR=0.87 (0.36–2.12) [7] Level 3 HR=0.96 (0.43–2.16) [10] *p*-trend = 0.90 **CML** Peak exposure: Level 1 HR=1.00 (Ref. value) [6] Level 2 HR=2.62 (0.64–10.66) [3] Level 3 HR=3.07 (0.83–11.40) [4] *p*-trend = 0.07 Cumulative exposure: Level 1 HR=1.00 (Ref. value) [6] Level 2 HR=0.97 (0.24–3.93) [3] Level 3 HR=0.92 (0.25–3.36) [4] *p*-trend = 0.90

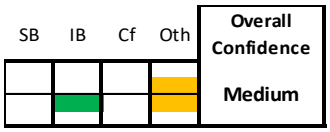
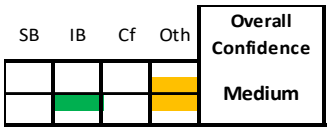
Study	Exposures	Results: effect estimate (95% CI) [# of cases]
exposures >2 ppm as unexposed—if they were either very rare or very common.		
Reference: Hauptmann et al. (2009) **Population:** 6,808 embalmers and funeral directors who died during 1960–1986. Identified from registries of the National Funeral Directors' Association, licensing boards and state funeral directors' associations, NY State Bureau of Funeral Directors, and CA Funeral Directors and Embalmers. Deaths were identified from the National Death Index. Next of kin interviews conducted for 96% of cases and 94% of controls. **Outcome definition:** Death certificates used to determine UCOD from myeloid leukemia (ICD-8: 205). **Design:** Nested case-control study within a prospective cohort mortality study using two internal comparison groups; the first composed of those who had never embalmed (1 case and 55 controls) and the second composed of those who had fewer than 500 embalmings (five cases and 83 controls). **Analysis:** ORs calculated using unconditional logistic regression adjusted for date of birth, age at death, sex, data source, and smoking. Lagged exposures were evaluated to account for cancer latency. These results are shown in table 3 of Hauptmann et al. (2009). Results from the second internal comparison group with <500 embalmings were selected to increase statistical stability. These results are shown in table 4 of Hauptmann et al. (2009) **Related studies:** Hayes et al. (1990) Walrath and Fraumeni (1983) Walrath and Fraumeni (1984) **Note:** The original cohorts from these three original studies were combined in Hauptmann et al. (2009) and follow-	**Exposure assessment:** Occupational history obtained by interviews with next of kin and coworkers using detailed questionnaires. Exposure was assessed by linking questionnaire responses to an exposure assessment experiment providing measured exposure data. Exposure levels (peak, intensity, and cumulative) were assigned to each individual using a predictive model based on the exposure data. The model explained 74% of the observed variability in exposure measurements. Multiple exposure metrics including duration (mean = 33.1 yrs in cases), # of embalming, peak, average, and cumulative exposures were evaluated using categorical and continuous data. **Duration and timing:** Exposure period from <1932 through 1986. Duration of exposure was evaluated. Duration is also a surrogate for time because first exposure since dates of death was closely related to cessation of workplace exposures. **Variation in exposure:** For variations in exposure from table 3 of the publication: Level 1 (no exposure to embalming) For variations in exposure from table 4 of the publication: Level 1 (<500 embalming) Duration of exposure: Level 2 (<20 years) Level 3 (20–34 years) Level 4 (>34 years) Number of embalming: Level 2 (500–1,422) Level 3 (1,423–3,068) Level 4 (>3,068) Cumulative exposure: Level 2 (≤4,058 ppm-hrs) Level 3 (4,059–9,253 ppm-hrs)	**Internal comparisons (*from table 3 in the paper*):** Never embalming: OR = 1.00 (Ref. value) [1] Ever embalming: OR = 11.2 (1.3–95.6) [33] Duration of exposure: Level 1 OR = 1.00 (Ref. value) [1] Level 2 OR = 5.0 (0.5–51.6) [6] Level 3 OR = 12.9 (1.4–117.1) [13] Level 4 OR = 13.6 (1.6–119.7) [14] Number of embalming: Level 1 OR = 1.0 (Ref. value) [1] Level 2 OR = 7.6 (0.8–73.5) [7] Level 3 OR = 12.7 (1.4–116.7) [12] Level 4 OR = 12.7 (1.4–112.8) [14] Cumulative exposure: Level 1 OR = 1.0 (Ref. value) [1] Level 2 OR = 10.2 (1.1–95.6) [9] Level 3 OR = 9.4 (1.0–85.7) [10] Level 4 OR = 13.2 (1.5–115.4) [14] Average intensity (while embalming): Level 1 OR = 1.0 (Ref. value) [1] Level 2 OR = 11.1 (1.2–106.3) [10] Level 3 OR = 14.8 (1.6–136.9) [13] Level 4 OR = 9.5 (1.1–86.0) [10] TWA8 formaldehyde intensity: Level 1 OR = 1.0 (Ref. value) [1] Level 2 OR = 8.4 (0.8–79.3) [8] Level 3 OR = 13.6 (1.5–125.8) [13] Level 4 OR = 12.0 (1.3–107.4) [12] Peak exposure: Level 1 OR = 1.0 (Ref. value) [1] Level 2 OR = 15.2 (1.6–141.6) [12] Level 3 OR = 8.0 (0.9–74.0) [9] Level 4 OR = 13.0 (1.4–116.9) [12] **Internal comparisons (from table 4):** Duration of exposure: Level 1 OR = 1.0 (Ref. value) [5] Level 2 OR = 0.5 (0.1–2.9) [2] Level 3 OR = 3.2 (1.0–10.1) [13] Level 4 OR = 3.9 (1.2–12.5) [14] Number of embalming:

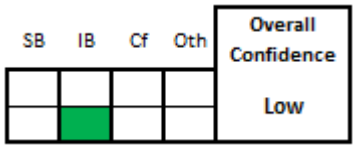
Study	Exposures	Results: effect estimate (95% CI) [# of cases]
up was extended so the case-series overlap and are not independent. However, the three original cohorts used external reference groups for comparison while Hauptmann et al. (2009) selected internal controls, which were independent of the reference groups used in the original studies. **Confidence in effect estimates:**[a] SB IB Cf Oth | Overall Confidence High **HIGH** ● (No appreciable bias) **IB**: Exposure Group A	Level 4 (≥9253 ppm-hrs) Average intensity (while embalming): Level 2 (≤1.4 ppm) Level 3 (>1.4–1.9 ppm) Level 4 (>1.9 ppm) TWA8 formaldehyde intensity: Level 2 (≤0.10 ppm) Level 3 (>0.10–0.18 ppm) Level 4 (>0.18 ppm) Peak exposure: Level 2 (<7.0 ppm) Level 3 (7.0 to <9.3 ppm) Level 4 (>9.3 ppm) **Coexposures:** None evaluated as potential confounders. [As noted in Appendix A.5.9: Coexposures may have included: phenol, methyl alcohol, glutaraldehyde, mercury, arsenic, zinc, and ionizing radiation. Chemical coexposures are not known risk factors for this outcome. Radiation exposure likely to be poorly correlated with formaldehyde so confounding is unlikely.]	Level 1 OR = 1.0 (Ref. value) [5] Level 2 OR = 1.2 (0.3–5.5) [3] Level 3 OR = 2.9 (0.9–9.1) [12] Level 4 OR = 3.0 (1.0–9.2) [14] Cumulative exposure: Level 1 OR = 1.0 (Ref. value) [5] Level 2 OR = 2.1 (0.5–8.1) [5] Level 3 OR = 2.2 (0.7–7.1) [10] Level 4 OR = 3.1 (1.0–9.6) [14] Average intensity (while embalming): Level 1 OR = 1.0 (Ref. value) [5] Level 2 OR = 2.6 (0.8–8.7) [10] Level 3 OR = 2.8 (0.8–9.1) [10] Level 4 OR = 2.3 (0.7–7.5) [9] TWA8 formaldehyde intensity: Level 1 OR = 1.0 (Ref. value) [5] Level 2 OR = 2.4 (0.7–8.2) [8] Level 3 OR = 2.6 (0.8–8.7) [10] Level 4 OR = 2.6 (0.8–8.3) [11] **Internal comparisons (from table 4):** Peak exposure: Level 1 OR = 1.0 (Ref. value) [5] Level 2 OR = 2.9 (0.9–9.8) [9] Level 3 OR = 2.0 (0.6–6.6) [9] Level 4 OR = 2.9 (0.9–9.5) [11] **Additional:** Acute ML (ICD-8: 205.0) **Internal comparisons (from table 4):** Duration of exposure: Level 1 OR = 1.0 (Ref. value) [3] Level 2 OR = 0.4 (0.04–4.9) [1] Level 3 OR = 2.9 (0.7–12.2) [8] Level 4 OR = 3.1 (0.7–13.7) [8] Number of embalming: Level 1 OR = 1.0 (Ref. value) [3] Level 2 no cases Level 3 OR = 2.9 (0.7–12.0) [8] Level 4 OR = 2.9 (0.7–11.6) [9] Cumulative exposure: Level 1 OR = 1.0 (Ref. value) [3] Level 2 OR = 1.3 (0.2–9.4) [2] Level 3 OR = 1.9 (0.4–8.2) [6] Level 4 OR = 3.2 (0.8–13.1) [9] Average intensity (while embalming): Level 1 OR = 1.0 (Ref. value) [3] Level 2 OR = 2.5 (0.6–10.9) [6] Level 3 OR = 2.0 (0.4–9.4) [5] Level 4 OR = 2.3 (0.5–10.3) [6] TWA8 formaldehyde intensity: Level 1 OR = 1.0 (Ref. value) [3] Level 2 OR = 1.4 (0.3–7.8) [3] Level 3 OR = 2.6 (0.6–11.4) [7]

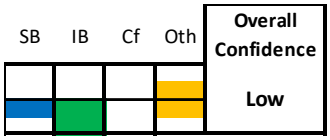
Study	Exposures	Results: effect estimate (95% CI) [# of cases]
		Level 4 OR = 2.6 (0.6–11.3) [7] Peak exposure: Level 1 OR = 1.0 (Ref. value) [3] Level 2 OR = 1.8 (0.4–9.3) [4] Level 3 OR = 2.1 (0.5–9.2) [5] Level 4 OR = 2.9 (0.7–12.5) [7]
Reference: Meyers et al. (2013) **Population:** 11,043 workers in three U.S. garment plants exposed for at least 3 months. Women comprised 82% of the cohort. Vital status was followed through 2008 with 99.7% completion. **Outcome definition:** Death certificates used to determine both the UCOD from myeloid leukemia (ICD code in use at time of death). **Design:** Prospective cohort mortality study with external and internal comparison groups. **Analysis:** SMRs calculated using sex, age, race, and calendar-year-specific U.S. mortality rates. SRRs calculated using LTAS.NET. Rate ratios calculated using Poisson regression analysis based on internal referents. **Related studies:** Stayner et al. (1985) Stayner et al. (1988) Pinkerton et al. (2004) **Confidence in effect estimates:**[a] SB IB Cf Oth | Overall Confidence High **HIGH** ● (No appreciable bias) **IB**: Exposure Group A	**Exposure assessment:** Individual-level exposure estimates for 549 randomly selected workers during 1981 and 1984 with 12–73 within each department. Formaldehyde levels across all departments and facilities were similar. Geometric TWA8 exposures ranged from 0.09-0.20 ppm. Overall geometric mean concentration of formaldehyde was 0.15 ppm, (GSD 1.90 ppm). Area measures showed constant levels without peaks. Historically earlier exposures may have been substantially higher. **Duration and timing:** Exposure period from 1955 through 1983. Median duration of exposure was 3.3 years. More than 40% exposures <1963. Median time since first exposure was 39.4 years. Duration and timing since first exposure were evaluated. **Variation in exposure:** Duration of exposure: Level 1 (<3 years) Level 2 (3–9 years) Level 3 (10 + years) Time since first exposure: Level 1 (<10 years) Level 2 (10–19 years) Level 3 (20 + years) Duration of exposure (Poisson modeling–lagged 2 years): Level 1 (<1.6 years) Level 2 (1.6 to <6.5 years) Level 3 (6.5 to <16 years) Level 4 (16 to <19 years) Level 5 (19 + years) **Coexposures:** Study population specifically selected because industrial hygiene surveys at the plants did not identify any chemical exposures other than formaldehyde that were likely to influence findings.	**External comparisons:** SMR = 1.28 (0.79–1.96) [21] **Within-study external comparisons:** Duration of exposure: Level 1 SMR = 0.65 (0.18–1.65) [4] Level 2 SMR = 1.46 (0.59–3.02) [7] Level 3 SMR = 1.84 (0.88–3.28) [10] TSFE: Level 1 SMR = 0.90 (0.02–4.99) [1] Level 2 SMR = 0.40 (0.01–2.21) [1] Level 3 SMR = 1.49 (0.90–2.32) [19] Year of first exposure: <1963 SMR = 1.37 (0.75–2.30) [14] 1963-1970 SMR = 1.13 (0.37–2.63) [5] 1971 + SMR = 1.15 (0.14–4.17) [2] **Internal comparisons:** Duration of exposure: Level 1 SRR = 1.00 (Ref. value) [4] Level 2 SRR = 2.12 (0.57-7.85) [7] Level 3 SRR = 3.25 (0.84–12.63) [10] Duration of exposure (Poisson modeling–lagged 2 years) [# of cases not given]: Level 1 rate ratio = 1.00 (Ref. value) Level 2 rate ratio = 1.38 (0.39–5.51) Level 3 rate ratio = 0.43 (0.06–2.39) Level 4 rate ratio = 6.42 (1.40–32.2) Level 5 rate ratio = 1.71 (0.25–11.0) **Additional:** Acute myeloid leukemia (ICD: 205.0) SMR = 1.22 (0.67–2.05) [14] Chronic myeloid leukemia (ICD: 205.1) SMR = 1.35 (0.44–3.15) [5] Acute myeloid leukemia (ICD: 205.0) **Internal comparisons:** Duration of exposure: Level 1 SMR = 0.46 (0.06–1.68) [2] Level 2 SMR = 1.52 (0.49–3.56) [5] Level 3 SMR = 1.81 (0.73–3.73) [7] Time since first exposure: Level 1 SMR = 0 (0.00–6.66) [0]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
		Level 2 SMR = 0 (0.00–2.32) [0] Level 3 SMR = 1.50 (0.82–2.52) [14] Year of first exposure: <1963 SMR = 1.55 (0.77–2.77) [11] 1963-1970 SMR = 0.64 (0.08–2.30) [2] 1971 + SMR = 0.83 (0.02–4.60) [1]
Reference: Coggon et al. (2014) **Population:** 14,008 British men employed in six chemical industry factories which produced formaldehyde. Cohort mortality followed from 1941 through 2012. Cause of deaths was known for 99% of 5,185 deaths through 2000. Similar cause of death information not provided on 7,378 deaths through 2012. Vital status was 98.9% complete and only 1.1% lost to follow-up through 2003. Similar information not provided on deaths through 2012. **Outcome definition:** Death certificates used to determine cause of deaths from myeloid leukemia (ICD-9: 205). **Design:** Cohort mortality study with external comparison group with a nested case-control study. **Analysis:** SMRs based on English and Welsh age- and calendar-year-specific mortality rates. **Related studies:** Acheson et al. (1984) Gardner et al. (1993) Coggon et al. (2003) **Confidence in effect estimates:**[a]  **MEDIUM ↓** **(Potential bias toward the null↓)** **IB**: Exposure is Group B; lack of latency analysis	**Exposure assessment:** Exposure assessment based on data abstracted from company records. Jobs categorized as background, low, moderate, high, or unknown levels. **Duration and timing:** Occupational exposure during 1941−1982. Duration was evaluated as more, or less, than one year only among the high exposure group. Timing since first exposure was not evaluated. **Variation in exposure:** Highest exposure level attained Level 1 (Background) Level 2 (low/moderate) Level 3 (High) Duration of "High" exposures Level 1 (Background) Level 2 (<1 year) Level 3 (1 year or more) **Coexposures:** Not evaluated as potential confounders. Potential low-level exposure to styrene, ethylene oxide, epichlorhydrin, solvents, asbestos, chromium salts, and cadmium; explanation for underlining: [As noted in Appendix A.5.9: Styrene is associated with LHP cancers. Asbestos is associated with URT cancers, but not with LHP cancers. Other coexposures are not known risk factors for this outcome. Authors stated that the extent of coexposures was expected to be low. Potential for confounding may be mitigated by low coexposures.]	**External comparisons:** SMR = 1.20 (0.84-1.66) [36] **Within-study external comparisons:** Highest exposure level attained Level 1 SMR = 1.16 (0.60-2.02) [12] Level 2 SMR = 1.46 (0.84-2.38) [16] Level 3 SMR = 0.93 (0.40-1.82) [8] **Internal comparisons:** Highest exposure level attained Level 1 OR = 1.00 (Ref. value) [17] Level 2 OR = 1.10 (0.51-2.38) [19] Level 3 OR = 1.26 (0.39-4.08) [9] Duration of high exposures Level 1 OR = 1.00 (Ref. value) [17] Level 1 OR = 1.77 (0.45-7.03) [5] Level 2 OR = 0.96 (0.24-3.82) [4]
Reference: Hayes et al. (1990)	**Exposure assessment:** Presumed exposure to formaldehyde tissue	**External comparisons:** PMR = 1.57 (1.01-2.34) [24]

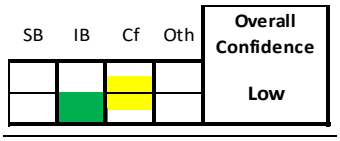
Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Population: 4,046 deceased U.S. male embalmers and funeral directors, derived from licensing boards and funeral director associations in 32 states and the District of Columbia who died during 1975–1985. Death certificates obtained for 79% of potential study subjects (*n* = 6,651) with vital status unknown for 21%. **Outcome definition:** Death certificates and licensing boards used to determine cause of death from myeloid leukemia (ICD-8: 205). **Design:** Proportionate mortality cohort study with external comparison group. **Analysis:** PMRs calculated using sex, race, age, and calendar-year-expected numbers of deaths from the U.S. population. **Confidence in effect estimates:**[a]  **MEDIUM ↓** **(Potential bias toward the null↓)** **SB:** Missing death certificates considered to missing at random **IB**: Exposure: Group A; latency not evaluated	fixative. Exposure based on occupation which was confirmed on death certificate. Authors subsequently measured personal embalming exposures ranging from 0.98 ppm (high ventilation) to 3.99 ppm (low ventilation) with peaks up to 20 ppm. Authors state that major exposures are to formaldehyde and possibly glutaraldehyde and phenol. **Duration and timing:** Occupational exposure preceding death during 1975–1985. Of 115 deaths from LHP cancer, 66 (57%) were aged 60–74 years. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** None evaluated as potential confounders. [As noted in Appendix A.5.9: Coexposures may have included: phenol, methyl alcohol, glutaraldehyde, mercury, arsenic, zinc, and ionizing radiation. Chemical coexposures are not known risk factors for this outcome. Radiation exposure likely to be poorly correlated with formaldehyde so confounding is unlikely.]	**Additional:** Acute myeloid leukemia (ICD-8: 205.0) PMR = 1.52 (0.85-2.52) [# not given] Chronic myeloid leukemia (ICD-8: 205.1) PMR = 1.84 (0.79-3.62) [# not given]
Reference: Walrath and Fraumeni (1984) **Population:** 1,007 deceased white male embalmers from the California Bureau of Funeral Directing and Embalming who died during 1925–1980. Death certificates obtained for all. **Outcome definition:** Myeloid leukemia (ICD-8: 205) listed as cause of death on death certificates. **Design:** Proportionate mortality cohort study with external comparison group.	**Exposure assessment:** Presumed exposure to formaldehyde tissue fixative. **Duration and timing:** Occupational exposure preceding death during 1916–1978. Birth year ranged from 1847 through 1959. Median age of death was 62 years. Most deaths were among embalmers with active licenses. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** None evaluated as potential confounders.	**External comparisons:** Observed: 8 myeloid leukemia deaths (including 2 acute monocytic leukemia) Expected: 4.3 myeloid leukemia deaths (including 0.3 acute monocytic leukemia) PMR = 1.86 (0.86–3.53)† [8] **Additional:** Observed: 6 acute myeloid leukemia deaths (including 2 acute monocytic leukemia) Expected: With 4.3 myeloid leukemia deaths expected, EPA used data from Selvin et al. (1983) on the expected ratio of AML:CML (2.2:1) among males ages

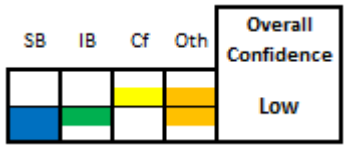
Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Analysis: PMRs calculated using sex, race, age, and calendar-year-expected number of deaths from the U.S. population. **Confidence in effect estimates:**[a]  **MEDIUM ↓** **(Potential bias toward the null↓)** **IB**: Exposure Group A; latency was not evaluated	[As noted in Appendix A.5.9: Coexposures may have included: phenol, methyl alcohol, glutaraldehyde, mercury, arsenic, zinc, and ionizing radiation. Radiation exposure likely to be poorly correlated with formaldehyde so confounding is unlikely.]	25+ to estimate 2.96 expected cases of AML out of the 4.3 expected myeloid leukemia deaths. Acute myeloid leukemia (ICD-8: 205.0) PMR = 2.03 (0.82–4.22)† [6] †**Note:** EPA derived CIs using the Mid-P Method (See Rothman and Boice, 1979)
Reference: Walrath and Fraumeni (1983) **Population:** 1,132 deceased white male embalmers licensed to practice during 1902–1980 in New York who died during 1925–1980 identified from registration files. Death certificates obtained for 75% of potential study subjects (*n* = 1,678). **Outcome definition:** Myeloid leukemia (ICD-8: 205) listed as cause of death on death certificates. **Design:** Proportionate mortality cohort study with external comparison group. **Analysis:** PMRs calculated using sex, race, age, and calendar-year-expected numbers of deaths from the U.S. population. **Confidence in effect estimates:**[a]  **MEDIUM ↓** **(Potential bias toward the null↓)** **SB:** Missing death certificates considered to missing at random **IB**: Exposure Group A; latency was not evaluated	**Exposure assessment:** Presumed exposure to formaldehyde tissue fixative. **Duration and timing:** Occupational exposure preceding death during 1902–1980. Median year of birth was 1901. Median year of initial license was 1931. Median age at death was 1968. Expected median duration of exposure was 37 years. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** None evaluated as potential confounders. [As noted in Appendix A.5.9: Coexposures may have included: phenol, methyl alcohol, glutaraldehyde, mercury, arsenic, zinc, and ionizing radiation. Radiation exposure likely to be poorly correlated with formaldehyde so confounding is unlikely.]	**External comparisons:** Observed: 7 myeloid leukemia deaths (including 1 acute monocytic leukemia) Expected: 4.4 myeloid leukemia deaths (including 0.3 acute monocytic leukemia) PMR = 1.59 (0.70–3.15)† [7] **Additional:** Observed: 6 acute myeloid leukemia deaths (including 1 acute monocytic leukemia) Expected: With 4.4 myeloid leukemia deaths expected, EPA used data from Selvin et al. (1983) on the expected ratio of AML:CML (2.2:1) among males ages 25+ to estimate 3.03 expected cases of AML out of the 4.4 expected myeloid leukemia deaths. Acute myeloid leukemia (ICD-8: 205.0) PMR = 1.98 (0.80–4.12)† [6] †**Note:** EPA derived CIs using the Mid-P Method (See Rothman and Boice, 1979)
Reference: Talibov et al. (2014) **Population:** Individuals from Finland, Iceland, Norway, and Sweden who were	**Exposure assessment:** Occupational history from census records were linked to the Nordic Occupational Cancer Study (NOCCA) JEM to code	**Internal comparisons:** Acute Myeloid Leukemia (ICD-9: 205.0) Level 1 OR = 1.00 (ref value) [13781] Level 2 OR = 0.89 (0.81-0.97) [580]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
recorded in various censuses from 1960 to 1990. Acute myeloid leukemia cases identified by national registries up until 2003–2005 depending on the country. **Outcome definition:** Diagnosis of incident cancer reported to the National Cancer Registries. **Design:** Multicountry case-control study. **Analysis:** HRs calculated for categories of cumulative formaldehyde exposure using conditional logistic regression controlling for year of birth, sex, country, solvents and other coexposures. A 10-year latency period was assumed. **Confidence in effect estimates:**[a]  **LOW ↓** **(Potential bias toward the null↓)** **IB**: Exposure Group D	each cohort member as exposed to formaldehyde. Exposures were quantified based on the proportion of people in each occupation considered to be exposed and the mean level of exposure during specific periods. Coexposures to solvents was evaluated. **Duration and timing:** Exposure period based on occupational histories prior to 1983. Duration and timing since first exposure were considered in the exposure metric but were not evaluated separated. **Variation in exposure:** Cumulative exposure: Level 1 (unexposed) Level 2 (low): ≤0.171 ppm-yrs Level 3 (moderate): 0.171–1.6 ppm-yrs Level 4 (high): >1.6 ppm-yrs **Coexposures:** Solvents and coexposures controlled for in multivariate models included: aliphatic and alicyclic hydrocarbons, aromatic hydrocarbons, benzene, toluene, trichloroethylene, 111-trichloroethane, methylene chloride, perchloroethylene, other organic solvents, and ionizing radiation.	Level 3 OR = 0.92 (0.83-1.03) [485] Level 4 OR = 1.17 (0.91-1.51) [136] *p*-trend = 0.07

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Reference: Pira et al. (2014) **Population:** 2,750 workers employed at a laminated plastic factory in Italy for at least 180 days between 1947 and 2011 followed until May 2011. Deaths were identified from population registries. Vital status was 96.9% complete and only 3.1% lost to follow-up. **Outcome definition:** Death certificates used to determine UCOD from myeloid leukemia (ICD-9: 205). **Design:** Prospective cohort mortality study with external comparison group. **Analysis:** RRs estimated using Poisson regression stratified by calendar year, age, sex, and race; adjusted for pay category compared to workers in lowest exposed category. Lagged exposures were evaluated to account for cancer latency. SMRs calculated using sex, age, and 5-year calendar periods using mortality rates from the Piedmont region. **Confidence in effect estimates:**[a]  **Low ↓** (Potential bias toward the null, low sensitivity) **SB: Healthy worker effect possible.** **IB**: Exposure Group B (Appendix A.5.9) **Oth**: Low power	**Exposure assessment:** Formaldehyde is a byproduct from the resins used in production process and all workers were presumed to have been exposed. **Duration and timing:** Exposure period from 1947 through 2011. Median length of follow-up: 23.6 years. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** Not evaluated.	**External comparisons:** Observed: 3 myeloid leukemia deaths Expected: 2.16 myeloid leukemia deaths based on authors' assumption that 40% of leukemia deaths are from myeloid leukemia and 5.3 leukemia deaths were expected. Myeloid Leukemia (ICD-9: 205) SMR = 1.39 (0.35-3.78)† [3] †**Note:** EPA derived CIs using the Mid-P Method [See Rothman and Boice (1979)]
Reference: Saberi Hosnijeh et al. (2013) **Population:** 241,465 men and women recruited from 10 European countries during 1992–2000. Participants were predominantly ages 35–70 at recruitment and were followed up through 2010. **Outcome definition:** Incident primary leukemias.	**Exposure assessment:** Individual occupational histories obtained by questionnaire about ever working in any of 52 occupations considered to be at high risk of developing cancer. Occupational exposures estimated as "high," "low," and no exposure by linking to a JEM. **Duration and timing:** Duration and timing since first exposure were not evaluated. **Variation in exposure:**	**Internal comparisons:** Exposure to formaldehyde: Level 1 RR = 1.00 (Ref. value) [130] Level 2 RR = 1.02 (0.73-1.42) [49] Level 3 RR = No data [0]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Design: Prospective multinational cohort incidence study with internal comparison groups. **Analysis:** HRs calculated controlling for age, sex, smoking, alcohol, physical activity, education, BMI, family history of cancer, country, other occupational exposures, and radiation. **Confidence in effect estimates:**[a]  **LOW** ↓ (Potential bias toward the null; low sensitivity) **IB**: Exposure Group C; latency was not evaluated **Cf**: Confounding possible **Oth**: Low power	Exposure to formaldehyde: Level 1 (none) Level 2 (low) Level 3 (high) **Coexposures:** Coexposure included pesticides, herbicides, insecticides, aromatic solvents, benzene, chlorinated solvents, trichloroethylene, metals, and contact with animals or animal products, ionizing radiation. [As noted in Appendix A.5.9: Coexposures were not controlled for. Potential for confounding is unknown but could have inflated the observed effect. Potential for confounding may be mitigated by low correlation between exposures in the general population.]	
Reference: Blair et al. (2001) **Population:** White men, 30 years of age or older, identified from the Iowa cancer registry and the Minnesota hospital surveillance network during 1980–1983. Participation of eligible cases was 86% and approximately 77–79% for controls including 77% for surrogate respondents for deceased subjects. **Outcome definition:** Diagnosis of leukemia was confirmed by pathology review for all cases. **Design:** Population-based case-control study of 513 white men with leukemia from Iowa and Minnesota cancer surveillance networks. 1,087 controls were frequency matched on 5-yr age groups, vital status, and state. **Analysis:** ORs calculated for job titles, employment duration, and exposure intensity using unconditional logistic regression controlling for age, state, direct/surrogate response, and coexposures, including smoking. Analyses by year of first exposure were also conducted to evaluate latency.	**Exposure assessment:** Individual-level exposure estimates developed based on a JEM for each job held for more than 1 year, the industry where employed, and starting and ending year the job was held. Exposure intensity and probability assessed for formaldehyde and other exposures. Exposure intensity refers to the level likely experienced and considered a TWA8 over a year. **Duration and timing:** Exposure period based on occupational histories prior to 1983. Duration and timing since first exposure were evaluated. **Variation in exposure:** Intensity of exposure: Level 1 (unexposed) Level 2 (low) Level 3 (high) **Coexposures:** None evaluated as potential confounders. [As noted in Appendix A.5.9: Other exposures evaluated included **benzene**, other organic solvents, petroleum-based oils and greases, cooking oils, ionizing radiation, paper	**Internal comparisons:** Acute myeloid leukemia (ICD-9: 205.0) Level 1 OR = 1.0 (Ref. value) [118] Level 2 OR = 0.9 (0.5-1.6) [14] Level 3 no cases Chronic myeloid leukemia (ICD-9: 205.1) Level 1 OR = 1.0 (Ref. value) [38] Level 2 OR = 1.3 (0.6-3.1) [7] Level 3 OR = 2.9 (0.3-24.5) [1] No notable findings were reported for duration of time since first exposure to formaldehyde.

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Confidence in effect estimates:[a]  **LOW ↓** **(Potential bias toward the null↓)** **IB**: Exposure Group C; lack of latency analysis **Cf**: Potential confounding although relationship between formaldehyde and coexposures is unknown.	dusts, gasoline and exhaust vapors, **paints**, **metals**, **wood dust**, **asbestos**, asphalt, cattle, meat, solder fumes. However, analyses of formaldehyde exposures did not control for other exposures.]	
Reference: Ott et al. (1989) **Population:** 29,139 men employed at two large chemical manufacturing facilities and a research and development center who worked during 1940–1978. Vital status was known for 96.4%. Death certificates were available for 5,785 known descendants (95.4%). **Outcome definition:** Death certificates used to determine UCOD from lymphatic leukemia based on the ICD code in used at the time of death. **Design:** Nested case-control study within a prospective cohort mortality study. Twenty cases of lymphatic leukemia were frequency matched to 100 controls on time from hire to death. **Analysis:** ORs calculated using unconditional logistic regression. **Related studies:** Rinsky et al. (1988) **Confidence in effect estimates:**[a]  **LOW ↓** **(Potential bias toward the null↓)** **IB**: Exposure Group B; latency evaluation likely to be underpowered to detect any effects beyond a 5-year period **Cf**: Benzene is a potential confounder	**Exposure assessment:** Individual-level exposure ascertained from employee's work assignments linked to records on departmental usage of formaldehyde. **Duration and timing:** Occupational exposures during 1940–1978. Timing of formaldehyde exposure not evaluated. **Variation in exposure:** Ever/never **Coexposures:** None evaluated as potential confounders. [As noted in Appendix A.5.9: 21 different chemicals were evaluated including **benzene** with much cross exposure. Benzene was not evaluated as a potential confounder and may be positively correlated with formaldehyde exposure. Potential for confounding is unknown but could have inflated the observed effect. Potential for confounding may be mitigated by rarity of coexposures among cases.]	**Internal comparisons:** OR = 2.6 (0.44-8.59)† [2] †**Note:** EPA derived CIs using the Mid-P Method (See Rothman and Boice, 1979)

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Oth: Low power due to the rarity of exposure		
Reference: Stroup et al. (1986) **Population:** 2,239 white male members of the American Association of Anatomists from 1888 to 1969 who died during 1925−1979. Death certificates obtained for 91% with 9% lost to follow-up. **Outcome definition:** Myeloid leukemia (ICD-8: 205) listed as cause of death on death certificates. **Design:** Cohort mortality study with external comparison group. **Analysis:** SMRs calculated using sex, race, age, and calendar-year-expected number of deaths from the U.S. population. **Confidence in effect estimates:**[a]  **LOW ↓** **(Potential bias toward the null↓)** **SB:** Health worker effect **IB**: Exposure Group A; latency not evaluated **Cf**: Potential confounding	**Exposure assessment:** Presumed exposure to formaldehyde tissue fixative. **Duration and timing:** Occupational exposure preceding death during 1925–1979. Median birth year was 1912. By 1979, 33% of anatomists had died. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** None evaluated as potential confounders. [As noted in Appendix A.5.9: Coexposures may have included: phenol, methyl alcohol, glutaraldehyde, mercury, arsenic, zinc, and **ionizing radiation**. Radiation exposure likely to be poorly correlated with formaldehyde so confounding is unlikely. Anatomists may also be coexposed to stains, benzene, toluene, xylene, chlorinated hydrocarbons, dioxane, and osmium tetroxide. Benzene was not evaluated as a potential confounder and may be positively correlated with formaldehyde exposure. Potential for confounding is unknown but could have inflated the observed effect.]	**Leukemias:** 10 total reported 1 lymphatic 5 myeloid (3 chronic, 1 acute, 1 unspecified) 1 acute monocytic 3 leukemia not otherwise specified **External comparisons:** Chronic myeloid leukemia (ICD-8: 205.1) SMR = 8.8 (1.8–25.5) [3]

[a]Evaluation of sources of bias or study limitations (see details in Appendix A.5.9). SB = selection bias; IB = information bias; Cf = confounding; Oth = other feature of design or analysis. Extent of column shading reflects degree of limitation. Direction of anticipated bias indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact would be likely to be away from the null (i.e., spurious or inflated effect estimate).

Results from *low* confidence studies are shaded; these findings are considered less reliable.

Abbreviations: RR = relative risk; SMR = standardized mortality ratio; UCOD = underlying cause of death; OR = odds ratio; SRR = summary relative risk; SB = selection bias; IB = information bias; Cf = confounding; Oth = other feature of design or analysis; TSFE = time since first exposure; URT = upper respiratory tract; LHP = lymphohematopoietic; HR = hazard ratio; PMR = proportionate mortality ratio; BMI = body mass index; JEM = job-exposure matrix.

Lymphatic leukemia

Epidemiological evidence

The most specific level of lymphatic leukemia diagnosis that is commonly reported across the epidemiological literature has been based on the first three digits of the Eighth or Ninth Revision of the ICD code (i.e., Lymphatic leukemia ICD-8: 204 and Lymphoid leukemia ICD-9: 204). Evidence describing the association between formaldehyde exposure and the specific risk of lymphatic leukemia was available from nine epidemiological studies—two case-control studies (Hauptmann et al., 2009; Blair et al., 2001) and seven cohort studies (Meyers et al., 2013; Saberi Hosnijeh et al., 2013; Beane Freeman et al., 2009; Hayes et al., 1990; Ott et al., 1989; Walrath and Fraumeni, 1984, 1983). Six of the cohort studies all ascertained lymphatic leukemia diagnoses from death certificates and one examined incident cases (Saberi Hosnijeh et al., 2013). All studies reported lymphatic leukemia outcomes based on the ICD-8 or ICD-9 diagnostic code 204 without separate results for acute lymphocytic leukemia and CLL. One case-control study (Hauptmann et al., 2009) ascertained lymphatic leukemia diagnoses from death certificates whereas the other ascertained incident cases of lymphatic leukemia from a cancer registry and a hospital network (Blair et al., 2001). Both studies reported specific results for CLL; however, while diagnoses of lymphatic leukemia reviewed here are those identified according to the ICD codes used at the time of diagnoses, in the ICD-10 coding rubric, CLL would be included as NHL. Study details are provided in the evidence table for lymphatic leukemia (see Table 1-61). Study results for ICD-7 code 204 were not included because this code includes all leukemias. The outcome-specific evaluations of confidence in the reported effect estimate of an association from each study are provided in Appendix A.5.9 and the confidence conclusions are provided in the evidence table for lymphatic leukemia (see Table 1-61) following the causal evaluation.

Consistency of the observed association

The point estimates and CIs of all eight informative studies were consistently around the null, which does not provide evidence of an association between formaldehyde exposure and the risk of developing or dying from lymphatic leukemia. The range of central relative effect estimates (selecting the highest exposure level results when there was more than one result) was from zero ((Walrath and Fraumeni, 1984); [zero cases]) to 2.6 ((Ott et al., 1989); [1 case]) and both of these results were classified with *low* confidence. The three results classified with *high* or *medium* confidence were SMR = 0.71 in Meyers et al. (2013), OR = 1.0 in Hauptmann et al. (2009), and SMR = 1.15 in Beane Freeman et al. (2009). The study results presented in Table 1-61 (by confidence level and publication date) detail all of the reported associations between exposures to formaldehyde and the risks of developing or dying from lymphatic leukemia along with a summary graphic of any major limitation and the confidence classification of the effect estimate. Results are plotted in Figure 1-40.

Strength of the observed association

Summary effect estimates for the association between formaldehyde exposure and the risk of mortality from lymphatic leukemia ranged from zero to 2.6 and clustered around the null.

Temporal relationship of the observed association

In each of the studies, the formaldehyde exposures among the study participants occurred before their lymphatic leukemia was detected and in the studies that ascertained individual-level exposures, the estimation of formaldehyde exposures was based on job titles and was done in a blinded fashion with respect to outcome status. None of the eight studies provided analyses of a temporal relationship between the timing of exposure and the diagnoses of lymphatic leukemia or deaths from lymphatic leukemia.

Exposure-response relationship

None of the studies evaluated the effect of duration of formaldehyde exposure on the mortality risk of lymphatic leukemia. There were only two sets of results, one classified with *medium* confidence and one with *low* confidence, which evaluated any form of exposure-response for increasing measures of formaldehyde exposure (Beane Freeman et al., 2009; Blair et al., 2001) and neither showed a pattern of increasing risk with increasing formaldehyde exposure.

Potential impact of selection bias, information bias, confounding bias, and chance

There was potential for selection bias in two studies that were only able to ascertain death certificated for 75–79% of the decedents (Ott et al., 1989; Walrath and Fraumeni, 1983), but there was no evidence that inclusion rates may have been related to either exposure or outcome, and thus, there is little concern about selection bias. Among the studies reporting on the risk of lymphatic leukemia, which only indicated the equivalent of ever/never exposure to formaldehyde, there was little potential for information bias. In fact, results consistently showed no evidence of an association—regardless of the quality of exposure assessment further. Confounding is another potential bias that could arise if another cause of lymphatic leukemia was statistically associated with formaldehyde exposure. However, there does not appear to be any evidence of negative confounding, which could have obscured a real but unobserved effect. While there did not appear to be an association between exposure to formaldehyde and the risk of lymphatic leukemia, given the limited database of specific results, and the possibility of biases that could obscure any true effect, the available epidemiological data are inadequate to conclude that formaldehyde is not likely to be carcinogenic to humans.

Causal evaluation

The causal evaluation for formaldehyde exposure and the risk of developing or dying from lymphatic leukemia placed the greatest weight on four particular considerations: (1) the generally consistent pattern of null results across *high*, *medium,* and *low* confidence studies; (2) the absence

of exposure-response relationships showing that increased exposure to formaldehyde was associated with increased risk of lymphatic leukemia; (3) the limited database from which to evaluate the association; and (4) the absence of evidence to evaluate the potential risk to sensitive populations or lifestages. Although consistent observations of genotoxicity in peripheral blood lymphocytes, exfoliated buccal cells or nasal mucosal cells have been observed across several occupational studies, these data were not interpreted as sufficient to further strengthen the judgment on the human evidence of lymphatic leukemia.

Conclusion

- The available epidemiological studies provide *indeterminate* evidence to assess the carcinogenic potential evidence of an association between formaldehyde exposure and an increased risk of lymphatic leukemia.

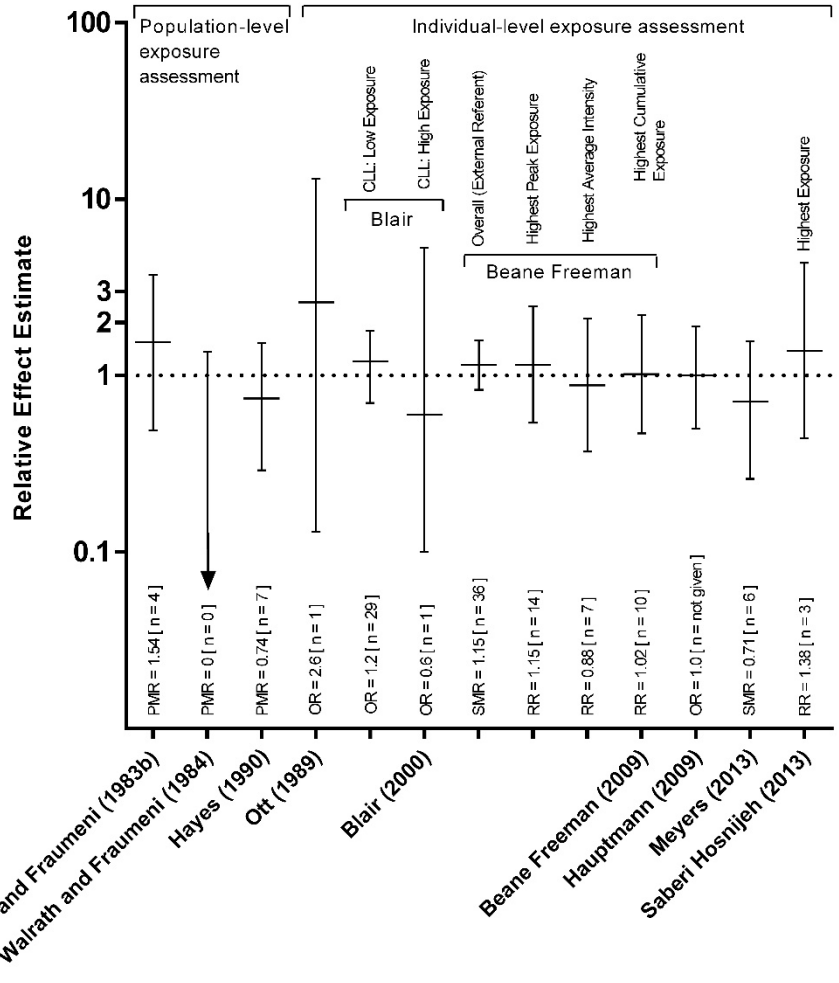
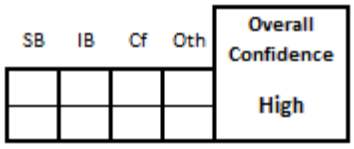


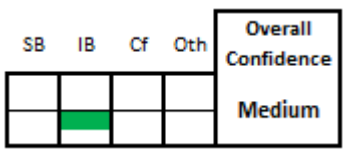
Figure 1-40. Epidemiological studies reporting lymphatic leukemia risk estimates.

Results specifically for chronic lymphatic leukemia (CLL) are noted by these abbreviations: SMR = standardized mortality ratio; PMR = proportionate mortality ratio; RR = relative risk; OR = odds ratio. For each measure of association, the number of exposed cases is provided in brackets (e.g., [*n* = 4]). For studies reporting results on multiple metrics of exposure, each metric is included; however, only the highest category of each exposure metric is presented in the figure.

Table 1-61. Epidemiological studies of formaldehyde exposure and risk of lymphatic leukemia

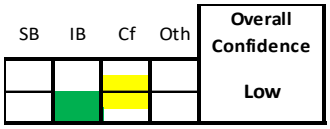
Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Reference: Meyers et al. (2013) **Population:** 11,043 workers in three U.S. garment plants exposed for at least 3 months. Women comprised 82% of the cohort. Vital status was followed through 2008 with 99.7% completion. **Outcome definition:** Death certificates used to determine both the UCOD from lymphocytic leukemia (ICD code in use at time of death). **Design:** Prospective cohort mortality study with external and internal comparison groups. **Analysis:** SMRs calculated using sex, age, race, and calendar-year-specific U.S. mortality rates. Poisson regression analysis based on internal referents. **Related studies:** Stayner et al. (1985) Stayner et al. (1988) Pinkerton et al. (2004) **Confidence in effect estimates:**[a] SB IB Cf Oth | Overall Confidence: High **HIGH** • **IB**: Exposure Group A	**Exposure assessment:** Individual-level exposure estimates for 549 randomly selected workers during 1981 and 1984. Geometric TWA8 exposures ranged from 0.09 to 0.20 ppm. Overall geometric mean concentration of formaldehyde was 0.15 ppm (GSD 1.90 ppm). Area measures showed constant levels without peaks. Historically earlier exposures may have been substantially higher. **Duration and timing:** Exposure period from 1955 through 1983. Median duration of exposure was 3.3 years. More than 40% exposures <1963. Median time since first exposure was 39.4 years. Duration and timing since first exposure were not evaluated. **Coexposures:** Study population specifically selected because industrial hygiene surveys at the plants did not identify any chemical exposures other than formaldehyde that were likely to influence findings.	**External comparisons:** SMR = 0.71 (0.26–1.56) [6]
Reference: Beane Freeman et al. (2009) with supplemental online tables.	**Exposure assessment:** Individual-level exposure estimates based on job titles, tasks, visits to plants by study industrial hygienists, and monitoring data through 1980.	**Internal comparisons:** Peak exposure Unexposed RR = 0.27 (0.03–2.13) [1] Level 1 RR = 1.00 (Ref. value) [14] Level 2 RR = 0.81 (0.33–1.96) [8]

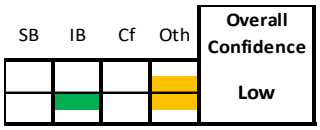
Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Population: 25,619 workers employed at 10 formaldehyde-using or formaldehyde-producing plants in the U.S. followed from either the plant start-up or first employment through 2004. Deaths were identified from the National Death Index with remainder assumed to be living. Vital status was 97.4% complete and only 2.6% lost to follow-up. **Outcome definition:** Death certificates used to determine UCOD from lymphatic leukemia (ICD-8: 204). **Design:** Prospective cohort mortality study with external and internal comparison groups. **Analysis:** RRs estimated using Poisson regression stratified by calendar year, age, sex, and race; adjusted for pay category compared to workers in lowest exposed category. Lagged exposures were evaluated to account for cancer latency. SMRs calculated using sex, age, race, and calendar-year-specific U.S. mortality rates. **Related studies:** Blair et al. (1986) Hauptmann et al. (2003) **Confidence in effect estimates:**[a]  **HIGH** ● (No appreciable bias) **IB**: Exposure Group A	Median TWA (over 8 hours) = 0.3 ppm (range 0.01–4.3). Median cumulative exposure = 0.6 ppm-years (range 0–107.4). Multiple exposure metrics including peak, average, and cumulative exposures were evaluated using categorical and continuous data. **Duration and timing:** Exposure period from <1946 through 1980. Median length of follow-up: 42 years. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Peak exposure: Level 1 (>0 to <2.0 ppm) Level 2 (2.0 to <4.0 ppm) Level 3 (≥4.0 ppm) Average intensity: Level 1 (>0 to <0.5 ppm) Level 2 (0.5 to <1.0 ppm) Level 3 (≥1.0 ppm) Cumulative exposure: Level 1 (>0 to <1.5 ppm-yrs) Level 2 (1.5 to <5.5 ppm-yrs) Level 3 (≥5.5 ppm-yrs) **Coexposures:** Exposures to 11 other compounds were identified and evaluated as potential confounders.	Level 3 RR = 1.15 (0.54–2.47) [14] *p*-trend (exposed) >0.50; *p*-trend (all) = 0.30 Average intensity Unexposed RR = 0.26 (0.03–2.01) [1] Level 1 RR = 1.00 (Ref. value) [22] Level 2 RR = 0.92 (0.39–2.16) [7] Level 3 RR = 0.88 (0.37–2.11) [7] *p*-trend (exposed) >0.50; *p*-trend (all) >0.50 Cumulative exposure Unexposed RR = 0.24 (0.03–1.88) [1] Level 1 RR = 1.00 (Ref. value) [21] Level 2 RR = 0.57 (0.21–1.54) [5] Level 3 RR = 1.02 (0.47–2.21) [10] *p*-trend (exposed) = 0.46; *p*-trend (all) = 0.41 **External comparisons:** $SMR_{Unexposed}$ = 0.26 (0.04–1.82) [1] $SMR_{Exposed}$ = 1.15 (0.83–1.59) [36]
Reference: Hauptmann et al. (2009) **Population:** 6,808 embalmers and funeral directors who died during 1960–1986. Identified from registries of the National Funeral Directors' Association, licensing boards, and state funeral directors' associations, NY State Bureau of Funeral Directors,	**Exposure assessment:** Occupational history obtained by interviews with next of kin and coworkers using detailed questionnaires. Exposure was assessed by linking questionnaire responses to an exposure assessment experiment providing measured exposure data. Exposure levels (peak, intensity, and cumulative) were assigned to each individual using a predictive model based	**Internal comparisons:** **Embalming:** Never: OR = 1.0 (Ref. value) [# not given] Ever: OR = 1.0 (0.5–1.9) [# not given]

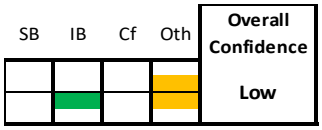
Study	Exposures	Results: effect estimate (95% CI) [# of cases]
and CA Funeral Directors and Embalmers. Deaths were identified from the National Death Index. Next of kin interviews conducted for 96% of cases and 94% of controls. **Outcome definition:** Death certificates used to determine UCOD from CLL (ICD-8: 204.1). [Note that while CLL was classified as lymphocytic leukemia in ICD-8, in ICD-10, it is included as non-Hodgkin lymphoma] **Design:** Nested case-control study within a prospective cohort study. **Analysis:** ORs calculated using unconditional logistic regression adjusted for date of birth, age at death, sex, data source, and smoking. Lagged exposures were evaluated to account for cancer latency. **Related studies:** Hayes et al. (1990) Walrath and Fraumeni (1983) Walrath and Fraumeni (1984) **Note:** The original cohorts from these three related studies were combined in Hauptmann et al. (2009) and follow-up was extended so the case-series overlap and are not independent. However, the three related cohorts used external reference groups for comparison while Hauptmann et al. (2009) select internal controls, which were independent of the reference groups used in the other studies. **Confidence in effect estimate:**[a]  **MEDIUM ↓** **(Potential bias toward the null↓)** **IB**: Exposure Group A	on the exposure data. The model explained 74% of the observed variability in exposure measurements. Multiple exposure metrics including duration (mean = 33.1 yrs in cases), # of embalming, peak, average, and cumulative exposures were evaluated using categorical and continuous data. **Duration and timing:** Exposure period from <1932 through 1986. Duration of exposure was evaluated. Duration is also a surrogate for time because first exposure since dates of death were closely related to cessation of workplace exposures **Variation in exposure:** For variations in exposure from table 3 in the publication: Level 1 (no exposure to embalming) For variations in exposure from table 4 in the publication: Level 1 (<500 embalming) Duration of exposure: Level 2 (<20 years) Level 3 (20–34 years) Level 4 (>34 years) Number of embalming: Level 2 (500−1,422) Level 3 (1,423–3,068) Level 4 (>3,068) Cumulative exposure: Level 2 (≤4,058 ppm-hrs) Level 3 (4,059–9,253 ppm-hrs) Level 4 (≥9,253 ppm-hrs) Average intensity (while embalming): Level 2 (≤1.4 ppm) Level 3 (>1.4–1.9 ppm) Level 4 (>1.9 ppm) TWA8 formaldehyde intensity: Level 2 (≤0.10 ppm) Level 3 (>0.10–0.18 ppm) Level 4 (>0.18 ppm) Peak Exposure: Level 2 (<7.0 ppm) Level 3 (7.0 to <9.3 ppm) Level 4 (>9.3 ppm) **Coexposures:** None evaluated.	

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
	[As noted in Appendix A.5.9: Coexposures may have included: phenol, methyl alcohol, glutaraldehyde, mercury, arsenic, zinc, and ionizing radiation. Chemical coexposures are not known risk factors for this outcome. Radiation exposure likely to be poorly correlated with formaldehyde so confounding is unlikely.]	
Reference: Hayes et al. (1990) **Population:** 4,046 deceased U.S. male embalmers and funeral directors, derived from licensing boards and funeral director associations in 32 states and the District of Columbia who died during 1975–1985. Death certificates obtained for 79% of potential study subjects (*n* = 6,651) with vital status unknown for 21%. **Outcome definition:** Death certificates and licensing boards used to determine cause of death from lymphatic leukemia (ICD-8: 204). **Design:** Proportionate mortality cohort study with external comparison group. **Analysis:** PMRs calculated using sex, race, age, and calendar-year-expected deaths from the U.S. population. **Confidence in effect estimates:**[a] SB IB Cf Oth | Overall Confidence: Medium **MEDIUM ↓** **(Potential bias toward the null↓)** **SB:** Missing death certificates considered to missing at random **IB**: Exposure Group A; latency not evaluated. Possible undercounting of cases due to abbreviated death certificate	**Exposure assessment:** Presumed exposure to formaldehyde tissue fixative. Exposure based on occupation, which was confirmed on death certificate. Authors subsequently measured personal embalming exposures ranging from 0.98 ppm (high ventilation) to 3.99 ppm (low ventilation) with peaks up to 20 ppm. Authors state that major exposures are to formaldehyde and possibly glutaraldehyde and phenol. **Duration and timing:** Occupational exposure preceding death during 1975–1985. Of 115 deaths from LHP cancer, 66 (57%) were aged 60–74 years. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** None evaluated as potential confounders. [As noted in Appendix A.5.9: Coexposures may have included: phenol, methyl alcohol, glutaraldehyde, mercury, arsenic, zinc, and ionizing radiation. Chemical coexposures are not known risk factors for this outcome. Radiation exposure likely to be poorly correlated with formaldehyde so confounding is unlikely.]	**External comparisons:** PMR = 0.74 (0.29–1.53) [7]
Reference: Saberi Hosnijeh et al. (2013)	**Exposure assessment:** Individual occupational histories obtained by questionnaire about ever working in any	**Internal comparisons:** Exposure to formaldehyde:

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Population: 241,465 men and women recruited from 10 European countries during 1992–2000. Participants were predominantly aged 35–70 at recruitment and were followed up through 2010. **Outcome definition:** Incident primary leukemias. **Design:** Prospective multinational cohort incidence study with internal comparison groups. **Analysis:** HRs calculated controlling for age, sex, smoking, alcohol, physical activity, education, BMI, family history of cancer, country, other occupational exposures, and radiation. **Confidence in effect estimates:**[a]  **LOW ↓** (Potential bias toward the null; low sensitivity) **IB**: Exposure Group C; Latency was not evaluated **Cf**: Confounding possible **Oth**: Low power	of 52 occupations considered to be at high risk of developing cancer. Occupational exposures estimated as "high," "low," and no exposure by linking to a JEM. **Duration and timing:** Duration and timing since first exposure were not evaluated. **Variation in exposure:** Exposure to formaldehyde: Level 1 (none) Level 2 (low) Level 3 (high) **Coexposures:** Coexposure included pesticides, herbicides, insecticides, aromatic solvents, benzene, chlorinated solvents, trichloroethylene, metals, contact with animals or animal products, ionizing radiation. [As noted in Appendix A.5.9: Coexposures were not controlled for. Potential for confounding is unknown but could have inflated the observed effect. Potential for confounding may be mitigated by low correlation between exposures in the general population.]	Level 1 RR = 1.00 (Ref. value) [130] Level 2 RR = 1.08 (0.81–1.45) [64] Level 3 RR = 1.38 (0.44–4.35) [3]
Reference: Blair et al. (2001) **Population:** White men, 30 years of age or older, identified from the Iowa cancer registry and the Minnesota hospital surveillance network during 1980–1983. Participation of eligible cases was 86% and approximately 77–79% for controls including 77% for surrogate respondents for deceased subjects. **Outcome definition:** Diagnosis of leukemia was confirmed by pathology review for all cases. **Design:** Population-based case-control study of 513 white men with leukemia from Iowa and Minnesota cancer surveillance networks. 1,087 controls were frequency matched on	**Exposure assessment:** Individual-level exposure estimates developed based on a JEM for each job held for more than 1 year, the industry where employed, and starting and ending year the job was held. Exposure intensity and probability assessed for formaldehyde and other exposures. Exposure intensity refers to the level likely experienced and considered a TWA8 over a year. **Duration and timing:** Exposure period based on occupational histories prior to 1983. Duration and timing since first exposure were evaluated. **Variation in exposure:** Intensity of exposure: Level 1 (unexposed) Level 2 (low)	**Internal comparisons:** Acute lymphatic leukemia (ICD-9:204.0) No exposed cases Chronic lymphatic leukemia (ICD-9: 204.1) Level 1 OR = 1.0 (Ref. value) [483] Level 2 OR = 1.2 (0.7–1.8) [29] Level 3 OR = 0.6 (0.1–5.3) [1] No notable findings were reported for duration of time since first exposure to formaldehyde.

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
5-yr age groups, vital status, and state. **Analysis:** ORs calculated for job titles, employment duration and exposure intensity using unconditional logistic regression controlling for age, state, direct/surrogate response and coexposures, including smoking. Analyses by year of first exposure conducted. **Confidence in effect estimates:**[a]  **LOW ↓** **(Potential bias toward the null↓)** **IB**: Exposure Group C; lack of latency analysis **Cf**: Potential confounding	Level 3 (high) **Coexposures:** None evaluated as potential confounders. [As noted in Appendix A.5.9: Other exposures evaluated included benzene, other organic solvents, petroleum-based oils and greases, cooking oils, ionizing radiation, paper dusts, gasoline and exhaust vapors, paints, metals, wood dust, asbestos, asphalt, cattle, meat, solder fumes. However, analyses of formaldehyde exposures did not control for other exposures.]	
Reference: Ott et al. (1989) **Population:** 29,139 men employed at two large chemical manufacturing facilities and a research and development center who worked during 1940–1978. Vital status was known for 96.4%. Death certificates were available for 5,785 known descendants (95.4%). **Outcome definition:** Death certificates used to determine UCOD from lymphatic leukemia based on the ICD code in used at the time of death. **Design:** Nested case-control study within a prospective cohort mortality study. Twenty cases of lymphatic leukemia were frequency matched to 100 controls on time from hire to death. **Analysis:** ORs calculated using unconditional logistic regression. **Related studies:** Rinsky et al. (1988) **Confidence in effect estimates:**[a]	**Exposure assessment:** Individual-level exposure ascertained from employee's work assignments linked to records on departmental usage of formaldehyde. **Duration and timing:** Occupational exposures during 1940–1978. Timing of formaldehyde exposure not evaluated. **Variation in exposure:** Ever/never **Coexposures:** None evaluated as potential confounders. [As noted in Appendix A.5.9: 21 different chemicals were evaluated including benzene with much cross exposure. Benzene was not evaluated as a potential confounder and may be positively correlated with formaldehyde exposure. Potential for confounding is unknown but could have inflated the observed effect. Potential for confounding may be mitigated by rarity of coexposures among cases.]	**Internal comparisons:** OR = 2.6 (0.13–13.0)† [1] †**Note:** EPA derived CIs using the Mid-P Method (See Rothman and Boice, 1979)

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
 **LOW ↓** **(Potential bias toward the null↓)** Low power due to the rarity of exposure. **IB**: Exposure Group B; latency evaluation likely to be underpowered to detect any effects beyond a 5-year period **Cf**: Benzene is a potential confounder **Oth**: Low power due to the rarity of exposure		
Reference: Walrath and Fraumeni (1984) **Population:** 1,007 deceased white male embalmers from California who died during 1925–1980. Death certificates obtained for all. **Outcome definition:** Lymphatic leukemia (ICD-8: 204) listed as cause of death on death certificate. **Design:** Proportionate mortality cohort study with external comparison group. **Analysis:** PMRs calculated using sex, race, age, and calendar-year-expected deaths from the U.S. population. **Confidence in effect estimates:**[a]  **LOW ↓** **(Potential bias toward the null↓)** **IB**: Exposure Group A; latency was not evaluated **Oth**: Low power for lymphatic leukemia	**Exposure assessment:** Presumed exposure to formaldehyde tissue fixative. **Duration and timing:** Occupational exposure preceding death during 1916–1978. Birth year ranged from 1847 through 1959. Median age of death was 62 years. Most deaths were among embalmers with active licenses. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** None evaluated as potential confounders. [As noted in Appendix A.5.9: Coexposures may have included: phenol, methyl alcohol, glutaraldehyde, mercury, arsenic, zinc, and ionizing radiation. Radiation exposure likely to be poorly correlated with formaldehyde so confounding is unlikely.]	**External comparisons:** Observed: 0 lymphatic leukemia deaths Expected: 2.2 lymphatic leukemia deaths PMR = 0 (0–1.36)† [0 vs. 2.2 expected] †**Note:** EPA derived CIs using the Mid-P Method (See Rothman and Boice, 1979)
Reference: Walrath and Fraumeni (1983) **Population:** 1,132 deceased white male embalmers licensed to practice during 1902–1980 in New York who	**Exposure assessment:** Presumed exposure to formaldehyde tissue fixative. **Duration and timing:** Occupational exposure preceding death during 1902–1980. Median year of birth	**External comparisons:** Observed: 4 lymphatic leukemia deaths Expected: 2.6 lymphatic leukemia deaths PMR = 1.54 (0.49–3.71)† [4]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
died during 1925–1980 identified from registration files. Death certificates obtained for 75% of potential study subjects (*n* = 1,678). **Outcome definition:** Lymphatic leukemia (ICD-8: 204) listed as cause of death on death certificate. **Design:** Proportionate mortality cohort study with external comparison group. **Analysis:** PMRs calculated using sex, race, age, and calendar-year-expected deaths from the U.S. population. **Confidence in effect estimates:**[a]  **LOW ↓** **(Potential bias toward the null↓)** **SB:** Missing death certificates considered to missing at random **IB**: Exposure Group A ; latency was not evaluated **Oth**: Low power for lymphatic leukemia	was 1901. Median year of initial license was 1931. Median age at death was 1968. Expected median duration of exposure was 37 years. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** None evaluated as potential confounders. [As noted in Appendix A.5.9: Coexposures may have included: phenol, methyl alcohol, glutaraldehyde, mercury, arsenic, zinc, and ionizing radiation. Radiation exposure likely to be poorly correlated with formaldehyde so confounding is unlikely.]	†**Note:** EPA derived CIs using the Mid-P Method (See Rothman and Boice, 1979)

[a]Evaluation of sources of bias or study limitations (see details in Appendix A.5.9). SB = selection bias; IB = information bias; Cf = confounding; Oth = other feature of design or analysis. Extent of column shading reflects degree of limitation. Direction of anticipated bias indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact would be likely to be away from the null (i.e., spurious or inflated effect estimate).
Results from *low* confidence studies are shaded; these findings are considered less reliable.
Abbreviations: SB = selection bias; IB = information bias; Cf = confounding; Oth = other feature of design or analysis; UCOD = underlying cause of death; GSD = geometric standard deviation; SMR = standardized mortality ratio; RR = relative risk; TWA8 = 8-hour time-weighted average; LHP = lymphohematopoietic; PMR = proportionate mortality ratio; BMI = body mass index; JEM = job-exposure matrix; OR = odds ratio.

Multiple myeloma

Epidemiological evidence

The most specific classification of multiple myeloma diagnosis that is commonly reported across the epidemiological literature has been based on the first three digits of the Eighth or Ninth Revision of the ICD code without further differentiation (i.e., Multiple myeloma ICD-8/9: 203). Evidence describing the association between formaldehyde exposure and the risk of developing or dying from multiple myeloma was available from 14 epidemiological studies—five case-control

studies (Hauptmann et al., 2009; Heineman et al., 1992; Pottern et al., 1992; Boffetta et al., 1989; Ott et al., 1989) and nine cohort studies (Coggon et al., 2014; Pira et al., 2014; Meyers et al., 2013; Beane Freeman et al., 2009; Stellman et al., 1998; Band et al., 1997; Dell and Teta, 1995; Hayes et al., 1990; Edling et al., 1987b). Study details are provided in the evidence table for multiple myeloma (see Table 1-62). The outcome-specific evaluations of confidence in the reported effect estimate of an association from each study are provided in Appendix A.5.9 and the confidence conclusions are provided in the evidence table for multiple myeloma (see Table 1-62) following the causal evaluation. Details of the reported results of *high*, *medium*, and *low* confidence are provided in the evidence table for multiple myeloma (see Table 1-62) following the causal evaluation.

Consistency of the observed association

The results of these studies appear to be mixed with some showing non-significant increases in risk and other showing non-significant decreases in risk. Nine of the 14 studies were low confidence (Pira et al., 2014; Stellman et al., 1998; Dell and Teta, 1995; Pottern et al., 1992; Boffetta et al., 1989; Ott et al., 1989; Edling et al., 1987b) with many results based on fewer than five cases.626235 However, only the study by Beane Freeman et al. (2009) reported a result with *high* confidence showing an association between peak formaldehyde exposure and risk of multiple myeloma. The study results presented in Table 1-62 (by confidence level and publication date) and plotted in Figure 1-41 detail all of the reported associations between exposures to formaldehyde and the risks of developing or dying from multiple myeloma

The first four studies shown at the left in Figure 1-41 followed the health of groups of occupationally exposed workers in three different industries and did not have individual-level exposure estimates (Dell and Teta, 1995; Hayes et al., 1990; Edling et al., 1987b). Respectively, these were: (1) workers making grinding wheels bound with formaldehyde resins, (2) embalmers, and (3) workers manufacturing plastics—professions known to be exposed to formaldehyde. Importantly, all of these professions were exposed to high peak concentrations of formaldehyde. Edling et al. (1987b) reported that the workers making grinding wheels bound with formaldehyde resins were exposed to peak formaldehyde levels of up to 20–30 mg/m^3 (15–23 ppm). Embalmers (Hayes et al., 1990) were also exposed to high peak formaldehyde concentrations with mean exposures of more than 2 ppm and peaks as high as 8.7 ppm (Stewart et al., 1992). Workers at the plastics manufacturing facilities studied by Dell and Teta (1995) were exposed to formaldehyde, formaldehyde resins, and formaldehyde molding compounds. An independent occupational hygiene survey of facilities producing similar products reported peak exposure for these activities of 1.88 ppm, 30.45 ppm, and 60.77 ppm, respectively (Stewart et al., 1987). The results of these three studies are displayed beneath the header of "Population-level exposure assessment." All three studies showed elevated RRs of multiple myeloma mortality as measured by the mortality ratios; although, none of the three was statistically robust enough to decrease the likelihood of chance as an alternative explanation. The Hayes et al. (1990) result (PMR = 1.37; 95% CI 0.84–2.12; *n* = 20) was classified with *medium* confidence but the other two results from Edling et al. (1987b)

(SMR = 4.0; 95% CI 0.45–14.44; *n* = 2) and Dell and Teta (1995) (SMR = 2.62; 95% CI 0.85–6.11; *n* = 8) were classified with *low* confidence.

The second set of studies (*n* = 10) is displayed in Figure 1-41 (Coggon et al., 2014; Meyers et al., 2013; Beane Freeman et al., 2009; Hauptmann et al., 2009; Stellman et al., 1998; Band et al., 1997; Heineman et al., 1992; Pottern et al., 1992; Boffetta et al., 1989; Ott et al., 1989) beneath the header of "Individual-level exposure assessment." In principle, a general strength of this second set of studies was their use of individualized exposure data; however, the quality of the exposure assessment for each individual varied considerably across this set of studies. These 10 studies with individual-level exposure assessment can be divided into two groups based on the methods of individual exposure assessment. The first grouping gathered minimal information (e.g., questionnaire data on "ever" exposure to formaldehyde) on formaldehyde exposure (Stellman et al., 1998; Heineman et al., 1992; Pottern et al., 1992; Boffetta et al., 1989). The second grouping focused on workers who were occupationally exposed to formaldehyde and used work assignments or job histories matched to exposure data to assess workers' formaldehyde exposures (Coggon et al., 2014; Meyers et al., 2013; Beane Freeman et al., 2009; Hauptmann et al., 2009; Band et al., 1997; Ott et al., 1989).

The exposure assessment methodology for the first grouping of four studies with individual-level exposures was especially crude. Exposure assessment was limited to either a one-time questionnaire asking participants to check off a box if they were "ever" exposed to formaldehyde in the workplace or in daily life (Stellman et al., 1998; Boffetta et al., 1989) or using the occupation listed on individuals' most recent annual tax records to estimate previous occupational formaldehyde exposure as "none," "possible," or "probable" (Heineman et al., 1992; Pottern et al., 1992). While the large size of these studies was considered to be a strength, the weaknesses of their relatively low-quality exposure assessment outweighed that strength. It is well known that the use of low-quality exposure data in epidemiological studies may preclude the ability to detect all but the strongest association.

The second grouping of studies, with relatively higher quality individual-level exposure to formaldehyde, examined occupational histories at different points in time and linked this to measured or estimated exposures (Coggon et al., 2014; Meyers et al., 2013; Beane Freeman et al., 2009; Hauptmann et al., 2009; Band et al., 1997; Ott et al., 1989). While the relative effect estimates for multiple myeloma mortality in each of these cohorts compared to the general population did not show elevated risks (relative effect estimates of: 0.8, 1.4, 1.0, 0.94, 1.24, 0.99), two studies (Coggon et al., 2014; Beane Freeman et al., 2009) showed somewhat higher risks when analyses focused on the workers with highest peak exposure. Beane Freeman et al. (2009) evaluated results by each worker's highest formaldehyde concentration during a "peak" exposure event, by average intensity of exposure, by cumulative exposure, and by duration of exposure. Peak exposure events were defined as short-term exposures (<15 minutes) that exceeded the TWA formaldehyde intensity (Beane Freeman et al., 2009). Workers' peak exposures were defined as the highest concentration

among their peak exposure events. In Beane Freeman et al. (2009), the highest peak exposure category represents the workers who had ever experienced short-term peak exposure to ≥4.0 ppm. The Beane Freeman et al. (2009) results in the high category of peak exposures were RR = 2.04 (95% CI 1.01–4.12). In Coggon et al. (2014), the "high" category of exposure represented workers who ever had a job in the highest formaldehyde exposure category (≥2 ppm). The Coggon et al. (2014) results in the high exposure category were, however, relatively weak SMR = 1.18 versus 0.99 for all workers.

Hauptmann et al. (2009) and Ott et al. (1989) assessed individual-level exposure but only presented results specific to formaldehyde exposures for the study population as a whole. Similarly, the study of garment workers (Meyers et al., 2013) relied on individual measures of the timing of exposure but did not have formaldehyde concentration data beyond the industrial hygiene data used to plan the study (Stayner et al., 1988). Continuous area monitoring showed that formaldehyde levels were relatively constant with no substantial peak levels over the work shift (Stayner et al., 1988). The results from Meyers et al. (2013) are mixed, with the strongest evidence showing a statistically significant decreased risk among workers with the longest duration of formaldehyde exposure in analyses compared to internal referents with less than a 3-year exposure duration (SRR = 0.28; 95% CI 0.08–0.99).

In summary, among all the studies that used individual-level exposure assessment, the study with the highest quality exposure assessment methodology was the National Cancer Institute study (Beane Freeman et al., 2009) among industrial workers at facilities either using formaldehyde or producing formaldehyde. Beane Freeman et al. (2009) reported on three different, but related, measures of exposure to formaldehyde based on different exposure assessment techniques highlighting peak, cumulative and average exposures and showed elevated risk across all three measures; the most pronounced effects showed a two-fold increased risk of mortality from multiple myeloma associated with the highest level of peak exposure to formaldehyde (RR = 2.04; 95% CI 1.01–4.12).

The three studies with population-level exposure assessment, (Dell and Teta, 1995; Hayes et al., 1990; Edling et al., 1987b), all had very high peak exposure and were consistent with Beane Freeman et al. (2013) in showing an elevated risk although none was able to rule out chance. The large population studies with only crude measures of formaldehyde exposure reported mixed results with only a slightly higher risk for those judged to be "Probably" exposed (see Figure 1-41). The studies of industrial workers did not show increased risks in their populations as a whole but did report somewhat higher risks among the workers with highest exposure when individual-level exposures were considered (Coggon et al., 2014; Beane Freeman et al., 2009).

A better understanding of the etiologic progression of multiple myeloma may be needed to interpret these findings but there is some consistent epidemiological evidence suggesting an association between peak formaldehyde exposures and increased risk of multiple myeloma and possibly an increased risk at shorter durations, which could select out the responsive individuals

leaving the nonresponsive individuals without additional risks. However, it could also be the case from these data that only peak exposures are associated with multiple myeloma.

Strength of the observed association

While reported relative effect estimates were consistently elevated above the null value of one across the studies, the magnitude of the relative effect estimates varied with the quality of the exposure assessment. Studies with higher quality exposure data based on individual-level exposure assessment generally reported higher relative effect estimates (stronger associations)

Setting aside the large population-based studies with crude exposure assessment (Stellman et al., 1998; Heineman et al., 1992; Pottern et al., 1992; Boffetta et al., 1989) and focusing on individual-level exposure results where possible, the strength of the associations ranged from 1.2 to 4.0, but the upper end of that range was based on two studies with very few formaldehyde-exposed cases. The results at the highest levels of peak formaldehyde exposure showed an approximately two-fold relative increase in risk of death from multiple myeloma (Beane Freeman et al., 2009).

Temporal relationship of the observed association

In each of the studies, the formaldehyde exposures among the study participants started prior to their multiple myeloma diagnosis and in the studies that ascertained individual-level exposures, the estimation of formaldehyde exposures was based on job titles and was done in a blinded fashion with respect to outcome status. The epidemiological literature for formaldehyde and multiple myeloma describes only one study that evaluates the impact of TSFE (Meyers et al., 2013); however, while those results showed what appeared to be a slight downward trend toward lower risks at shorter times since first exposure, the CIs around those estimated risks were wide and overlapped substantially. Such findings do not add much additional information.

Exposure-response relationship

There was limited evidence of exposure-response relationships in three multiple myeloma studies. The study by Beane Freeman et al. (2009) reported on three different measures of exposure to formaldehyde and showed elevated risk across all three measures, most strongly for peak exposure (RR = 2.04; 95% CI 1.01–4.12) for the highest category (trend $p = 0.08$). There was also a finding of greater risks of multiple myeloma at shorter durations of exposure compared to longer durations; in two analyses of duration using both internal and external comparison groups, those workers with the longest duration of exposure (10+ years) were at lower risk than those with 3–9 years of exposure. This would be inconsistent with an exposure-response pattern for duration of exposure or cumulative exposure but is not necessarily inconsistent with the finding of an exposure-response for higher levels of peak exposure. Coggon et al. (2014) reported a very modest increase in risk among those workers in the high exposure category (SMR = 1.18; 95% CI 0.57–2.18); however, the risk among workers in the low/moderate category was even higher (SMR = 1.47; 95% CI 0.82–2.43). Pottern et al. (1992) reported increasing relative risks with the

qualitative likelihood of exposure with "possible" exposure having RR = 1.1 (95% CI 0.8–1.6) and "probable" exposure having RR = 1.6 (95% CI 0.4–5.3).

Potential impact of selection bias, information bias, confounding bias, and chance

Selection bias is an unlikely bias in the epidemiological studies of multiple myeloma as the case-control studies evaluated exposure status without regard to outcome status and had participation levels of 77–100% and each of the cohort studies included at least 79% of eligible participants and lost fewer than 6% of participants over the course of mortality follow-up. The healthy worker effect and the healthy worker survivor effect could obscure a truly larger effect of formaldehyde exposure in analyses based on "external" comparisons with mortality in the general population (Coggon et al., 2014; Meyers et al., 2013; Beane Freeman et al., 2009; Dell and Teta, 1995; Hayes et al., 1990; Ott et al., 1989; Edling et al., 1987b), but would not influence analyses using "internal" or matched comparison groups (Beane Freeman et al., 2009; Hauptmann et al., 2009; Stellman et al., 1998; Heineman et al., 1992; Pottern et al., 1992; Boffetta et al., 1989).

Differential exposure misclassification is considered unlikely among these studies of multiple myeloma mortality. Random measurement error or nondifferential misclassification has the effect of causing bias toward the null, thereby obscuring potentially real effects by underestimating their magnitude. This may explain the generally null findings of the four large studies that relied on very crude assessments of exposure (Stellman et al., 1998; Heineman et al., 1992; Pottern et al., 1992; Boffetta et al., 1989).

Confounding is a potential bias that could arise if another cause of multiple myeloma was also associated with formaldehyde exposure. There does not appear to be any evidence of confounding that would provide an alternative explanation for the observed association of formaldehyde exposure with increased risk of multiple myeloma seen in these studies. Known risk factors for multiple myeloma include age, sex, race, and exposure to benzene (Vlaanderen et al., 2011). Chemical, and other coexposures that have not been independently associated with multiple myeloma are not expected to confound results. Pentachlorophenol is considered to be a likely carcinogen (U.S. EPA, 2010) and the only study with likely coexposure to pentachlorophenol was classified as uninformative due to the likelihood of confounding (Robinson et al., 1987). Risks of multiple myeloma are higher with advancing age, among men, and the age-adjusted mortality rate in black Americans was more than twice as high as among white Americans in 2008 (NCI, 2012). All of the epidemiological studies controlled for age and sex. Only one study reported results according to race (Hayes et al., 1990) who reported statistically significant increased risks among "nonwhites" showing a PMR = 3.69 (95% CI 1.59–7.26).

Benzene was not noted as a coexposure in the studies of workers making grinding wheels (Edling et al., 1987b), garment plant workers (Meyers et al., 2013), or embalmers (Hayes et al., 1990) and consequently, would not be expected to be a confounder of those results. In the study of workers manufacturing plastics, Dell and Teta (1995) examined possible coexposures with benzene but concluded that there were no obvious common exposures. Benzene exposures were not

reported in the study of British industrial workers (Coggon et al., 2003); although, it is a possible coexposure. However, in a cohort of U.S. industrial workers with similar occupational activities, benzene was specifically assessed as a potential confounder among the U.S. industrial workers (Beane Freeman et al., 2009) and found not to be a confounder.

A single *high* confidence result supports an association between peak formaldehyde exposures and increased risks of multiple myeloma (Beane Freeman et al., 2009) with support from three results of studies of high peak formaldehyde exposure settings with *low* to *medium* confidence (Dell and Teta, 1995; Hayes et al., 1990; Edling et al., 1987b). However, risk estimates using other exposure metrics from the same study with the high confidence result (Beane Freeman et al., 2009) did not find increased risks and it is not known which metric of exposure is likely to be the most biologically relevant. Bias is unlikely to explain these findings but chance could be an alternative explanation.

Causal evaluation

The causal evaluation for formaldehyde exposure and the risk of developing or dying from multiple myeloma placed the greatest weight on five particular considerations: (1) the observations of increases in risk across one *high*, one *medium*, and two *low* confidence studies of occupational formaldehyde levels, but limited to groups of people who experienced high peak exposures; analyses based on other exposure metrics did not report associations in several populations; (2) the strength of the association showing an approximate 1.2- to 4-fold increase in risk with the highest quality evidence showing a two-fold increase in risk with high peak exposures; (3) the limited evidence of an exposure-response trend from a single high confidence study showing that increased exposure to formaldehyde was associated with increased risk of multiple myeloma; (4) reasonable confidence that alternative explanations are ruled out, including bias and confounding within individual studies or across studies, but chance could be an alternative explanation; and (5) confidence was diminished by reports of inverse relationships with duration of exposure and TSFE. Given the uncertainties outlined above, and although formaldehyde is genotoxic, the consistent observations of genotoxicity in peripheral blood lymphocytes observed across several occupational studies were not interpreted as sufficient to further strengthen the judgment on the human evidence of multiple myeloma beyond *slight*.

Conclusion

- The available epidemiological studies provide *slight* evidence of an association consistent with causation between formaldehyde exposure and an increased risk of multiple myeloma—primarily with respect to peak exposure.

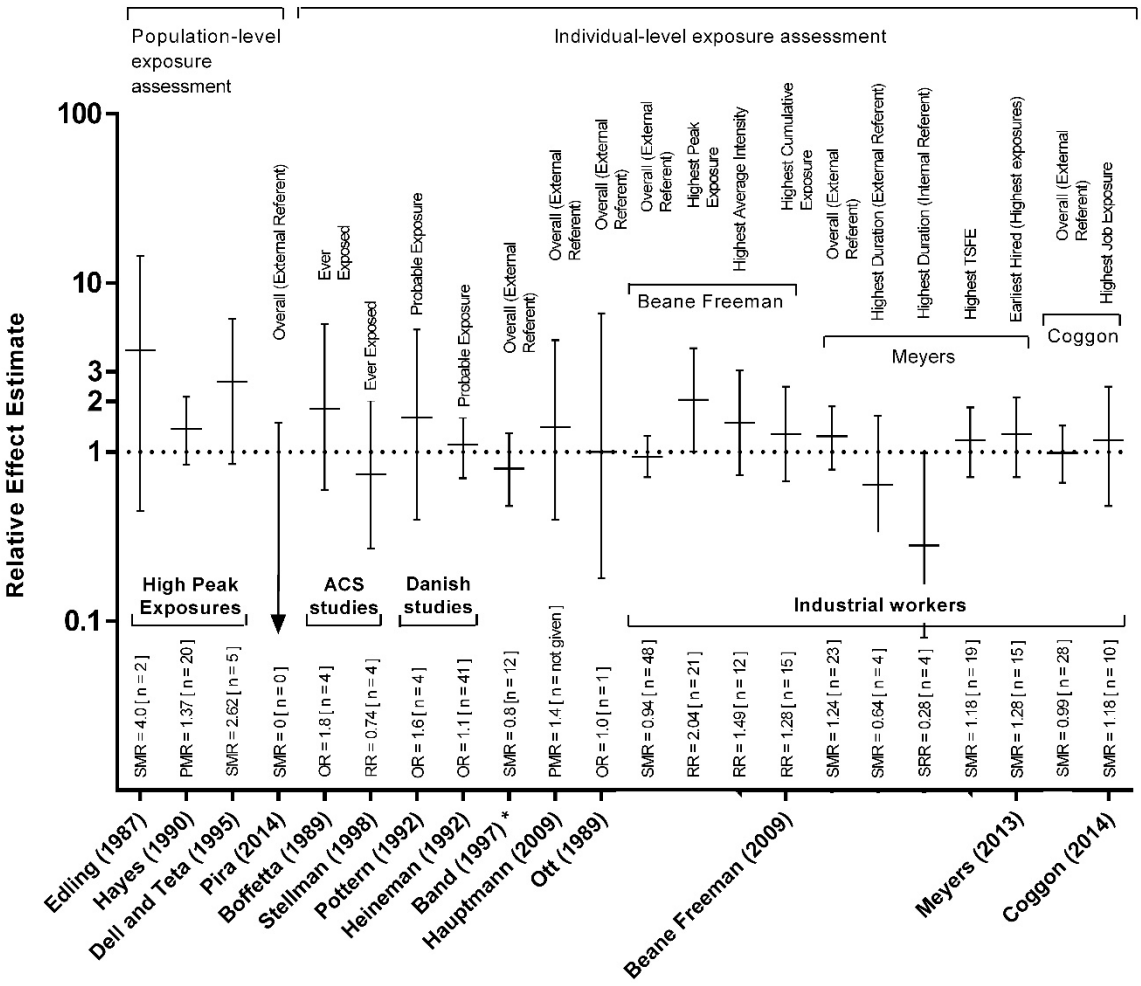
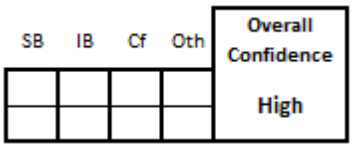


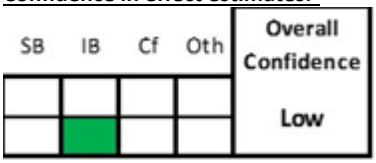
Figure 1-41. Epidemiological studies reporting multiple myeloma risk estimates.

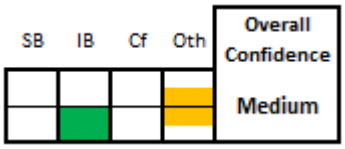
SMR = standardized mortality ratio; PMR = proportionate mortality ratio; RR = relative risk; OR = odds ratio. For each measure of association, the number of exposed cases is provided in brackets (e.g., [*n* = 3]). Results are grouped by the exposure-assessment methodology (e.g., population-level versus individual-level) and the source of the cancer data (e.g., American Cancer Society or Danish Cancer Registry) or type of occupation of exposed workers (e.g., industrial workers). For studies reporting results on multiple metrics of exposure, each metric is included; however, only the highest category of each exposure metric is presented in the figure. *Note that the CIs for Band et al. (1997) are 90% rather than 95%.

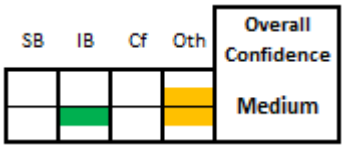
1

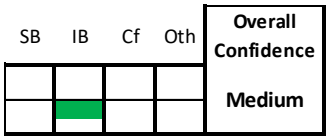
Table 1-62. Epidemiological studies of formaldehyde exposure and risk of multiple myeloma

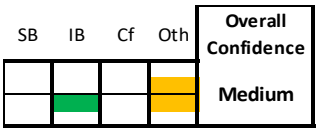
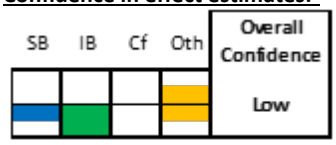
Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Reference: Beane Freeman et al. (2009) with supplemental online tables **Population:** 25,619 workers employed at 10 formaldehyde-using or formaldehyde-producing plants in the U.S. followed from either the plant start-up or first employment through 2004. Deaths were identified from the National Death Index with remainder assumed to be living. 676 workers (3%) were lost to follow-up. Vital status was 97.4% complete and only 2.6% lost to follow-up. **Outcome definition:** Death certificates used to determine UCOD from multiple myeloma (ICD-8: 203). **Design:** Prospective cohort mortality study with external and internal comparison groups. **Analysis:** RRs estimated using Poisson regression stratified by calendar year, age, sex, and race; adjusted for pay category compared to workers in lowest exposed category. Lagged exposures were evaluated to account for cancer latency. SMRs calculated using sex, age, race, and calendar-year-specific U.S. mortality rates. **Related studies:** Blair et al. (1986) Hauptmann et al. (2003) **Confidence in effect estimates:**[a]  **HIGH** **IB**: Exposure Group A **[NB:** Checkoway et al. (2015) **below]**	**Exposure assessment:** Individual-level exposure estimates based on job titles, tasks, visits to plants by study industrial hygienists, and monitoring data through 1980. Median TWA (over 8 hours) = 0.3 ppm (range 0.01–4.3). Median cumulative exposure = 0.6 ppm-years (range 0–107.4). Multiple exposure metrics including peak, average, and cumulative exposures were evaluated using categorical and continuous data. **Duration and timing:** Exposure period from <1946 to 1980. Median length of follow-up: 42 years. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Peak exposure: Level 1 (>0 to <2.0 ppm) Level 2 (2.0 to <4.0 ppm) Level 3 (≥4.0 ppm) Average intensity: Level 1 (>0 to <0.5 ppm) Level 2 (0.5 to <1.0 ppm) Level 3 (≥1.0 ppm) Cumulative exposure: Level 1 (>0 to <1.5 ppm-yrs) Level 2 (1.5 to <5.5 ppm-yrs) Level 3 (≥5.5 ppm-yrs) **Coexposures:** Exposures to 11 other compounds were identified and evaluated as potential confounders and found not be confounders. [As noted in Appendix A.5.9: There was no information on smoking; however, according to Blair et al. (1986), "The lack of a consistent elevation for tobacco-related causes of death, however, suggests that the smoking habits among this cohort did not differ substantially from those of the general population."	**Internal comparisons:** Peak exposure Unexposed RR = 2.74 (1.18–6.37) [11] Level 1 RR = 1.00 (Ref. value) [14] Level 2 RR = 1.65 (0.76–3.61) [13] Level 3 RR = 2.04 (1.01-4.12) [21] *p*-trend (exposed) = 0.08; *p*-trend (all) >0.50 Average intensity Unexposed RR = 2.18 (1.01–4.70) [11] Level 1 RR = 1.00 (Ref. value) [25] Level 2 RR = 1.40 (0.68–2.86) [11] Level 3 RR = 1.49 (0.73–3.04) [12] *p*-trend (exposed) >0.50; *p*-trend (all) >0.50 Cumulative exposure Unexposed RR = 1.79 (0.83–3.89) [11] Level 1 RR = 1.00 (Ref. value) [28] Level 2 RR = 0.46 (0.18–1.20) [5] Level 3 RR = 1.28 (0.67–2.44) [15] *p*-trend (exposed) >0.50; *p*-trend (all) >0.50 **External comparisons:** $SMR_{Unexposed}$ = 1.78 (0.99–3.22) [11] $SMR_{Exposed}$ = 0.94 (0.71–1.25) [48]

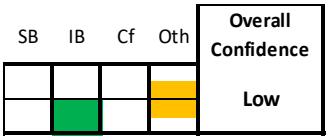
Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Reference: Beane Freeman et al. (2009) as re-analyzed by Checkoway et al. (2015) with differences noted **Population:** No differences. **Outcome definition:** Death certificates used to determine UCOD from acute and chronic myeloid leukemia (ICD-8: 205.0 and 205.1). **Design:** No differences. **Analysis:** HRs estimated using Cox proportional hazards models controlling for age, sex, and race; adjusted for pay category compared to workers in the redefined lowest exposed category. Did not control for calendar year as did Beane Freeman et al. (2009). Lagged exposures were evaluated to account for cancer latency. SMRs calculated using sex, age, race, and calendar-year-specific U.S. mortality rates. **Related studies:** Blair et al. (1986) Hauptmann et al. (2003) Checkoway et al. (2015) [reviewed here] **Confidence in effect estimates:**[a]  **LOW** ● (Potential bias ↓) **IB**: Exposure Group A [from Beane Freeman et al. (2009)] (Appendix A.5.9) downgraded to Group D based on authors' decision to reclassify all peak exposures <2 ppm as unexposed and to reclassify peak exposures >2 ppm as unexposed—if they were either very rare or very common.		**Checkoway** **External comparisons:** $SMR_{Unexposed}$ = 1.82 (1.01–3.29) [11] $SMR_{Exposed}$ = 0.93 (0.70–1.24) [48]
Reference: Coggon et al. (2014) **Population:** 14,008 British men employed in six chemical industry factories that	**Exposure assessment:** Exposure assessment based on data abstracted from company records. Jobs	**External comparisons:** SMR = 0.99 (0.66–1.43) [28] **Within-study external comparisons:**

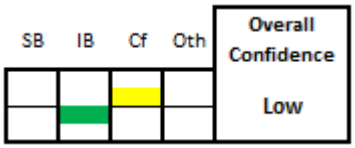
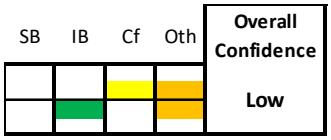
Study	Exposures	Results: effect estimate (95% CI) [# of cases]
produced formaldehyde. Cohort mortality followed from 1941 through 2012. Cause of deaths was known for 99% of 5,185 deaths through 2000. Similar cause of death information not provided on 7,378 deaths through 2012. Vital status was 98.9% complete and only 1.1% lost to follow-up through 2003. Similar information not provided on deaths through 2012. **Outcome definition:** Death certificates used to determine cause of deaths from multiple myeloma (ICD-9: 203). **Design:** Cohort mortality study with external comparison group. **Analysis:** SMRs based on English and Welsh age- and calendar-year-specific mortality rates. **Related studies:** Acheson et al. (1984) Gardner et al. (1993) Coggon et al. (2003) **Confidence in effect estimates:**[a]  **MEDIUM ↓** **(Potential bias toward the null↓)** **IB**: Exposure Group B; latency was not evaluated.	categorized as background, low, moderate, high, or unknown levels. **Duration and timing:** Occupational exposure during 1941–1982. Duration was evaluated as more, or less, than 1 year only among the high exposure group. Timing since first exposure was not evaluated. **Variation in exposure:** Highest exposure level attained Level 1 (Background) Level 2 (low/moderate) Level 3 (High) Duration of high exposures Level 1 (<1 year) Level 2 (1 year or more) **Coexposures:** Not evaluated as potential confounders. Potential low-level exposure to styrene, ethylene oxide, epichlorhydrin, solvents, asbestos, chromium salts, and cadmium. [As noted in Appendix A.5.9: Styrene is associated with LHP cancers. Asbestos is associated with URT cancers, but not with LHP cancers. Other coexposures are not known risk factors for this outcome. Authors stated that the extent of coexposures was expected to be low. Potential for confounding may be mitigated by low coexposures.]	Highest exposure level attained Level 1 SMR = 0.31 (0.06–0.91) [3] Level 2 SMR = 1.47 (0.82–2.43) [15] Level 3 SMR = 1.18 (0.57–2.18) [10]
Reference: Meyers et al. (2013) **Population:** 11,043 workers in three U.S. garment plants exposed for at least 3 months. Women comprised 82% of the cohort. Vital status was followed through 2008 with 99.7% completion **Outcome definition:** Death certificates used to determine both the UCOD from myeloid leukemia (ICD code in use at time of death).	**Exposure assessment:** Individual-level exposure estimates for 549 randomly selected workers during 1981 and 1984. Geometric TWA8 exposures ranged from 0.09 to 0.20 ppm. Overall geometric mean concentration of formaldehyde was 0.15 ppm (GSD 1.90 ppm). Area measures showed constant levels without peaks. Historically earlier exposures may have been substantially higher. **Duration and timing:** Exposure period from 1955 through 1983. Median	**External comparisons:** SMR = 1.24 (0.79–1.86) [23] **Within-study external comparisons:** Duration of exposure: Level 1 SMR = 1.16 (0.50–2.29) [8] Level 2 SMR = 2.03 (1.01–3.64) [11] Level 3 SMR = 0.64 (0.17–1.64) [4] Time since first exposure (TSFE): Level 1 SMR = 1.73 (0.04–9.61) [1] Level 2 SMR = 1.63 (0.34–4.76) [3] Level 3 SMR = 1.18 (0.71–1.84) [19]

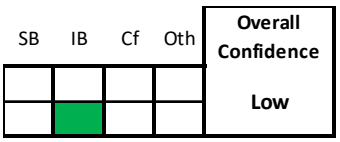
Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Design: Prospective cohort mortality study with external and internal comparison groups. **Analysis:** SMRs calculated using sex, age, race, and calendar-year-specific U.S. mortality rates. **Related studies:** Stayner et al. (1985) Stayner et al. (1988) Pinkerton et al. (2004) **Confidence in effect estimates:**[a]  **MEDIUM ↓** **(Potential bias toward the null↓)** **IB**: Exposure Group A; latency was not evaluated.	duration of exposure was 3.3 years. More than 40% exposures <1963. Median time since first exposure was 39.4 years. Duration and timing since first exposure were evaluated. **Variation in exposure:** Duration of exposure: Level 1 (<3 years) Level 2 (3–9 years) Level 3 (10+ years) Time since first exposure: Level 1 (<10 years) Level 2 (10–19 years) Level 3 (20+ years) **Coexposures:** Study population specifically selected because industrial hygiene surveys at the plants did not identify any chemical exposures other than formaldehyde that were likely to influence findings.	Year of first exposure: <1963 SMR = 1.28 (0.71–2.11) [15] 1963–70 SMR = 0.81 (0.22–2.08) [4] 1971+ SMR = 2.16 (0.59–5.52) [4] **Internal comparisons:** Duration of exposure: Level 1 SRR = 1.00 (Ref. value) [8] Level 2 SRR = 1.22 (0.46–3.26) [11] Level 3 SRR = 0.28 (0.08–0.99) [4]
Reference: Hauptmann et al. (2009) **Population:** 6,808 embalmers and funeral directors who died during 1960–1986. Identified from registries of the National Funeral Directors' Association, licensing boards and state funeral directors' associations, NY State Bureau of Funeral Directors, and CA Funeral Directors and Embalmers. Deaths were identified from the National Death Index. Next of kin interviews conducted for 96% of cases and 94% of controls. **Outcome definition:** Death certificates used to determine UCOD from multiple myeloma (ICD-8: 203). **Design:** Nested case-control study within a prospective cohort mortality study using two internal comparison groups; the first composed of those who had never embalmed (one case and 55 controls) and the second composed of those who had fewer than 500 embalmings (5 cases and 83 controls). **Analysis:** ORs calculated using unconditional logistic regression adjusted for date of birth, age at death, sex, data source, and smoking. Lagged exposures	**Exposure assessment:** Occupational history obtained by interviews with next of kin and coworkers using detailed questionnaires. Exposure was assessed by linking questionnaire responses to an exposure assessment experiment providing measured exposure data. Exposure levels (peak, intensity, and cumulative) were assigned to each individual using a predictive model based on the exposure data. The model explained 74% of the observed variability in exposure measurements. Multiple exposure metrics including duration (mean = 33.1 yrs in cases), # of embalming, peak, average, and cumulative exposures were evaluated using categorical and continuous data. **Duration and timing:** Exposure period from <1932 through 1986. Year of birth ranged from 1876 through 1959. Year of deaths ranged from 1960 through 1986. Duration of exposure was evaluated. Duration is also a surrogate for time since first exposure since dates of death were closely	**External comparisons:** Ever embalming: OR = 1.4 (0.4–5.6) [# not given]

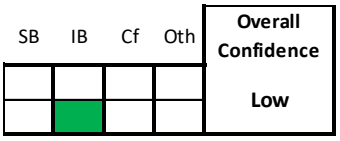
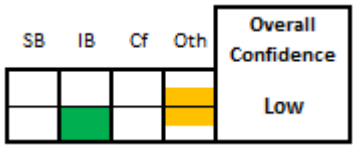
Study	Exposures	Results: effect estimate (95% CI) [# of cases]
were evaluated to account for cancer latency. Results from the second internal comparison group with <500 embalmings were selected to increase statistical stability. **Related studies:** Hayes et al. (1990) Walrath and Fraumeni (1983) Walrath and Fraumeni (1984) **Note:** The original cohorts from these three related studies were combined in Hauptmann et al. (2009) and follow-up was extended so the case-series overlap and are not independent. **Confidence in effect estimates:**[a]  **MEDIUM ↓** **(Potential bias toward the null↓)** **IB**: Exposure Group A; latency was not evaluated.	related to cessation of workplace exposures **Variation in exposure:** Ever/never **Coexposures:** None evaluated as potential confounders. [As noted in Appendix A.5.9: Coexposures may have included: phenol, methyl alcohol, glutaraldehyde, mercury, arsenic, zinc, and ionizing radiation. Chemical coexposures are not known risk factors for this outcome. Radiation exposure likely to be poorly correlated with formaldehyde so confounding is unlikely.]	
Reference: Hayes et al. (1990) **Population:** 4,046 deceased U.S. male embalmers and funeral directors, derived from licensing boards and funeral director associations in 32 states and the District of Columbia who died during 1975–1985. Death certificates obtained for 79% of potential study subjects (*n* = 6,651) with vital status unknown for 21%. **Outcome definition:** Death certificates and licensing boards used to determine cause of death from multiple myeloma (ICD-8: 205). **Design:** Proportionate mortality cohort study with external comparison group. **Analysis:** PMRs calculated using sex, race, age, and calendar-year-expected numbers of deaths from the U.S. population.	**Exposure assessment:** Presumed exposure to formaldehyde tissue fixative. Exposure based on occupation, which was confirmed on death certificate. Authors subsequently measured personal embalming exposures ranging from 0.98 ppm (high ventilation) to 3.99 ppm (low ventilation) with peaks up to 20 ppm. Authors state that major exposures are to formaldehyde and possibly glutaraldehyde and phenol. **Duration and timing:** Occupational exposure preceding death during 1975–1985. Of 115 deaths from LHP cancer, 66 (57%) were aged 60–74 years. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** None evaluated as potential confounders.	**External comparisons:** PMR = 1.37 (0.84–2.12) [20] **Additional:** By Race White PMR = 0.97 (0.50–1.69) [12] Nonwhite PMR = 3.69 (1.59–7.26) [8]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Confidence in effect estimates:[a]  **MEDIUM ↓** **(Potential bias toward the null↓)** **SB:** Missing death certificates considered to missing at random. **IB**: Exposure: Group A; latency not evaluated.	[As noted in Appendix A.5.9: Coexposures may have included: phenol, methyl alcohol, glutaraldehyde, mercury, arsenic, zinc, and ionizing radiation. Chemical coexposures are not known risk factors for this outcome. Radiation exposure likely to be poorly correlated with formaldehyde so confounding is unlikely.]	
Reference: Pira et al. (2014) **Population:** 2,750 workers employed at a laminated plastic factory in Italy for at least 180 days between 1947 and 2011 followed until May 2011. Deaths were identified from population registries. Vital status was 96.9% complete and only 3.1% lost to follow-up. **Outcome definition:** Death certificates used to determine UCOD from multiple myeloma (ICD-9: 203). **Design:** Prospective cohort mortality study with external comparison group. **Analysis:** RRs estimated using Poisson regression stratified by calendar year, age, sex, and race; adjusted for pay category compared to workers in lowest exposed category. Lagged exposures were evaluated to account for cancer latency. SMRs calculated using sex, age, and 5-year calendar periods using mortality rates from the Piedmont region. **Confidence in effect estimates:**[a]  **Low ↓** (Potential bias toward the null, low sensitivity) **SB:** Healthy worker effect possible **IB**: Exposure Group B (Appendix A.5.9) **Oth**: Low power	**Exposure assessment:** Formaldehyde is a byproduct from the resins used in production process and all workers were presumed to have been exposed. **Duration and timing:** Exposure period from 1947 through 2011. Median length of follow-up: 23.6 years. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** Not evaluated	**External comparisons:** Observed: 0 multiple myeloma deaths Expected: 2 multiple myeloma deaths Myeloid Leukemia (ICD-9: 205) SMR = 0 (0–1.50)† [0] †**Note:** EPA derived CIs using the Mid-P Method [See Rothman and Boice (1979)]

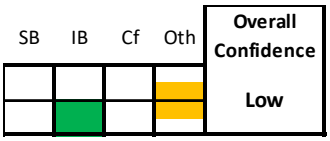
Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Reference: Stellman et al. (1998) **Population:** 317,424 U.S. men enrolled in the American Cancer Society's Cancer Prevention Study II during 1982 with sufficient data on occupation. Cohort mortality followed until August 1988 with 98% complete follow-up. **Outcome definition:** Death certificates used to determine cause of deaths from multiple myeloma (ICD-9: 203). **Design:** Prospective cohort study with internal comparison group. **Analysis:** RR calculated using Poisson regression controlling for sex, age, smoking. **Confidence in effect estimates:**[a]  **LOW ↓** **(Potential bias toward the null↓)** **IB**: Exposure Group C; latency was not evaluated. **Oth**: Low power	**Exposure assessment:** Individual-level exposure ascertained from questionnaire on occupation with specific exposure to formaldehyde based on checkbox. Formaldehyde analyses limited to workers not in wood-related occupations. **Duration and timing:** Occupational exposures prior to 1982. Timing of formaldehyde exposure not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** Wood dust excluded. [As noted in Appendix A.5.9: Coexposures included: asbestos and wood dust. However, these coexposures are not associated with LHP endpoints so confounding is unlikely.]	**Internal comparisons:** RR = 0.74 (0.27–2.02) [4]
Reference: Band et al. (1997) **Population:** 30,157 male workers with at least 1 year of employment accrued by January 1950. Followed through December 1982. Loss to follow-up was less than 6.5% for workers exposed to the sulfate process (67% of original cohort of 30,157) and less than 20% for workers exposed to the sulfite process. **Outcome definition**: Cause of death obtained from the National Mortality Database based on ICD version in effect at time of death and standardize to ICD-9 version; multiple myeloma (ICD-9 203). **Design:** Cohort mortality study with external comparison group. **Analysis:** SMRs calculated using sex, race, age, and calendar-year-expected numbers of deaths from the Canadian population.	**Exposure assessment:** Occupational data limited to hire and termination dates for all workers and type of chemical process of pulping (sulfate vs. sulfite). No job-specific data available. Presumed exposure to formaldehyde known to be used in the plant. Formaldehyde is known to be an exposure for pulp and paper mill workers: job-specific median exposures ranging from 0.04 to 0.4 ppm with peaks as high as 50 ppm (Korhonen et al., 2004). **Duration and timing:** Duration and timinge since first exposure were not evaluated. **Variation in exposure:** No variation in formaldehyde exposure was reported. Results presented by pulping process (sulfate vs. sulfite) but	**External comparisons:** All workers SMR = 0.80 (90% CI 0.48–1.29) [12]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Confidence in effect estimates:[a]  **LOW ↓** **(Potential bias toward the null ↓)** **IB**: Exposure Group C **Cf**: Potential confounding	there is no information on differential exposures between the two processes. **Coexposures:** Not evaluated as confounders. [As noted in Appendix A.5.9: Potential confounders for these outcomes include chlorophenols, acid mists, dioxin, and perchloroethylene and would likely be positively correlated with formaldehyde exposure. Potential for confounding is unknown but could have inflated the observed effect.]	
Reference: Dell and Teta (1995) **Population:** 5,932 men employed at a New Jersey plastics manufacturing plant for at least 7 months during 1946–1967. Cohort mortality followed through 1988. Vital status was 94% complete and only 6% lost to follow-up. Death certificates obtained for 98%. **Outcome definition:** Death certificates used to determine UCOD from multiple myeloma based on ICD code at time of death. **Design:** Cohort mortality study with external comparison group. **Analysis:** SMRs calculated using sex, race, age, and calendar-year-expected numbers of deaths from the U.S. and local populations. **Confidence in effect estimates:**[a]  **LOW (low sensitivity)** **IB**: Exposure Group C **Cf**: Potential confounding **Oth**: Low power due to rarity of exposure	**Exposure assessment:** Presumed exposure to formaldehyde known to be used in the plant. Only 111 men had assignments involving formaldehyde. **Duration and timing:** Exposures during 1946–1967. Duration and timing since first exposure were not evaluated. **Variation in exposure:** By department: Plant Services and Research and Development. By pay status: salaried and hourly. **Coexposures:** Not evaluated as confounders. [As noted in Appendix A.5.9 coexposures include: acrylonitrile, asbestos, benzene, carbon black, epichlorohydrin, PVC (vinyl chloride), styrene, and toluene and would likely be positively correlated with formaldehyde exposure. Asbestos is not associated with LHP cancers. Benzene and styrene were not evaluated as potential confounders and would likely be positively correlated with formaldehyde exposure. Potential for confounding is unknown but could have inflated the observed effect.]	**External comparisons:** All salaried workers SMR = 2.62 (0.85–6.11) [5] Research and Development: Hourly workers SMR = 2.73 (0.55–7.97) [3]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Reference: Pottern et al. (1992) **Population:** Danish women registered in both the National Cancer Registry and pension fund. All women with a specific occupational history other than "homemaker" were included. **Outcome definition:** Incident cases of multiple myeloma reported to the Danish Cancer Registry during 1970–1984. **Design:** Population-based case-control study of 363 women with 1,517 age- and sex-matched controls alive at time of case diagnosis. **Analysis:** ORs calculated for occupation, industry, and likelihood of exposure using logistic regression controlling for age. **Confidence in effect estimates:**[a]  **LOW ↓** **(Potential bias toward the null↓)** **IB**: Exposure Group D; latency not evaluated	**Exposure assessment:** Individual-level exposure estimated by industrial hygienists based on occupation listed on most recent annual income tax documents and the industry associated with that occupation. **Duration and timing:** Exposure period preceding cancer incidence (<1984). Duration and timing since first exposure were not evaluated. **Variation in exposure:** Likelihood of exposure: Level 1 (unexposed) Level 2 (possible) Level 3 (probable) **Coexposures:** Many other compounds were identified and evaluated as independent risk factors. [As noted in Appendix A.5.9: Other exposures evaluated included 19 categories grouping 47 substances. Coexposures were not evaluated for confounding but exposure to organic solvents (including benzene) and radiation were not risk factors for multiple myeloma so confounding is unlikely.]	**Internal comparisons:** Likelihood of exposure Level 1 RR = 1.0 (Ref. value) [303] Level 2 RR = 1.1 (0.8–1.6) [56] Level 3 RR = 1.6 (0.4–5.3) [4]
Reference: Heineman et al. (1992) **Population:** Danish men registered in both the National Cancer Registry and pension fund. All men with a specific occupational history were included. **Outcome definition:** Incident cases of multiple myeloma reported to the Danish Cancer Registry during 1970–1984. 92% of cases were histologically confirmed. **Design:** Population-based case-control study of 1,098 men with 4,169 age- and sex-matched controls alive at time of case diagnosis. **Analysis:** ORs calculated for occupation, industry, and likelihood of exposure using logistic regression controlling for age.	**Exposure assessment:** Individual-level exposure estimated by industrial hygienists based on occupation listed on most recent tax documents. **Duration and timing:** Exposure period preceding cancer incidence (<1984). Duration and timing since first exposure were not evaluated. **Variation in exposure:** Likelihood of exposure: Level 1 (unexposed) Level 2 (possible) Level 3 (probable) **Coexposures:** Other compounds were identified and evaluated as independent risk factors including: gasoline, oil products, engine exhausts,	**Internal comparisons:** Likelihood of exposure Level 1 RR = 1.0 (Ref. value) [913] Level 2 RR = 1.0 (0.8–1.3) [144] Level 3 RR = 1.1 (0.7–1.6) [41]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Confidence in effect estimates:[a]  **LOW ↓** **(Potential bias toward the null↓)** **IB**: Exposure Group D; latency not evaluated	**benzene**, dyes, phthalates, vinyl chloride, **asbestos**, and pesticides. [As noted in Appendix A.5.9: Other exposures evaluated included 19 categories grouping 47 substances. Asbestos is not a risk factor for LHP. "Possible" benzene exposure was associated with MM but not "probable" benzene exposure, so confounding is considered to be unlikely.]	
Reference: Boffetta et al. (1989) **Population:** 508,637 U.S. men and 676,613 women enrolled in the American Cancer Society's Cancer Prevention Study II during 1982 with sufficient data on occupation. Cohort mortality followed until August 1986 with 98.5% complete follow-up. **Outcome definition:** Death certificates used to determine cause of deaths from incident cases of multiple myeloma (ICD-9: 203) since follow-up began. **Design:** Population-based matched nested case-control within prospective cohort study. **Analysis:** RR calculated using Poisson regression controlling for sex, age, smoking, education, diabetes, X-ray treatment, farming, pesticide, and herbicide exposure. **Confidence in effect estimates:**[a]  **LOW ↓** **(Potential bias toward the null↓)** **IB**: Exposure: Group C; lack of latency analysis **Oth**: Low power (few exposed cases)	**Exposure assessment:** Individual-level exposure ascertained from questionnaire on occupation with specific exposure to formaldehyde based on checkbox. **Duration and timing:** Occupational exposures prior to 1982. Timing of formaldehyde exposure not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** Various coexposures were controlled for in the analyses. [As noted in Appendix A.5.9: Matching controlled for sex, age, ethnic group, residence, smoking, education, diabetes, X-ray treatment, farming, pesticide, and herbicide exposure. Other coexposures were not associated with LHP cancers.]	**Internal comparisons:** OR = 1.8 (0.6–5.7) [4]
Reference: Ott et al. (1989) **Population:** 29,139 men employed at two large chemical manufacturing facilities and a research and development center who	**Exposure assessment:** Individual-level exposure ascertained from employee's work assignments linked to records on departmental usage of formaldehyde.	**Internal comparisons:** OR = 1.0 (0.05–4.9) [1]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
worked during 1940–1978. Vital status was known for 96.4%. Death certificates were available for 5,785 known descendants (95.4%). **Outcome definition:** Death certificates used to determine UCOD from multiple myeloma based on the ICD code in used at the time of death. **Design:** Nested case-control study within a prospective cohort mortality study. Twenty cases of multiple myeloma were frequency matched to 100 controls on time from hire to death. **Analysis:** ORs calculated using unconditional logistic regression. **Related studies:** Rinsky et al. (1988) **Confidence in effect estimates:**[a]  **LOW ↓** **(Potential bias toward the null↓)** **IB**: Exposure Group B; latency evaluation likely to be underpowered to detect any effects beyond a 5-year period **Cf**: Benzene is a potential confounder **IB**: Low power due to the rarity of exposure	**Duration and timing:** Occupational exposures during 1940–1978. Timing of formaldehyde exposure not evaluated. **Variation in exposure:** Ever/never **Coexposures:** None evaluated as potential confounders. [As noted in Appendix A.5.9: 21 different chemicals were evaluated including benzene with much cross exposure. Benzene was not evaluated as a potential confounder and may be positively correlated with formaldehyde exposure. Potential for confounding is unknown but could have inflated the observed effect. Potential for confounding may be mitigated by rarity of coexposures among cases.]	†**Note:** EPA derived CIs using the Mid-P Method (See Rothman and Boice, 1979)
Reference: Edling et al. (1987b) **Population:** 521 Swedish male blue collar workers in an abrasive production plant with at least 5 years of employment between 1955 and 1983. Cohort mortality followed through 1983 with 97% known vital status. **Outcome definition:** Cancer mortality ascertained using UCOD from the National Death Registry. Cancer incidence ascertained from the National Cancer Registry. Mortality and incidence of multiple myeloma based on ICD-8:203. **Design:** Cohort mortality and incidence study with external comparison group.	**Exposure assessment:** Manufacture of grinding wheels bound by formaldehyde resins exposed workers to 0.1–1 mg/m^3 formaldehyde; 59 workers manufacturing abrasive belts had low exposure to abrasives with intermittent exposures with peaks up to 20–30 mg/m^3 formaldehyde. **Duration and timing:** Exposures during 1955–1983. Duration and timing since first exposure were evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** Aluminum oxide and silicon carbide were coexposures but were not evaluated as confounders.	**External comparisons:** Cancer mortality No increase reported Cancer Incidence SMR = 4.0 (0.67–13.2)† [2] †**Note:** EPA derived CIs using the Mid-P Method (See Rothman and Boice, 1979)

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Analysis: SMRs calculated using sex, age, and calendar-year-specific Swedish mortality rates. **Confidence in effect estimates:**[a]  **LOW ↓** **(Potential bias toward the null↓)** **IB**: Exposure: Group B; latency not evaluated **Oth**: Low power	[As noted in Appendix A.5.9: Coexposures are not known risk factors for this outcomes.]	

[a]Evaluation of sources of bias or study limitations (see details in Appendix A.5.9). SB = selection bias; IB = information bias; Cf = confounding; Oth = other feature of design or analysis. Extent of column shading reflects degree of limitation. Direction of anticipated bias indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact would be likely to be away from the null (i.e., spurious or inflated effect estimate).

Results from *low* confidence studies are shaded; these findings are considered less reliable.

Abbreviations: SB = selection bias; IB = information bias; Cf = confounding; Oth = other feature of design or analysis; UCOD = underlying cause of death; GSD = geometric standard deviation; SMR = standardized mortality ratio; RR = relative risk; TWA8 = 8-hour time-weighted average; URT = upper respiratory tract; LHP = lymphohematopoietic; PMR = proportionate mortality ratio; BMI = body mass index; JEM = job-exposure matrix; OR = odds ratio.

Hodgkin lymphoma

Epidemiological evidence

The most specific level of Hodgkin lymphoma diagnosis that is commonly reported across the epidemiological literature has been based on the first three digits of the Eighth or Ninth Revision of the ICD code (i.e., Hodgkin disease ICD-8/9: 201). Evidence describing the association between formaldehyde exposure and the specific risk of Hodgkin lymphoma was available from 15 epidemiological studies—one case-control study (Gérin et al., 1989) and 14 cohort studies (Meyers et al., 2013; Beane Freeman et al., 2009; Coggon et al., 2003; Band et al., 1997; Andjelkovich et al., 1995; Hansen and Olsen, 1995; Hall et al., 1991; Hayes et al., 1990; Matanoski, 1989; Solet et al., 1989; Robinson et al., 1987; Stroup et al., 1986; Walrath and Fraumeni, 1984, 1983). Study details are provided in the evidence table for Hodgkin lymphoma (see Table 1-63). The outcome-specific evaluations of confidence in the reported effect estimate of an association from each study are provided in Appendix A.5.9 and the confidence conclusions are provided in the evidence table for Hodgkin lymphoma (see Table 1-63) following the causal evaluation.

Note that the confidence judgments are for the confidence in the reported effect estimate of an association from each study and not a confidence judgment in the overall study. Three sets of

reported results from Hall et al. (1991), Solet et al. (1989), and Matanoski (1989) were classified as uninformative due to multiple biases and uncertainties; for details see Appendix A.5.9.

Consistency of the observed association

The results of the 12 informative studies were not consistent. The study of the largest cohort of formaldehyde-exposed workers (Beane Freeman et al., 2009) reported an elevated risk of dying from Hodgkin lymphoma for the cohort as a whole (SMR = 1.42; 95% CI 0.96–2.1; 27 cases) and a pronounced increase in risk among those workers with the highest peak formaldehyde exposures (RR = 3.96; 95% CI; 1.31–12.02; 11 cases)—results that were classified with *medium* confidence. However, the other *medium* confidence result from Gérin et al. (1989) was an OR = 0.5 (95% CI 0.2–1.2; 8 cases). The results of the other 10 studies (all *low* confidence) were largely based on small numbers of cases and yielded generally unstable CIs surrounding the RR (see Figure 1-42).

Compared with other LHP cancers, the 5-year survival rate for Hodgkin lymphoma is relatively high at 86% and mortality is rare. In contrast, the survival rate for myeloid leukemia is 38%. The high survival rate for Hodgkin lymphoma may indicate that mortality data are not as good a proxy for incidence data for this LHP cancer subtype. In this instance, these mortality data are potentially inadequate to evaluate causation. The low mortality rate for Hodgkin lymphoma results in few exposed cases and very low statistical power, which may have contributed to the apparently discordant results. Aside from the Beane Freeman et al. (2009) result (*medium* confidence), which reported 25 exposed deaths from Hodgkin lymphoma, only one other cohort study observed more than 10 deaths from Hodgkin lymphoma among exposed subjects (Hansen and Olsen, 1995); this study reported 12 observed deaths against 12 expected deaths—a result classified with *low* confidence.

The study results presented in Table 1-63 (by confidence level and publication date) detail all of the reported associations between exposures to formaldehyde and the risks of developing or dying from Hodgkin lymphoma along with a summary graphic of any major limitation and the confidence classification of the effect estimate. Results are plotted in Figure 1-42.

Strength of the observed association

Summary effect estimates for the association between formaldehyde exposure and Hodgkin lymphoma were highly variable and the risk of developing or dying from Hodgkin lymphoma were predominantly less than one (unity) and ranged from zero to 4.0 (Edling et al., 1987b). While the summary effect estimate from the study by Beane Freeman et al. (2009) was RR = 1.42 (95% CI 0.96–2.10), the strength of the association was substantially higher among those workers exposed to the highest peak levels (RR = 3.96). Beane Freeman et al. (2009) further showed plots presenting the RR from the internal analyses for each endpoint and for each year of follow-up. The association of Hodgkin lymphoma with formaldehyde exposure is not only seen for the complete 2004 follow-up when the average length of follow-up was 42 years, but throughout the cohort

experience (see Beane Freeman et al., 2009) (Figure 1). These plots show that during the 1970s and 1980s, the RR ≈ 8 and remained elevated at about RR = 4 through the end of follow-up in 2004. Such a consistent finding of a strong effect over many years of follow-up reduces the possibility that the results for the full follow-up period could be due to chance.

Temporal relationship of the observed association

In each of the studies, the formaldehyde exposures among the study participants occurred before their Hodgkin lymphoma was detected and in the studies that ascertained individual-level exposures, the estimation of formaldehyde exposures was based on job titles and was done in a blinded fashion with respect to outcome status. Only one study (Band et al., 1997) reported on analyses of the temporal relationship showing that risks were highest in workers with 15 or more years since first formaldehyde exposure and 15 or more years of exposure duration (SMR = 1.62; 95% CI 0.55–3.71). However, this finding is without corroboration for Hodgkin lymphoma.

Exposure-response relationship

Only two studies evaluated any other form of exposure-response for increasing measures of formaldehyde exposure (Beane Freeman et al., 2009; Coggon et al., 2003). Coggon et al. (2003) reported a lower risk of dying from Hodgkin lymphoma among "highly" exposed workers based on a single death. Beane Freeman et al. (2009) reported a clear exposure-response relationship between increasing levels of peak formaldehyde and increased risk of dying from Hodgkin lymphoma among exposed workers (p = 0.01). Compared to exposed workers in the lowest exposure category of peak exposure, those in the middle category were at more than two-fold higher risk (RR = 3.30; 95% CI 1.04–10.50) while those workers in the highest category were at four-fold higher risk (RR = 3.96; 95% CI 1.31–12.02). Beane Freeman et al. (2009) also reported exposure-response relationships between increased risk of dying from Hodgkin lymphoma among exposed workers based on average formaldehyde intensity (OR range: 1.61–2.48; p = 0.05) and cumulative exposure (OR range: 1.30–1.71; p = 0.08).

Potential impact of selection bias, information bias, confounding bias, and chance

Selection bias is an unlikely bias in the epidemiological studies of Hodgkin lymphoma as the one case-control study was population-based and used other cancer cases as controls with exposure status evaluated without regard to outcome status and had a participation level of 83%. Each of the cohort studies included at least 72% of eligible participants and lost fewer than 9% of participants over the course of mortality follow-up.

The healthy worker effect including the healthy worker survivor effect could obscure a truly larger effect of formaldehyde exposure in analyses based on "external" comparisons with mortality in the general population (Meyers et al., 2013; Beane Freeman et al., 2009; Coggon et al., 2003; Band et al., 1997; Andjelkovich et al., 1995; Hansen and Olsen, 1995; Hayes et al., 1990; Robinson et

al., 1987; Stroup et al., 1986; Walrath and Fraumeni, 1984, 1983), but would not influence analyses using "internal" or matched comparison groups (Beane Freeman et al., 2009; Gérin et al., 1989).

Information bias is unlikely to have resulted in bias away from the null—especially as the exposure assessment in these studies were generally of high quality; however, random measurement error or nondifferential misclassification is almost certain to have resulted in some bias toward the null among these studies of Hodgkin lymphoma.

Chemical exposures that have not been independently associated with Hodgkin lymphoma are not expected to confound results. The main support for concluding there is a slight association of formaldehyde exposure with increased risk of Hodgkin lymphoma is from the results for peak exposures reported by Beane Freeman et al. (2009) who specifically examined the potential for confounding from 11 substances including benzene and found that controlling for these exposures did not meaningfully change the results. This provides evidence against potential confounding by these coexposures. There does not appear to be any evidence of confounding that would provide an alternative explanation for the observed association of formaldehyde exposure with increased risk of Hodgkin lymphoma reported by Beane Freeman et al. (2009). The evidence of an association with peak exposures reported by Beane Freeman et al. (2009) suggests an association whose risk increases with greater exposure.

Causal evaluation

The causal evaluation for formaldehyde exposure and the risk of developing or dying from Hodgkin lymphoma placed the greatest weight on the following particular considerations: (1) the statistically robust evidence of increased risk of Hodgkin lymphoma in the highest peak exposure group among industrial workers, with a clear exposure-response relationship observed in one medium confidence study; (2) the consistent pattern of null results across 10 other studies, many of which had fewer than five exposed cases; (3) the high survival rate for Hodgkin lymphomas (86%), which may indicate that mortality data are not as good a proxy for incidence data for this LHP cancer subtype; and (4) the absence of evidence to evaluate the potential risk to sensitive populations or lifestages. Although consistent observations of genotoxicity in peripheral blood lymphocytes have been observed across several occupational studies, these data were not interpreted as sufficient to further strengthen the judgment on the human evidence of Hodgkin lymphoma.

Conclusion

- The available epidemiological studies provide *slight* evidence of an association consistent with causation between formaldehyde exposure and an increased risk of Hodgkin lymphoma.

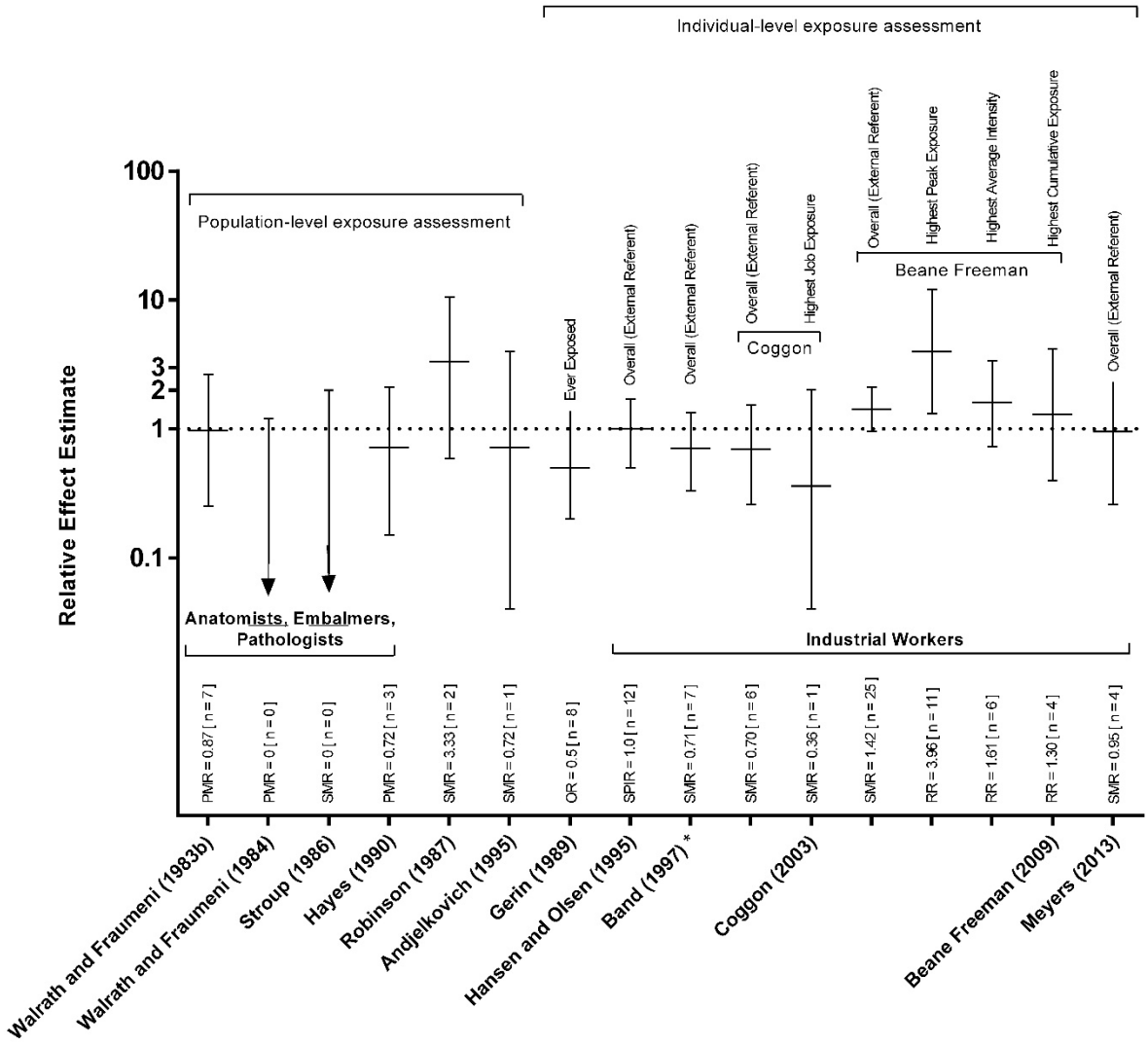


Figure 1-42. Epidemiological studies reporting multiple Hodgkin lymphoma estimates.

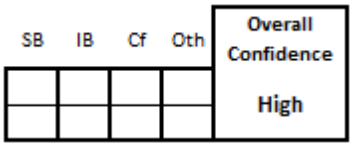
SMR = standardized mortality ratio; PMR = proportionate mortality ratio; RR = relative risk; OR = odds ratio. For each measure of association, the number of exposed cases is provided in brackets (e.g., [*n* = 7]). For studies reporting results on multiple metrics of exposure, each metric is included; however, only the highest category of each exposure metric is presented in the figure. *Note that the CIs for Band et al. (1997) are 90% rather than 95%.

1

Table 1-63. Epidemiological studies of formaldehyde exposure and risk of Hodgkin lymphoma

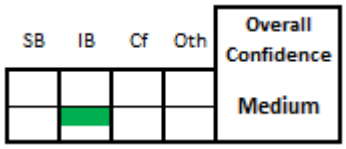
Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Reference: Beane Freeman et al. (2009) with supplemental online tables	**Exposure assessment:** Individual-level exposure estimates based on job titles,	**Internal comparisons:** Peak exposure

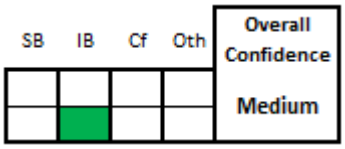
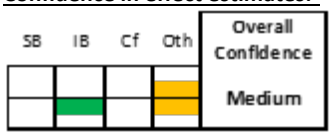
Study	Exposures	Results: effect estimate (95% CI) [# of cases]

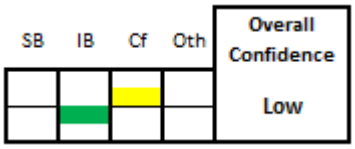
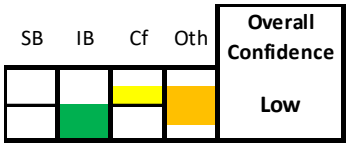
Population: 25,619 workers employed at 10 formaldehyde-using or formaldehyde-producing plants in the U.S. followed from either the plant start-up or first employment through 2004. Deaths were identified from the National Death Index with remainder assumed to be living. Vital status was 97.4% complete and only 2.6% lost to follow-up.
 	
Outcome definition: Death certificates used to determine underlying cause of death from Hodgkin disease (ICD-8: 201).
 	
Design: Prospective cohort mortality study with external and internal comparison groups.
 	
Analysis: RRs estimated using Poisson regression stratified by calendar year, age, sex, and race; adjusted for pay category compared to workers in lowest exposed category. Lagged exposures were evaluated to account for cancer latency.
 	
SMRs calculated using sex, age, race, and calendar-year-specific U.S. mortality rates.
 	
Related studies:
Blair et al. (1986)
Hauptmann et al. (2003)
 	
Confidence in effect estimates:[a]
 
 	
HIGH ● (No appreciable bias)
IB: Exposure Group A; higher survival rates
	tasks, visits to plants by study industrial hygienists, and monitoring data from 1966 through 1980.
	
	Median TWA (over 8 hours) = 0.3 ppm (range 0.01–4.3).
	
	Median cumulative exposure = 0.6 ppm-years (range 0–107.4).
	
	Multiple exposure metrics including peak, average, and cumulative exposures were evaluated using categorical and continuous data.
	
	Duration and timing: Exposure period from <1946 through 1980. Median length of follow-up: 42 years. Duration and timing since first exposure were evaluated.
	
	Variation in exposure:
	For all variations in exposure:
	Level 1 (unexposed)
	
	Peak exposure:
	Level 2 (>0 to <2.0 ppm)
	Level 3 (2.0 to <4.0 ppm)
	Level 4 (≥4.0 ppm)
	Average intensity:
	Level 2 (>0 to <0.5 ppm)
	Level 3 (0.5 to <1.0 ppm)
	Level 4 (≥1.0 ppm)
	Cumulative exposure:
	Level 2 (>0 to <1.5 ppm-yrs)
	Level 3 (1.5 to <5.5 ppm-yrs)
	Level 4 (≥5.5 ppm-yrs)
	
	Coexposures: Exposures to 11 other compounds were identified and evaluated as potential confounders and found not be confounders.
	
	[As noted in Appendix A.5.9: There was no information on smoking, however, according to Blair et al. (1986), "The lack of a consistent elevation for tobacco-related causes of death, however, suggests that the smoking habits among this cohort did not differ substantially from those of the general population."]
		1994 Follow-up:
		Highest peak RR = 3.30 (0.98–11.10)
		(*p*-trend = 0.04)
		2004 Follow-up:
		Peak exposure
		Level 1 RR = 0.67 (0.12–3.6) [2]
		Level 2 RR = 1.00 (Ref. value) [6]
		Level 3 RR = 3.30 (1.04–10.50) [8]
		Level 4 RR = 3.96 (1.31–12.02) [11]
		p-trend (exposed) = 0.01;
		p-trend (all) = 0.004
		
		Average intensity
		Level 1 RR = 0.53 (0.11–2.66) [2]
		Level 2 RR = 1.00 (Ref. value) [10]
		Level 3 RR = 2.48 (0.84–7.32) [9]
		Level 4 RR = 1.61 (0.73–3.39) [6]
		p-trend (exposed) = 0.05;
		p-trend (all) = 0.03
		
		Cumulative exposure
		Level 1 RR = 0.42 (0.09–2.05) [2]
		Level 2 RR = 1.00 (Ref. value) [14]
		Level 3 RR = 1.71 (0.66–4.38) [7]
		Level 4 RR = 1.30 (0.40–4.19) [4]
		p-trend (exposed) = 0.08;
		p-trend (all) = 0.06
		
		Duration of exposure
		No evidence of association (data not shown).
		
		Time since first exposure
		>0–15 yrs RR = 1.00 (Ref. value)
		>15–25 yrs RR = 1.54 (0.42–5.62)
		>25–35 yrs RR < 1.54
		>35 yrs RR < 1.54
		
		External comparisons:
		$SMR_{Unexposed}$ = 0.70 (0.17–2.80) [2]
		$SMR_{Exposed}$ = 1.42 (0.96–2.10) [25]

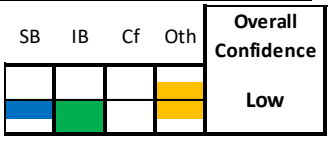
Reference: Gérin et al. (1989) **Population:** Male residents of Montreal, Canada aged 35–70 years. 4,510 eligible	**Exposure assessment:** Individual-level exposure estimates developed based on a complete and detailed occupational history ascertained by interviewers using a standardized questionnaire. A team of	**Internal comparisons:** Compared to other cancers OR = 0.5 (0.2–1.2) [8] Compared to population controls

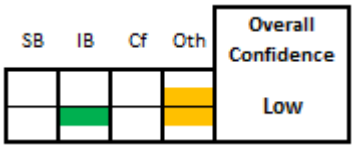
Study	Exposures	Results: effect estimate (95% CI) [# of cases]
incident cancer cases were identified during 1979–1985 from 19 major area hospitals, which report to the Quebec Tumor Registry over 97% of all cancer diagnoses from the Montreal area. Interviews and questionnaires completed for 3,726 subjects (83% of eligible cases). 18% of interviews were completed by next of kin. **Outcome definition:** Histologically confirmed diagnosis of Hodgkin lymphoma (ICD: 201) **Design:** Population-based case-control study of 53 formaldehyde-exposed men with Hodgkin lymphoma. Cases were compared with two groups; first, against other cancer cases excluding those diagnosed with lung cancer (*n* = 2,599), and second against 533 male population controls selected from electoral list in the Montreal area. **Analysis:** ORs calculated by levels of a composite exposure index using logistic regression controlling for age, ethnic group, socio-economic status, smoking, and dirtiness of jobs held (white vs. blue collar). **Related studies:** Siemiatycki et al. (1987) **Confidence in effect estimates:**[a] SB IB Cf Oth | Overall Confidence: Medium **MEDIUM ↓** **(Potential bias toward the null↓)** **IB**: Exposure Group B	chemists and hygienists translated each job into a list of potential formaldehyde exposures based on their confidence level, the frequency of exposure, and the duration of exposure. **Duration and timing:** Exposure period based on occupational histories prior to cancer diagnosis. Duration of exposure was evaluated. **Variation in exposure:** For cancer sites with fewer than 30 cases exposed to formaldehyde, results for the exposure subgroups were not shown. **Coexposures:** Additional occupational and nonoccupational potential confounders were included in analyses when the estimated exposure-disease OR changed by more than 10%.	OR = 0.5 (0.2–1.4) [8]
Reference: Meyers et al. (2013) **Population:** 11,043 workers in three U.S. garment plants exposed for at least 3 months. Women comprised 82% of the cohort. Vital status was followed through 2008 with 99.7% completion **Outcome definition:** Death certificates used to determine both the underlying	**Exposure assessment:** Individual-level exposure estimates for 549 randomly selected workers during 1981 and 1984. Geometric TWA8 exposures ranged from 0.09 to 0.20 ppm. Overall geometric mean concentration of formaldehyde was 0.15 ppm (GSD 1.90 ppm). Area measures showed constant levels without peaks. Historically earlier exposures may have been substantially higher.	**External comparisons:** SMR = 0.95 (0.26–2.44) [4]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
cause of death from Hodgkin lymphoma (ICD code in use at time of death). **Design:** Prospective cohort mortality study with external and internal comparison groups. **Analysis:** SMRs calculated using sex, age, race, and calendar-year-specific U.S. mortality rates. **Related studies:** Stayner et al. (1985) Stayner et al. (1988) Pinkerton et al. (2004) **Confidence in effect estimates:**[a]  **MEDIUM ↓** **(Potential bias toward the null)** **IB**: Exposure Group A; latency not evaluated. **Oth**: Low power	**Duration and timing:** Exposure period from 1955 through 1983. Median duration of exposure was 3.3 years. More than 40% exposures <1963. Median time since first exposure was 39.4 years. Duration and timing since first exposure were evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** Study population specifically selected because industrial hygiene surveys at the plants did not identify any chemical exposures other than formaldehyde that were likely to influence findings.	
Reference: Coggon et al. (2003) **Population:** 14,014 British men employed in six chemical industry factories that produced formaldehyde. Cohort mortality followed from 1941 through 2000. Vital status was 98.9% complete and only 1.1% lost to follow-up. **Outcome definition:** Death certificates used to determine cause of deaths from Hodgkin disease (ICD-9: 201). **Design:** Cohort mortality study with external comparison group. **Analysis:** SMRs based on English and Welsh age- and calendar-year-specific mortality rates. **Related studies:** Acheson et al. (1984) Gardner et al. (1993) Coggon et al. (2014)	**Exposure assessment:** Exposure assessment based on data abstracted from company records. Jobs categorized as background, low, moderate, high, or unknown levels. **Duration and timing:** Occupational exposure during 1941–1982. Duration and timing since first exposure were not evaluated. **Variation in exposure:** TWA exposure Level 1 (low) Level 2 (moderate) Level 3 (high) **Coexposures:** Not evaluated as potential confounders. Potential low-level exposure to styrene, ethylene oxide, epichlorhydrin, solvents, asbestos, chromium salts, and cadmium. [As noted in Appendix A.5.9: Styrene is associated with LHP cancers. **Asbestos** is associated with URT cancers, but not with LHP cancers.	**External comparisons:** SMR = 0.70 (0.26–1.53) [6] **Within-study external comparisons:** Worked in high exposure jobs SMR = 0.36 (0.01–2.01) [1]

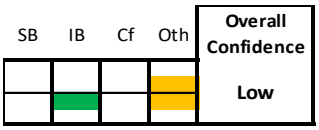
Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Confidence in effect estimates:[a]  **MEDIUM ↓** **(Potential bias toward the null↓)** **IB**: Exposure Group B; latency was not evaluated **Cf:** Potential confounding	Other coexposures are not known risk factors for this outcome. Authors stated that the extent of coexposures was expected to be low. Potential for confounding may be mitigated by low coexposures.]	
Reference: Walrath and Fraumeni (1983) **Population:** 1,132 deceased white male embalmers licensed to practice during 1902–1980 in New York who died during 1925–1980 identified from registration files. Death certificates obtained for 75% of potential study subjects (*n* = 1,678). **Outcome definition:** Hodgkin disease (ICD-8: 201) listed as cause of death on death certificates. **Design:** Proportionate mortality cohort study with external comparison group. **Analysis:** PMRs calculated using sex, race, age, and calendar-year-expected numbers of deaths from the U.S. population. **Confidence in effect estimates:**[a]  **MEDIUM ↓** **(Potential bias toward the null↓)** **IB**: Exposure Group A; latency not evaluated	**Exposure assessment:** Presumed exposure to formaldehyde tissue fixative. **Duration and timing:** Occupational exposure preceding death during 1902–1980. Median year of birth was 1901. Median year of initial license was 1931. Median age at death was 1968. Expected median duration of exposure was 37 years. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** None evaluated as potential confounders. [As noted in Appendix A.5.9: Coexposures may have included: phenol, methyl alcohol, glutaraldehyde, mercury, arsenic, zinc, and ionizing radiation. Radiation exposure likely to be poorly correlated with formaldehyde so confounding is unlikely.]	**External comparisons:** Observed: 2 Hodgkin disease deaths Expected: 2.3 Hodgkin disease deaths PMR = 0.87 (0.15–2.87)† [7] †**Note:** EPA derived CIs using the Mid-P Method (See Rothman and Boice, 1979)
Reference: Band et al. (1997) **Population:** 30,157 male workers with at least 1 year of employment accrued by January 1950. Followed through December 1982. Loss to follow-up was less than 6.5% for workers exposed to the sulfate process (67% of original cohort of 30,157) and less than 20% for workers exposed to the sulfite process. **Outcome definition**: Cause of death obtained from the National Mortality	**Exposure assessment:** Occupational data limited to hire and termination dates for all workers and type of chemical process of pulping (sulfate vs. sulfite). No job-specific data available. Presumed exposure to formaldehyde known to be used in the plant. Formaldehyde is known to be an exposure for pulp and paper mill workers: job-specific median exposures ranging from 0.04 to 0.4 ppm with peaks as high as 50 ppm (Korhonen et al., 2004)	**External comparisons:** All workers SMR = 0.71 (90% CI 0.33–1.34) [7] Work duration <15 years TSFE < 15 years SMR = 0.53 (90% CI 0.14–1.37) [3] Work duration ≥15 years TSFE ≥ 15 years SMR = 1.62 (90% CI 0.55–3.71) [4]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Database based on ICD version in effect at time of death and standardize to ICD-9 version. Hodgkin lymphoma: ICD-9 201 **Design:** Cohort mortality study with external comparison group. **Analysis:** SMRs calculated using sex, race, age, and calendar-year-expected numbers of deaths from the Canadian population. **Confidence in effect estimates:**[a]  **LOW ↓** **(Potential bias toward the null↓)** **IB**: Exposure Group C **Cf**: Potential confounding	**Duration and timing:** Duration and timing since first exposure were evaluated. **Variation in exposure:** No variation in formaldehyde exposure was reported. Results presented by pulping process (sulfate vs. sulfite) but there is no information on differential exposures between the two processes **Coexposures:** Not evaluated as confounders. [As noted in Appendix A.5.9: Potential confounders for these outcomes include chlorophenols, acid mists, dioxin, and perchloroethylene and would likely be positively correlated with formaldehyde exposure. Potential for confounding is unknown but could have inflated the observed effect.]	
Reference: Andjelkovich et al. (1995) **Population:** 3,929 automotive industry iron foundry workers exposed from 1960 through 1987 and followed through 1989. **Outcome definition**: UCOD obtained from Social Security Administration, Pension Benefit Informations, and National Death Index) Hodgkin lymphoma: ICD 201 **Design:** Cohort mortality study with external comparison group. **Analysis:** SMRs calculated using sex-, age-, race-, and calendar-year-specific U.S. mortality rates. **Confidence in effect estimates:**[a]  **LOW ↓** **(Potential bias toward the null↓)** **IB**: Exposure Group B; latency not evaluated **Oth**: Low power.	**Exposure assessment**: Individual-level exposure status (yes/no, quartile) based on review of work histories by an industrial hygienist. Exposure assessment blinded to outcome. Independent testing of iron foundries by NIOSH reported a range from 0.02 ppm to 18.3 ppm (cited in WHO (1989) Env. Health Criteria 89: Formaldehyde). **Duration and timing:** Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** Not evaluated. [As noted in Appendix A.5.9: Nickel and **chromium** are associated with URT but not LHP. Other coexposures are not known risk factors for these outcomes.]	**External comparisons:** $SMR_{Unexposed}$ = 0.70 (0.01–3.88) [1] $SMR_{Exposed}$ = 0.72 (0.01–4.00) [1]
Reference: Hansen and Olsen (1995)	**Exposure assessment:** Individual occupational histories including industry	**External comparisons:**

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Population: 2,041 men with cancer who were diagnosed during 1970–1984 and whose longest work experience occurred at least 10 years before cancer diagnosis. Identified from the Danish Cancer Registry and matched with the Danish Supplementary Pension Fund. Ascertainment considered complete. Pension record available for 72% of cancer cases. **Outcome definition:** Hodgkin disease (ICD-7: 201) listed on Danish Cancer Registry file. **Design:** Proportionate incidence study with external comparison group. **Analysis:** Standardized proportionate incidence ratio calculated as the proportion of cases for a given cancer in formaldehyde-associated companies relative to the proportion of cases for the same cancer among all employees in Denmark. Adjusted for age and calendar time. **Confidence in effect estimates:**[a]  **LOW** ↓ (Potential bias toward the null) **IB**: Exposure Group D	and job title established through company tax records to the national Danish Product Register. Subjects were considered to be exposed to formaldehyde if: (1) they had worked in an industry known to use more than 1 kg formaldehyde per employee per year and (2) subjects longest single work experience (job) in that industry since 1964 was ≥10 years prior to cancer diagnosis. All subjects were stratified based on job title as either low exposure (white collar worker), above background exposure (blue collar worker), or unknown (job title unavailable). **Duration and timing:** Exposure period not stated. Based on date of diagnosis during 1970–1984, and the requirement of exposure more than 10 years prior to diagnosis, the approximate period was 1960–1974. **Variation in exposure:** Not evaluated. **Coexposures:** Not evaluated. [As noted in Appendix A.5.9: While other coexposures were not evaluated, the overall correlation between coexposures in multiple occupational industries is likely to be low.]	Overall (exposure to formaldehyde ≥10 years prior to cancer diagnosis) SPIR = 1.0 (0.5–1.7) [12]
Reference: Hayes et al. (1990) **Population:** 4,046 deceased U.S. male embalmers and funeral directors, derived from licensing boards and funeral director associations in 32 states and the District of Columbia who died during 1975–1985. Death certificates obtained for 79% of potential study subjects (*n* = 6,651) with vital status unknown for 21%. **Outcome definition:** Death certificates and licensing boards used to determine cause of death from Hodgkin disease (ICD-8: 201). **Design:** Proportionate mortality cohort study with external comparison group.	**Exposure assessment:** Presumed exposure to formaldehyde tissue fixative. Exposure based on occupation, which was confirmed on death certificate. Authors subsequently measured personal embalming exposures ranging from 0.98 ppm (high ventilation) to 3.99 ppm (low ventilation) with peaks up to 20 ppm. Authors state that major exposures are to formaldehyde and possibly glutaraldehyde and phenol. **Duration and timing:** Occupational exposure preceding death during 1975–1985. Of 115 deaths from LHP cancer, 66 (57%) were aged 60–74 years. Duration and timing since first exposure were not evaluated.	**External comparisons:** PMR = 0.72 (0.15–2.10) [3]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Analysis: PMRs calculated using sex, race, age, and calendar-year-expected deaths from the U.S. population. **Confidence in effect estimates:**[a]  **LOW ↓** **(Potential bias toward the null↓)** **SB:** Missing death certificates considered to be missing at random **IB**: Exposure: Group A; latency not evaluated **Oth**: Low power	**Variation in exposure:** Not evaluated. **Coexposures:** None evaluated as potential confounders. [As noted in Appendix A.5.9: Coexposures may have included: phenol, methyl alcohol, glutaraldehyde, mercury, arsenic, zinc, and ionizing radiation. Chemical coexposures are not known risk factors for this outcome. Radiation exposure likely to be poorly correlated with formaldehyde so confounding is unlikely.]	
Reference: Robinson et al. (1987) **Population:** 2,283 plywood mill workers employed at least one year during 1945–1955 followed for mortality until 1977 with vital status for 98% and death certificates for 97% of deceased. **Outcome definition:** Death certificates used to determine UCOD from Hodgkin disease as coded by trained nosologist using ICD-7:201. **Design:** Prospective cohort mortality study with external comparison group. A subcohort of 818 men coexposed to formaldehyde and pentachlorophenol were also evaluated. **Analysis:** SMRs calculated using sex, age, race, and calendar-year-specific U.S. mortality rates. **Confidence in effect estimates:**[a]  **LOW ↓** **(Potential bias toward the null↓)** **SB:** Healthy worker effect possible **IB**: Exposure Group D; latency not evaluated **Oth**: Low power	**Exposure assessment:** Presumed exposure to formaldehyde-based glues used to manufacture and patch plywood. Subcohort of 818 men coexposed to formaldehyde and pentachlorophenol worked for one year or more in the relevant exposure categories of veneer pressing and drying, glue mixing, veneer and panel gluing and patching. **Duration and timing:** Exposures during 1945–1955. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Duration of exposure Latency (time since first exposure) **Coexposures:** Pentachlorophenol [As noted in Appendix A.5.9: EPA concluded that pentachlorophenol is likely to be carcinogenic based on strong evidence from epidemiological studies of increased risk of multiple myeloma. Pentachlorophenol is not a known risk factor for Hodgkin lymphoma and thus is not expected to be a confounder.]	**External comparisons:** Whole cohort of mill workers (*n* = 2,283) SMR = 1.11(0.20–3.50) [2] Subcohort of highly exposed workers (*n* = 818) SMR = 3.33(0.59–10.49) [2]
Reference: Stroup et al. (1986)	**Exposure assessment:** Presumed exposure to formaldehyde tissue fixative.	**External comparisons:** SMR = 0 (0–2.0) [0]

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
Population: 2,239 white male members of the American Association of Anatomists from 1888 through 1969 who died during 1925−1979. Death certificates obtained for 91% with 9% lost to follow-up. **Outcome definition:** Hodgkin disease (ICD-8: 201) listed as cause of death on death certificates. **Design:** Cohort mortality study with external comparison group. **Analysis:** SMRs calculated using sex, race, age, and calendar-year-expected number of deaths from the U.S. population. **Confidence in effect estimates:**[a]  **LOW ↓** **(Potential bias toward the null↓)** **SB:** Health worker effect **IB**: Exposure Group A; latency not evaluated **Cf**: Potential confounding **Oth:** Low power	**Duration and timing:** Occupational exposure preceding death during 1925–1979. Median birth year was 1912. By 1979, 33% of anatomists had died. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** None evaluated as potential confounders. [As noted in Appendix A.5.9: Coexposures may have included: phenol, methyl alcohol, glutaraldehyde, mercury, arsenic, zinc, and ionizing radiation. Radiation exposure likely to be poorly correlated with formaldehyde so confounding is unlikely. Anatomists may also be coexposed to stains, benzene, toluene xylene, chlorinated hydrocarbons, dioxane, and osmium tetroxide. Benzene was not evaluated as a potential confounder and may be positively correlated with formaldehyde exposure. Potential for confounding is unknown but could have inflated the observed effect.]	
Reference: Walrath and Fraumeni (1984) **Population:** 1,007 deceased white male embalmers from the California Bureau of Funeral Directing and Embalming who died during 1925–1980. Death certificates obtained for all. **Outcome definition:** Hodgkin disease (ICD-8: 201) listed as cause of death on death certificates. **Design:** Proportionate mortality cohort study with external comparison group. **Analysis:** PMRs calculated using sex, race, age, and calendar-year-expected number of deaths from the U.S. population. **Confidence in effect estimates:**[a]	**Exposure assessment:** Presumed exposure to formaldehyde tissue fixative. **Duration and timing:** Occupational exposure preceding death during 1916–1978. Birth year ranged from 1847 through 1959. Median age of death was 62 years. Most deaths were among embalmers with active licenses. Duration and timing since first exposure were not evaluated. **Variation in exposure:** Not evaluated. **Coexposures:** None evaluated as potential confounders. [As noted in Appendix A.5.9: Coexposures may have included: phenol, methyl alcohol, glutaraldehyde, mercury, arsenic, zinc, and ionizing radiation.	**External comparisons:** Observed: 0 Hodgkin disease deaths Expected: 2.5 Hodgkin disease deaths PMR= 0 (0–1.20)† [0] †**Note:** EPA derived CIs using the Mid-P Method (See Rothman and Boice, 1979)

Study	Exposures	Results: effect estimate (95% CI) [# of cases]
 **LOW ↓** **(Potential bias toward the null↓)** **IB**: Exposure Group A; latency not evaluated **Oth**: Low power	Radiation exposure likely to be poorly correlated with formaldehyde so confounding is unlikely.]	

[a]Evaluation of sources of bias or study limitations (see details in Appendix A.5.9). SB = selection bias; IB = information bias; Cf = confounding; Oth = other feature of design or analysis. Extent of column shading reflects degree of limitation. Direction of anticipated bias indicated by arrows: "↓" for overall confidence indicates anticipated impact would be likely to be toward the null (i.e., attenuated effect estimate); "↑" for overall confidence indicates anticipated impact would be likely to be away from the null (i.e., spurious or inflated effect estimate).

Abbreviations: SB = selection bias; IB = information bias; Cf = confounding; Oth = other feature of design or analysis; UCOD = underlying cause of death; GSD = geometric standard deviation; SMR = standardized mortality ratio; RR = relative risk; TWA8 = 8-hour time-weighted average; URT = upper respiratory tract; LHP = lymphohematopoietic; PMR = proportionate mortality ratio; OR = odds ratio; SPIR = standardized proportional incidence ratio.

Lymphohematopoietic cancers in animals

Few animal bioassays have adequately evaluated the carcinogenic potential of inhaled formaldehyde with respect to LHP malignancies. The majority of formaldehyde exposure studies in animals focused primarily on the respiratory tract and did not provide routine examination of other tissues, limiting the detection of leukemia and lymphoma. The study conducted by Battelle-Columbus Laboratories for CIIT (Battelle, 1982) is currently the only chronic duration inhalation study to report detailed information on formaldehyde-induced leukemia or lymphoma in rodents (results not published). Given the paucity of available information and difficulties interpreting the Battelle (Battelle, 1982) results, the evidence available from animal studies is considered *indeterminate* for drawing conclusions as to whether or not formaldehyde exposure might cause leukemia or lymphoma.

Methodological issues considered in evaluation of studies

Given the assumed differential distribution of inhaled formaldehyde as compared to exposure by other routes, only inhalation studies were considered relevant to discussions of LHP cancers in animals. Detailed study evaluation tables of the four relevant inhalation studies are available in Appendix A.5.9. This section considers incidence data for histopathological lesions associated with leukemia or lymphoma; other evidence supportive of the development of these cancers (e.g., hematological changes) is discussed in the *Evidence on Mode of Action for Lymphohematopoietic Cancers* Section.

Lymphohematopoietic Cancers in Animal Studies

This discussion focuses on the few available studies evaluating tumors of the lympho-hematopoietic system (leukemia and lymphomas), with the evidence organized by species and study confidence (see Table 1-65). The largest and most comprehensive cancer bioassay evaluating formaldehyde inhalation exposure in animals is the *high* confidence chronic study (Battelle, 1982) conducted at the Battelle Columbus Laboratory in B6C3F1 mice and F344 rats. This was also the only study to evaluate the majority of tissues relevant to LHP cancers (e.g., no other study reported histopathological evaluation of the spleen or thymus). The summary reports of these experiments in the published literature do not discuss leukemia or lymphoma rates (Kerns et al., 1983; Swenberg et al., 1980b). However, tissue slides were examined histopathologically in all animals from the control and 17.6 mg/m^3 dose groups at each interim and terminal necropsy; the lesions examined included lymphoma and leukemia (note: increased bone marrow hyperplasia, a nonmalignant lesion that was significantly increased in exposed rats, is also included in Table 1-65 and further discussed in the *Evidence on Mode of Action for Lymphohematopoietic Cancers* Section). At the intermediate dose groups of 2.5 mg/m^3 and 6.9 mg/m^3 exposure concentrations, only the target (i.e., the nasal passages) tissues were examined unless unusual tissue masses or gross lesions were noted, or if the animals died spontaneously, and the study report does not provide incidence at these doses in their summary findings (Battelle, 1982). As stated in the report, survival rates for rats were decreased by formaldehyde exposure at the 17.6 mg/m^3 exposure for males and females. For the mice, there was no differential mortality across exposure groups; however, there appeared to be decreased survival in all exposure groups after 6 months. The cumulative incidences of lymphoma (in B6C3F1 mice) and leukemia (in F344 rats) as reported by Battelle (see Tables 7–10 in (Battelle, 1982)) are shown in Table 1-64. The *p*-values reported by the authors were based on a Cox-Tarone test for the comparison that adjusts for reduced survival (Battelle, 1982). There was a suggestion of a possible increased incidence in lymphoma (*p*-value, 0.06) in female mice, and a decreased incidence in leukemia in female rats (*p*-value, 0.006) at the high dose. The possible increase in lymphoma incidence in mice is of interest for future study, as low incidences of lymphomas were also observed in two strains of p53 deficient mice after formaldehyde exposure, whereas no lymphomas were observed in control groups [(Morgan et al., 2017); see additional discussion in the Evidence on Mode of Action for Lymphohematopoietic Cancers Section]. It is problematic to infer from these results because of the lack of information at the intermediate dose groups and the adverse effect on survival rates. It is also difficult to interpret the apparent slight increase in lymphoma in mice alongside the slight but statistically significant decrease in leukemia in female rats. Taken together with the exposure-induced increases in bone marrow hyperplasia in rats, this represents an area of uncertainty warranting additional study.

Table 1-64. Cumulative incidence of hematopoietic cancers in B6C3F1 mice and F344 rats

Endpoint, species	Sex	Incidence or percentage incidence		*p*-Values
		0 ppm	17.6 mg/m^3	
Lymphoma, mice	Male	0/119 (0%)	0/115 (0%)	
	Female	19/121 (16%)	27/121 (22%)	0.062
Leukemia, rats	Male	11/120 (9%)	5/120 (4%)	0.690
	Female	11/120 (9%)	7/120 (6%)	0.006

A separate, *medium* confidence study in rats did not report any significant differences in histopathological evaluations of tissues relevant to leukemia or lymphoma (Kamata et al., 1997), although specific incidence data for non-nasal lesions were not provided. Although the two other available studies also failed to observe statistically significant, treatment-related increases in LHP cancers in potentially sensitive mice (Morgan et al., 2017) or rats (Sellakumar et al., 1985), these results were interpreted with *low* confidence due primarily to concerns regarding insensitivity due to a very short exposure duration (8 weeks; (Morgan et al., 2017)), or histopathological evaluations of LHP tissues only when gross lesions were noted (Sellakumar et al., 1985).

Overall, the available data are ***indeterminate*** for drawing conclusions regarding the potential for formaldehyde exposure to induce LHP cancers in rodent bioassays. It should be emphasized that the detection of leukemia/lymphoma in the available animal studies (i.e., other than the 0 versus 17.6 mg/m^3 group comparisons in the Battelle study) may be limited by study design due to limited statistical power, a lack of routine evaluation of tissues potentially related to LHP cancers (studies focused on histopathological evaluation of nasal tissue), or early mortality from toxicities other than LHP cancer, particularly given the few suggestive changes that were reported (i.e., bone marrow hyperplasia in rats and slight but uncertain increases in lymphomas in mice). To make definitive conclusions regarding the development of LHP cancers in formaldehyde-exposed animals, there is a need for studies specifically designed to target these cancers as the main endpoint.

Table 1-65. Summary of animal evidence of lymphohematopoietic cancers and bone marrow histopathology following inhalation exposure to formaldehyde

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr><td colspan="2">Rats</td></tr>
<tr><td colspan="2">High confidence</td></tr>
<tr><td>Kerns et al. (1983), Battelle (1982)
Rats: Fischer 344; males and females; 119 to 121/sex/group
Exposure: whole-body 6 hr/d, 5 d/wk for up to 24 months; recovery examined at 27 and 30 months
Test article: Paraformaldehyde analytic concentrations: 0, 2.5 (± 0.01), 6.9 (± 0.02), and 17.6 (± 0.05) mg/m^3
Histopathology: Relevant tissues included femur, mandibular and mesenteric lymph nodes, spleen, and thymus. Note: Histopathological examination was carried out only for unusual tissue masses for 2.5 and 6.9 mg/m^3 groups (see text).</td><td>Rats, leukemia (all)
<table><tr><th></th><th>0 mg/m^3</th><th>2.5 mg/m^3</th><th>6.9 mg/m^3</th><th>17.6 mg/m^3</th></tr><tr><td>Female</td><td>11/109 (9%)</td><td>NA</td><td>NA</td><td>7/113 (6%)</td></tr><tr><td>Male</td><td>11/109 (9%)</td><td>NA</td><td>NA</td><td>5/115 (4%)</td></tr></table>Rats, bone marrow hyperplasia
<table><tr><th></th><th>0 mg/m^3</th><th>2.5 mg/m^3</th><th>6.9 mg/m^3</th><th>17.6 mg/m^3</th></tr><tr><td>Female</td><td>7/106 (6%)</td><td>NA</td><td>NA</td><td>28/87* (24%)</td></tr><tr><td>Male</td><td>6/108 (5%)</td><td>NA</td><td>NA</td><td>26/85* (23%)</td></tr></table>NA = Only nasal tissue was systematically analyzed
*p = 0.0001 (see Table 1-74 for leukemia p-values)</td></tr>
<tr><td colspan="2">Medium confidence</td></tr>
<tr><td>Kamata et al. (1997)
Rats: Fischer 344; male; 32/group
Exposure: nose-only 6 hours/day, 5 days/week for 28 months; interim sacrifices at months 12, 18, and 24
Test article: Formalin (and methanol control)
Analytic concentrations: 0, 0.40 (± 0.09), 2.67 (± 0.40), or 18.27 (± 2.73) mg/m^3. Methanol in the 0 and 18.27 groups was estimated at 5.2 mg/m^3. A room control served as a no exposure group.
Histopathology: Relevant tissues included mesenteric lymph nodes and femur; and other tissues with noted gross lesions.

Main limitations: Formalin (gaseous methanol levels were not analytically measured in the control and exposed groups, even though a methanol control was included); limited histopathological examinations of non-nasal tissues.</td><td>No lesions attributable to formaldehyde exposure were detected in organs other than the nasal cavity.</td></tr>
<tr><td colspan="2">Low confidence</td></tr>
<tr><td>Sellakumar et al. (1985)
Rats: SD; male; 99–100/group
Test article: Paraformaldehyde (slurry in paraffin oil)
Exposure: 6 hr/d, 5 d/wk for lifetime at 0 or 18.2 mg/m^3 (note: prior reporting of levels during first 588 days at 17.5 mg/m^3 (Albert et al., 1982)
Histopathology: Histopathology conducted for LHP-relevant tissues (not specified) only when gross lesions were noted
Related study: Albert et al. (1982)

Main limitations: LHP tissues were only evaluated if gross lesions were noted.</td><td>No differences in tumors outside of the respiratory tract were noted between treated and control groups.</td></tr>
</table>

<table>
<tr><th>Reference and study design</th><th>Results</th></tr>
<tr><td colspan="2">Mice</td></tr>
<tr><td colspan="2">High confidence</td></tr>
<tr><td>Battelle (1982)
Mice: B6C3F1 mice; males and females; 119 to 121/sex/group
Exposure: whole-body 6 hr/d, 5 d/wk for up to 24 months; recovery examined at 27 and 30 months
Test article: Paraformaldehyde
Analytic concentrations: 0, 2.5 (± 0.01), 6.9 (± 0.02), and 17.6 (± 0.05) mg/m^3
Histopathology: Relevant tissues included femur, mandibular and mesenteric lymph nodes, spleen, and thymus. Note: Histopathological examination was carried out only for unusual tissue masses at 2.5 and 6.9 mg/m^3 (see text).

Note: Somewhat limited sampling for potential LHP cancers and high mortality.</td><td>
Mice, lymphoma (all)
<table>
<tr><th></th><th>0 mg/m^3</th><th>2.5 mg/m^3</th><th>6.9 mg/m^3</th><th>17.6 mg/m^3</th></tr>
<tr><td>Female</td><td>19/102 (16%)</td><td>NA*</td><td>NA</td><td>27/121 (22%)</td></tr>
<tr><td>Male</td><td>0/119 (0%)</td><td>NA</td><td>NA</td><td>0/115 (0%)</td></tr>
</table>
Mice, lymphoid hyperplasia (mandibular lymph node)
<table>
<tr><th></th><th>0 mg/m^3</th><th>2.5 mg/m^3</th><th>6.9 mg/m^3</th><th>17.6 mg/m^3</th></tr>
<tr><td>Female</td><td>19/59 (24%)</td><td>NA</td><td>NA</td><td>24/63 (28%)</td></tr>
<tr><td>Male</td><td>7/58 (11%)</td><td>NA</td><td>NA</td><td>14/49 (22%)</td></tr>
</table>
Mice, lymphoid hyperplasia (spleen)
<table>
<tr><th></th><th>0 mg/m^3</th><th>2.5 mg/m^3</th><th>6.9 mg/m^3</th><th>17.6 mg/m^3</th></tr>
<tr><td>Female</td><td>25/90 (22%)</td><td>NA</td><td>NA</td><td>22/97 (18%)</td></tr>
</table>
*NA = Only nasal tissue was systematically analyzed.
</td></tr>
<tr><td colspan="2">Low confidence</td></tr>
<tr><td>Morgan et al. (2017)
Mice: C3B6.129F1-Trp53^{tm1Brd} (C3B6 TP53±) and B6.129-Trp53^{tm1Brd} (B6 TP53±); males; 24–35/group
Exposure: Mice were exposed to FA in dynamic whole-body chambers 6 hours/day, 5 day/week for 8 weeks.
Test article: Paraformaldehyde
Nominal concentrations were 0, 9.23, or 18.45 mg/m^3.[a]
Histopathology: Routine evaluations of relevant tissues included frontal plane sections of the femur (including bone marrow), and mesenteric, mandibular, mediastinal, and bronchial lymph nodes. Tissues with gross lesions were also evaluated.

Main limitations: Short duration and short follow-up period to allow for cancer development (note: authors based exposure duration, in part, on HSPC doubling).</td><td>The incidences of leukemia or lymphohematopoietic neoplasms were not statistically significantly increased by formaldehyde exposure in either strain.

Lymphomas were observed in several mice exposed to formaldehyde in both strains (i.e., in “B6” mice: 1/31 at 9.23 mg/m^3 and 1/35 at 18.45 mg/m^3; in “C3B6” mice: 1/24 at 9.23 mg/m^3 and 2/25 at 18.45 mg/m^3), while lymphomas were absent from control groups in both strains (the study authors determined these lesions were unrelated to treatment).</td></tr>
</table>

Abbreviations: LHP = lymphohematopoietic; FA = formaldehyde-specific antibody; HSPC = hematopoietic stem and progenitor cell.

Evidence on Mode of Action for Lymphohematopoietic Cancers

Introduction

This section evaluates evidence supporting plausible mechanisms of LHP carcinogenesis following inhalation exposure to formaldehyde. As previously discussed, the strength of the evidence in humans was determined to be *robust* for myeloid leukemia and *slight* for multiple myeloma, although evidence in experimental animals is considered *indeterminate*. As a mode(s)-of-action has not been established for how formaldehyde inhalation may result in LHP cancers, the available evidence relevant to interpreting the biological plausibility of the observed associations in humans is presented in this section. This discussion includes consideration of how genotoxicity

and other potential molecular and cellular events resulting from formaldehyde interactions in upper respiratory tract (URT) tissues might result in LHP cancers. Genotoxicity of formaldehyde in different experimental systems and in human populations is evaluated and described in detail in Appendix A.4; in this section, conclusions from these data are interpreted specifically as pertaining to LHP carcinogenesis. Additional evidence relevant to interpreting the biological plausibility of formaldehyde exposure-induced LHP carcinogenesis has been previously discussed, including DNA damage in peripheral blood cells, impacts on immune cell populations and inflammation in peripheral blood in human populations, systemic oxidative stress, and other health effects outside of the respiratory system, including developmental and reproductive toxicity, hazards for which the **evidence indicates** that effects in humans are likely. These data are discussed in Sections 1.2.3, 1.2.5, and 1.3.2.

Approach: consideration of mechanistic events plausibly relevant to LHP cancer induction following inhaled formaldehyde exposure

This section considers conclusions derived from the analyses of pertinent types of evidence as they relate to LHP cancer (discussed in detail elsewhere in this Toxicological Review), and further examines facets of the genotoxicity database and other mechanistic events specifically relevant to the potential cellular origins of LHP cancer. Rather than a single, linear MOA hypothesis to which formaldehyde-specific data can be applied and evaluated, a network of mechanistic events or pathways may be a more appropriate conceptual framework within which to consider the biological plausibility for many cancers, including LHP carcinogenesis potentially caused by formaldehyde inhalation. These plausible mechanistic events involve specific aspects of genotoxicity and mutagenicity, hematologic effects, and changes in gene expression or regulation, consistent with previous analytical frameworks employed in the evaluation of LHP carcinogenesis (NRC, 2014b). Additionally, this discussion includes consideration of mechanistic effects which have been previously described as hallmarks or enabling characteristics of cancer, as well as key characteristics of carcinogens [e.g., genomic instability and mutation, oxidative stress, inflammation, and avoidance of immune destruction; (Smith et al., 2016; Hanahan and Weinberg, 2011)].

Although there is evidence that exposure to formaldehyde is associated with changes in cell populations that are relevant to LHP cancer mechanisms, a number of studies have demonstrated that direct interactions of formaldehyde with cells in the bone marrow are not likely (see Appendix A.2). In the bone marrow of monkeys (Moeller et al., 2011), and in the bone marrow, liver, lung, spleen, thymus, and blood of rats (Lu et al., 2010a), DNA monoadducts were formed by interactions with endogenous formaldehyde, but adducts formed from exogenous formaldehyde were not found using highly sensitive detection methodology. Recently Lai et al. (2016) described an ultrasensitive mass spectrometry method, which distinguishes unlabeled DPX from $^{13}CD_2$-labeled DPXs induced from endogenous and exogenous formaldehyde, respectively. The authors demonstrated that inhalation exposure of stable isotope labeled ($^{13}CD_2$) formaldehyde to rats

(18.45 mg/m^3; 6 hours/day; 1, 2, or 4 days) and monkeys (7.38 mg/m^3; 6 hours/day; 2 days) induced DPXs linked to exogenous formaldehyde in nasal passages in both species, but not in distal tissues, such as bone marrow and peripheral blood monocytes (rats and monkeys) and liver (monkeys), although DPXs linked to endogenous formaldehyde were detectable in all tissues. In light of this evidence, in vitro studies of direct administration of formaldehyde to cells from distal tissues, such as bone marrow and blood, were considered less relevant to the evaluation of hazard.).

The approach taken in this section was to identify mechanistic events possibly linking inhaled formaldehyde-induced effects to LHP cancer risk in humans, and then to evaluate the supporting evidence for these events and relationships. The primary focus was on evidence from mechanistic studies of exposed humans where available, incorporating results from in vivo animal studies and in vitro experiments when such information was particularly instructive. The studies most informative to LHP mechanisms were those that examined changes in leukocyte populations or function along with genotoxicity in potential target cells (e.g., hematopoietic stem and progenitor cells [HSPCs], discussed below) or surrogate cell populations (e.g., peripheral blood lymphocytes [PBLs]) from the same human cohorts. Measuring genotoxicity in mature PBLs as surrogates for target cells of concern for LHP carcinogenesis (i.e., HSPCs) is a commonly adopted and reasonable experimental approach (Kirsch-Volders et al., 2014) because PBLs are much more abundant than HSPCs, which constitute only a fraction of a percentage of circulating leukocytes (de Kruijf et al., 2014; Massberg et al., 2007). Other studies selectively reporting hematotoxicity, altered immune function, or genotoxicity in circulating WBCs from formaldehyde-exposed humans or animals also provided useful information.

The mechanistic events specifically evaluated include:

1) Evidence of formaldehyde-induced DNA damage to peripheral blood leukocytes
    a. Genotoxicity in circulating myeloid progenitor cells (possible cancer target population)
    b. Genotoxicity in circulating lymphocytes (surrogate population)
2) Evidence of formaldehyde-induced impacts other than genotoxicity on circulating blood cell populations, including inflammatory changes or immune system dysfunction
3) Evidence of formaldehyde-induced systemic oxidative stress
4) Evidence of formaldehyde-induced changes in the bone marrow niche
5) Evidence of formaldehyde-induced changes in gene expression or posttranscriptional regulation in peripheral blood leukocytes or bone marrow

In each of the following sections, the formaldehyde-specific mechanistic evidence is briefly reviewed, then the relevance to LHP carcinogenesis is described alongside a discussion of the

evidence (or lack thereof) addressing how formaldehyde exposure might cause the observed effects.

To frame the discussion of the plausible mechanistic events related to LHP carcinogenesis, relevant elements of HSPC physiology are briefly reviewed. Hematopoietic stem cells (HSCs) are cells residing in the blood or bone marrow that are functionally defined by their ability to replenish their own numbers as well as divide asymmetrically into less plastic progenitor cells. The HSCs reside in localized microenvironments within the bone marrow called "niches," which control their survival, mobilization, proliferation, self-renewal, and differentiation (Wilson et al., 2009). For example, a single HSC can give rise to common myeloid or lymphoid progenitor cells, which can in turn yield blast cells with dedicated differentiation into specific cell lineages, with a fraction becoming myeloblasts and lymphoblasts, respectively (see Figure 1-43). HSCs and progenitor cells (e.g., myeloblasts, common myeloid or lymphoid progenitors, etc.) are described together as HSPCs (Granick et al., 2012; Massberg et al., 2007) (see Figure 1-43). As previously described (see Section 1.3.3, Overview of Lymphohematopoietic Cancer Biology), LHP cancers are a heterogeneous group. Most LHP cancers, including acute and chronic myeloid leukemias as well as multiple myeloma (i.e., LHP cancers best associated with formaldehyde exposure in epidemiology studies) are thought to arise from damage to HSPCs during hematopoietic and lymphopoietic development, or as a result of environmental exposure, often in a specific HSPC-type and lifestage-dependent manner (Greaves, 2004). However, some LHP cancer subtypes, including CLL and some lymphomas, may arise from mature leukocytes (Eastmond et al., 2014). Thus, this section discusses HSPCs as the most likely proximal target for LHP cancers (i.e., those of primary interest in the context of formaldehyde exposure), while mature leukocytes are discussed as surrogate populations for cancer target cells.

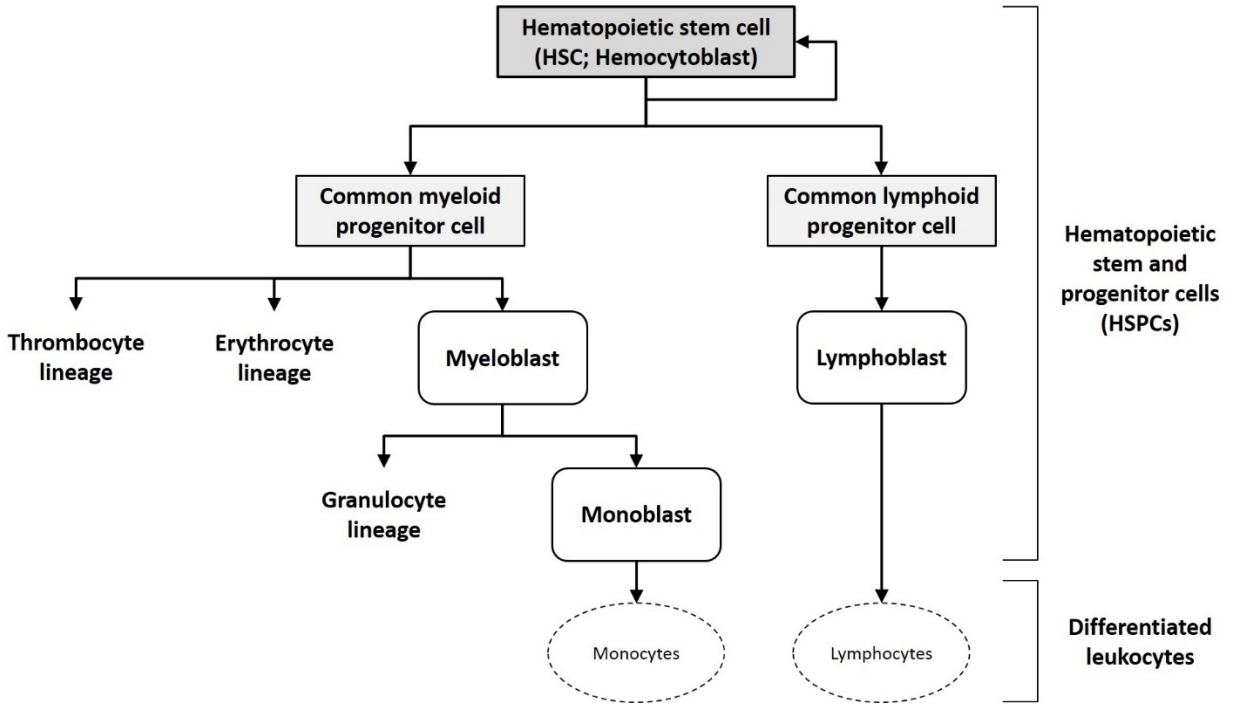


Figure 1-43. Simplified hematopoiesis.

Hematopoietic stem cells (HSC) are capable of self-renewal, and can asymmetrically divide to create progenitors committed to either myeloid or lymphoid lineages; together, the HSCs and more committed progenitors comprise hematopoietic stem and progenitor cells (HSPCs; (Granick et al., 2012; Massberg et al., 2007)). The progenitors then supply the precursor cells responsible for maintaining the population of more differentiated cell types within the committed lineage, as depicted. The likely candidate cellular targets for lymphohematopoietic (LHP) cancers are the varied progenitors associated with the monocyte and lymphocyte lineages (a few examples illustrated), as well as HSCs themselves.

Evidence of formaldehyde-induced DNA damage to peripheral blood leukocytes

The most pertinent and direct available evidence of formaldehyde-induced effects on target cells relevant to LHP carcinogenesis (i.e., those that may ultimately become neoplastic) is from two studies of the same cohort reporting genotoxicity in myeloid progenitor cells in the peripheral blood of exposed human workers (Appendix A.4). In addition, several studies have been conducted documenting several measures of DNA and chromosomal damage and instability in PBLs of workers exposed to formaldehyde. As these exposures occurred in vivo and the effects are not formaldehyde-specific, no assumptions can be made regarding whether or not formaldehyde must directly interact with the HSPCs or PBLs (e.g., potentially while migrating through URT tissues) to induce the observed changes, or, alternatively, if these represent indirect effects. In vitro formaldehyde exposure of isolated PBLs may also provide some minimal supportive information, although substantially lower confidence exists regarding the relevance of these data, given the limited distribution of inhaled formaldehyde beyond the URT and the assumption that the inhaled formaldehyde concentrations these cells might encounter in URT tissues, if any, would be much lower than the in vitro levels applied. Notably, human PBLs may be less sensitive to potential in

vivo genotoxicity compared with HSPCs, as murine HSPCs are more susceptible to aldehyde-induced DNA damage than mature, differentiated leukocytes (Oberbeck et al., 2014; Garaycoechea et al., 2012).

Genotoxic effects on circulating myeloid progenitor cells

Among the human occupational studies with formaldehyde exposure, two studies of the same cohort reported effects on myeloid progenitor cells cultured from peripheral blood of exposed workers (Lan et al., 2015; Zhang et al., 2010); (see Appendix A.4) compared to cells cultured from controls without occupational formaldehyde exposure. The specific hematopoietic progenitor cells assessed were identified as CFU-GMs, but not lymphocytes (i.e., myeloblasts in Figure 1-43). CFUs of less committed HSPC colonies (e.g., CFU-GEMMS which can give rise to granulocytes, erythrocytes, macrophages, and megakaryocytes) could not be directly assessed for technical reasons (Lan et al., 2015; Zhang et al., 2010). No information is available to determine if either progenitor cell type would be more or less susceptible to formaldehyde-induced genotoxicity.

In an initial pilot study, increased monosomy of chromosome 7 and trisomy of chromosome 8 was reported in CFU-GMs cultured from a group of 10 highly exposed subjects and 12 controls (8 hr TWA 2.6 versus 0.032 mg/m^3, respectively) evaluated only for aneuploidy in chromosomes 7 and 8. Decreased WBC counts and a 20% decrease in CFU-GM colony formation was also noted, suggesting hematotoxicity (Zhang et al., 2010). The initial finding of chromosome 7 monosomy was confirmed in a larger, more comprehensive analysis of the same cohort with 29 occupationally exposed subjects and 23 referents (1.7 versus 0.032 mg/m^3) wherein chromosome-wide aneuploidy and structural aberrations of all 24 chromosomes were examined (Lan et al., 2015). This follow-up study also reported significantly: (a) increased frequencies of monosomy in numerous chromosomes, with the greatest response for chromosomes 1, 5, and 7; (b) increased polysomy in several chromosomes including 1 and 5; and (c) increased tetrasomy in various other chromosomes. In addition to aneuploidy, increased breaks, deletions, and translocations of chromosome 5 were also reported, while trisomy of chromosome 8 was not significantly elevated (Lan et al., 2015). Although the pilot study methods were criticized for not adhering to the assay protocol (Gentry et al., 2013), a clarification of the assay protocol was provided by the investigators with a description of how the study adhered to it (Rothman et al., 2017). Additional findings of monosomy, trisomy, tetrasomy, and structural aberrations of multiple chromosomes that were increased in formaldehyde-exposed workers in comparison to the unexposed referent group indicate that formaldehyde exposure is associated with a potential tendency toward cytotoxicity in CFU-GM cells that may arise either in vivo or during the in vitro cell culture period.

A more recent study in mice from the same researchers similarly suggests that *in vivo* formaldehyde exposure (3 mg/m^3 for 2 weeks) might affect the viability of progenitor cells of the granulocyte/monocyte (CFU-GM) or erythroid (BFU-E) lineage based on the ability to generate colonies of these cells in culture (Zhao et al., 2020a). Although they did not specifically examine changes in the blood, the authors reported consistent decrements (across two independent

experiments) in BFU-E from the nose; BFU-E and CFU-GM from the bone marrow; and CFU-GM from the spleen. The authors also reported mixed evidence of decrements (across experiments) for CFU-GM from the nose; BFU-E and CFU-GM from the lung; and BFU-E from the spleen. However, the study results cannot be reliably interpreted as clear evidence of formaldehyde-induced effects due to use of formalin as the test article and small sample sizes.

In vitro formaldehyde exposure of cells isolated from healthy, unexposed humans provided mixed results. Formaldehyde exposure-induced aneuploidy in cultured human erythroid progenitor cells (Ji et al., 2014), but not in cultured myeloid progenitor cells (Kuehner et al., 2012). These results suggest either a more complex biological basis for susceptibility to chromosomal damage, or an inability of in vitro test conditions to detect or replicate formaldehyde-associated effects observed in the in vivo studies.

Of interest in the context of susceptibility, in mice, knockout of the genes encoding enzymes responsible for removal of endogenous formaldehyde, namely *Aldh2* and *Aldh5*, results in a phenotype of severely disrupted hematopoiesis and leukemia, including mutated and abnormal HSPCs, which is presumably linked to elevated formaldehyde levels (Dingler et al., 2020; Burgos-Barragan et al., 2017b; Pontel et al., 2015). Likewise, direct treatment of *Aldh5-/-* bone marrow cells with formaldehdye causes genotoxic effects and reduces HSPC formation, effects which are further exacerbated by loss of *Fancd2* (this latter deficiency is associated with increased sensitivity to DNA damage) (García-Calderón et al., 2018; Burgos-Barragan et al., 2017b). As reviewed and tested by Dingler et al. (2020), genetic deficiencies in these Aldh family genes has been linked to bone marrow failure and related diseases in humans, including specifically in children. Other changes in these mouse models and humans with reduced ALDH2 or ALDH5 activity that may be caused, at least in part, by uncontrolled endogenous formaldehyde include postnatal lethality, stunted growth, cognitive effects (see Section 1.3.1) and various cancers arising from DNA damage or deficient repair (Dingler et al., 2020; Nakamura et al., 2020). While formaldehyde inhalation does not seem to cause appreciable changes in formaldehyde levels in nonrespiratory regions (see Appendix A.2), HSPCs expressing these enzymes are known to exist in many tissues. However, no studies in any species have specifically examined these possible linkages in relation to inhaled formaldehyde, limiting the use of the currently available studies in hazard identification to the identification of factors of interest to future studies on susceptibility.

Relevance to LHP carcinogenesis and mode of action interpretation

As described above, the cells used in these experiments represent a potential primary target for LHP carcinogenesis. The aneuploidy observed in chromosomes 5 and 7 is of particular relevance for chemically induced LHP carcinogenesis because the loss of whole or part of chromosomes 5 or 7 are common aberrations in therapy-related myelodysplastic syndrome (MDS) and acute myelogenous leukemia (Lessard et al.), particularly those resulting from alkylation drug therapy (Lan et al., 2015; Pedersen-Bjergaard et al., 2006; Smith et al., 2003). Therefore, the observations of similar cytogenetic effects in asymptomatic formaldehyde-exposed workers

supports the biological plausibility of the association between chronic formaldehyde exposure and elevated incidence of LHP cancers in other human cohorts (see Section 1.2.5, Evidence on Mode of Action for URT Cancers). Although exogenous formaldehyde may not be transported to or specifically affect the bone marrow in a fashion akin to other well-studied human leukemogens (e.g., benzene, chemotherapeutics, ionizing radiationEastmond et al., 2014), and may therefore not act via a similar MOA, similar aneuploidies in CFU-GMs from formaldehyde-exposed and benzene-exposed workers have been observed (i.e., monosomy and trisomy in chromosomes 5 and 7; (Zhang et al., 2011). Thus, the presence and type of aneuploidies observed in circulating myeloid progenitor cells from formaldehyde-exposed asymptomatic human workers are consistent with those reported in patients with leukemia, specifically MDS and AML, as well as those effects reported in other worker cohorts at increased risk of developing leukemias, providing further support for the plausibility of an association between chronic formaldehyde exposure and leukemogenesis.

While this evidence links formaldehyde exposure to chromosomal toxicity relevant to leukemogenesis, mechanistic evidence is lacking for how these events may occur. Although no evidence exists to evaluate the following potential scenarios, there are at least three ways in which formaldehyde exposure (with distribution limited to the URT) might cause these genotoxic effects: (1) direct interaction of formaldehyde with HSPCs in the URT; (2) indirect effects on circulating or bone marrow HSPCs due to secondary, systemic effects following formaldehyde-induced changes in the URT; and (3) modification and mobilization of precursor-type cells residing in the URT.

As part of their physiological function, HSPCs migrate via the vasculature to extramedullary tissues (outside medullary bone) such as the liver, lung, small intestine, skin, and kidneys, and return via lymphatics to the bone marrow by a process termed "homing," which is mediated by cytokines, growth factors, and hormones (Granick et al., 2012; Schulz et al., 2009; Massberg et al., 2007). Although their numbers in the peripheral blood at any one time constitute a small fraction of the total circulating leukocyte population in both mice (Massberg et al., 2007) and humans (de Kruijf et al., 2014; Zhang et al., 2010), these cells can completely replenish bone marrow stem cell populations (Massberg et al., 2007). Unlike mature lymphocytes, HSPCs do not necessarily accumulate in lymphatic tissues (e.g., nasopharynx-associated lymphoid tissue or NALT), but travel primarily through the lymphatic vasculature (Massberg et al., 2007). HSPCs accumulate to some extent in peripheral nonlymphoid tissues and are replenished every few days; alternatively, HSPCs can divide locally and replenish populations of long-lived resident myeloid cells (e.g., macrophages, dendritic cells). In addition to triggering local differentiation, inflammatory stimuli can induce HSPC mobilization from the bone marrow (Wilson et al., 2009), and may increase recruitment of mobilized HSPCs to nonlymphoid epithelial tissues (Massberg et al., 2007). Such inducible migration to and from sites of inflammation (e.g., formaldehyde-induced URT inflammation, see Section 1.2.3) could be a mechanism by which HSPCs become more frequent targets of formaldehyde-induced toxicity. The available data suggest that very little, if any, inhaled

formaldehyde penetrates beyond the URT (the portal of entry; POE), although it is likely that small amounts of formaldehyde are able to reach the superficial capillary layer of the URT in some exposure contexts (see Appendix A.2). In addition, whereas formaldehyde appears to preferentially target the respiratory and transitional epithelium of the nasal cavity, it is unclear which specific URT compartments (e.g., respiratory, transitional, or olfactory epithelium; stromal tissue layers) HSPCs may circulate through. Finally, although HSPCs may be more sensitive to genotoxic effects than other cell types, even if inhaled formaldehyde did directly encounter HSPCs, no data exist to draw inferences regarding theoretical concentrations of inhaled formaldehyde that might be required for genotoxicity. Despite these important uncertainties, it is possible that formaldehyde may be able to directly interact with potential target cell types present at the POE.

Alternatively, secondary effects resulting from toxicity, irritation, or other processes disrupted in the affected URT might be capable of causing genotoxicity in HSPCs at sites distal to the URT or in vascular regions proximal to the URT. Such secondary effects might include increased production of mediators of inflammation and oxidative stress, which have been reported after formaldehyde exposure in some studies (see Section 1.2.3), and which may result, indirectly, in cytotoxicity, genotoxicity, or other perturbations at distal sites containing HSPCs, resulting in genotoxicity in these cells. However, no data exist to evaluate this hypothesis, including the potential secondary mediators or what levels of these mediators might be required at target sites.

Lastly, some URT (i.e., rat nasal olfactory epithelium) cells have been shown to be "multipotent" in nature, in that they can repopulate rat hematopoietic tissues and differentiate into various leukocyte lineages in irradiated hosts; although, these cells act more similar to neural stem cells than to bone marrow stem cells (Murrell et al., 2005). While it might be possible that formaldehyde could interact with such a cell population, cause genotoxicity, and modify it in such a way that it becomes more HSPC-like and migrates to the bone marrow, this theory is somewhat implausible and without supportive evidence.

Overall, the evidence largely does not exist to determine whether any of the proposed processes explain how formaldehyde exposure might cause genotoxicity in HSPCs.

Genotoxic effects on circulating lymphocytes

Consistent with formaldehyde-induced genotoxicity in circulating myeloid precursor cells, formaldehyde exposure is associated with DNA and chromosomal damage in PBLs (see Appendix A.4 for detailed discussions). The studies in which we had more confidence based on evaluations of study methods reported consistent associations of formaldehyde exposure with DNA strand breaks or alkali-labile sites visualized using the comet assay, CAs, MN formation, and sister chromatid exchange (SCE). Formaldehyde was associated with a higher prevalence of chromosomal aberrations among workers in pathology laboratories (Costa et al., 2015; Musak et al., 2013; Santovito et al., 2011; Jakab et al., 2010); these effects included chromatid-type aberrations, chromosome-type aberrations, chromosomal exchange, and premature centromere division. Costa et al. (2015) also reported an increase in aneuploidies and in the number of aberrant and

multiaberrant cells. Micronuclei frequency in PBLs was higher in exposed compared to referent workers by 40–50% with a concentration-related response beginning at concentrations of 0.1–0.2 mg/m^3 and above (Costa et al., 2019; Wang et al., 2019; Jiang et al., 2010). Micronuclei frequency (and centromeric micronuclei) increased with cumulative exposure (Wang et al., 2019; Suruda et al., 1993). A 1.5 to 3-fold difference in measures of DNA damage using the Comet assay was observed comparing exposed workers to their referent groups at average concentrations as low as 0.09 mg/m^3 (Zendehdel et al., 2017), 0.14 mg/m^3 (Jiang et al., 2010) or 0.04–0.11 mg/m^3 (Peteffi et al., 2015) and a clear concentration-related response was observed in plywood plant workers (Lin et al., 2013; Jiang et al., 2010). Costa et al. (2019) reported that the frequency of micronuclei in PBL and EBC were correlated in their study population. In addition, increased DPXs were observed in circulating WBCs from human workers exposed to formaldehyde concentrations ≥0.5 mg/m^3. In experimental animals, inhalation studies at relatively high formaldehyde concentrations (i.e., 12.3 and 18.45 mg/m^3) using paraformaldehyde as the test article have not observed genotoxicity including DNA adducts, chromosome aberrations, or SCEs in PBLs of rats (Lu et al., 2010a; Kligerman et al., 1984). Results of other studies using formalin as the inhalation source were mixed (Speit et al., 2009; Im et al., 2006), although these data are less reliable. While evidence from in vitro formaldehyde exposures is likely of minimal value in relation to LHP carcinogenesis, such evaluations also report increased mutations, DPX, and other DNA damage in human PBLs, whole blood cells or cultured human lymphoblast cell lines (i.e., TK6 cells) (see Appendix A.4).

Relevance to LHP carcinogenesis

Genotoxicity in PBLs may reflect formaldehyde-induced effects in HSPCs; because PBLs are more amenable to experimentation, primarily because they are far more abundant, they can allow for far more robust analyses (e.g., in terms of sample size), and possibly better detect changes. Formaldehyde-induced chromosome damage may result from some combination of direct DNA reactivity in the URT, including downstream sequelae, and numerous indirect mechanisms such as deficiencies in DNA repair, chromosome segregation, DNA methylation and increased oxidative stress (see Section 1.2.5 Evidence on MOA for URT Cancers; (Kirsch-Volders et al., 2014). Similar to the discussion of the HSPC-specific evidence, direct interactions of formaldehyde with DNA of lymphocytes and less committed progenitor cells could occur in URT tissue regions, although this has not been documented experimentally, or through indirect mechanisms occurring systemically (e.g., as a result of increased oxidative stress). Evidence exists supporting both aneuploidy in PBLs and clastogenicity in URT tissues; notably, the aneuploidy reported in PBLs is consistent with that observed in DNA of CFU-GM cells studied by Zhang et al. (2010) and Lan et al. (2015), and observed in relation to therapy-related MDS and AML as discussed above.

Evidence of formaldehyde-induced impacts other than genotoxicity on circulating blood cell populations, including inflammatory changes or immune system dysfunction

A number of studies indicate that formaldehyde exposure causes changes in hematopoietic cell constituents in blood (see Section 1.2.3); however, an understanding of the observed pattern of these changes in specific immune cell subtypes across studies, as well as how any of these changes might be induced, remains incomplete. While there are inconsistencies in the database that introduce uncertainty, the overall evidence indicates that it is probable that formaldehyde inhalation causes blood cell changes including decreased total WBCs, CD8 + lymphocytes, and RBCs, particularly at higher formaldehyde concentrations (e.g., ≥1 mg/m^3; see Section 1.2.3). Relating to formaldehyde-induced decreases in CD8+ lymphocytes, one of the mouse studies discussed in Section 1.2.3 (Ma et al., 2020) provided evidence consistent with the possibility that formaldehyde exposure inhibits commitment to the CD8 lineage at early stages of cell development. Perhaps most relevant to LHP cancers, evidence of pancytopenia (i.e., decrease in RBCs, WBCs, and platelets in the same exposed population) was reported in peripheral blood samples from formaldehyde-melamine workers exposed to median formaldehyde concentrations of 1.6 mg/m^3, along with a 20% decrease in CFU-GM colony formation in vitro (Zhang et al., 2010), suggesting both a decrease in the circulating numbers of mature RBCs and WBCs as well as possible decreases in the replicative capacity of myeloblasts. This potential for formadehyde to selectively impact immature cells or progenitors is consistent with observations in mice by Liu et al. (2017) and Zhao et al. (2020b), although the use of formalin in these studies prevents reliable interpretation. Perhaps relatedly, a decrease in HSPC colony formation was reported for various CFU populations, including both CFU-GMs and CFU-GEMMs, cultured from human whole blood and exposed in vitro to 100–200 μM formaldehyde (Zhang et al., 2010); however, these experiments carry the same uncertainties as other in vitro assays (see above) including coexposure of the cells to methanol, which prevents reliable interpretation of these findings. In addition, a study of two strains of p53 deficient mice exposed to high levels of formaldehyde (>9 mg/m^3) for 8 weeks (a duration selected based on the HSPC pool turning over every 8 weeks) did not observe any significant increases in LHP cancers, including leukemia (Morgan et al., 2017). Although studies other than Zhang et al. (2010) do not identify pancytopenia specifically, some report decreases in one or two of these cell types, but not all three (Zhang et al., 2013b; Lyapina et al., 2004; Kuo et al., 1997), or in one or more of these cell populations without examining all three (Ye et al., 2005; Thrasher et al., 1990); while other studies reported no changes or significant increases for specific cell subsets (Aydın et al., 2013; Costa et al., 2013; Erdei et al., 2003), these latter studies tested formaldehyde concentrations of approximately ≤0.36 mg/m^3. Interestingly, some effects (e.g., changes in T cell populations) tended to increase at lower formaldehyde concentrations (~ <0.5 mg/m^3), while decreases were observed at higher levels (~1 mg/m^3). While the data suggest biologic complexity, pancytopenia such as that reported by Zhang et al. (2010), is known to be associated with MDS and AML development (Paiva and

Calado, 2014) and may be one of the hematotoxic consequences of exposure to formaldehyde, possibly only at concentrations >1 mg/m^3.

In an effort to examine potential linkages between effects observed in AML patients and those induced by formaldehyde, several studies have evaluated genotoxicity measures along with immune system effects in the same cohort of occupationally exposed human workers. These studies are considered highly informative to understanding the potential relationship between formaldehyde exposure and systemic toxicity pertaining to LHP carcinogenesis. In several analyses of the same occupationally exposed cohort in China with median exposures of 1.6 mg/m^3 formaldehyde, lower total peripheral blood cell counts (Hosgood et al., 2013; Zhang et al., 2010), including CTL memory cells, and changes in cytokine levels (Seow et al., 2015) were observed concurrently with genotoxicity in myeloid precursor cells [(Lan et al., 2015) and discussed above]. Findings in this cohort were consistent with findings from Chinese workers and students evaluated by another research group following short-term average formaldehyde exposures of approximately 0.51–0.99 mg/m^3, which observed decreases in various T lymphocyte populations, including CTLs (Ye et al., 2005; Ying et al., 1999), with a corresponding higher incidence of SCEs in worker lymphocytes at approximately 0.99 mg/m^3 (Ye et al., 2005). While CTLs were unchanged in several other studies testing lower formaldehyde concentrations (0.2–0.8 mg/m^3; (Jia et al., 2014; Aydın et al., 2013; Costa et al., 2013), one of these studies did report increased CD4 + T cells alongside evidence of genotoxicity at 0.36 mg/m^3 (Costa et al., 2013). While CTLs were generally decreased (increasing the ratio of CD4 + T cells to CTLs) in the blood of individuals exposed to formaldehyde concentrations >0.5 mg/m^3 (see Section 1.2.3), an understanding of how the observed cell number changes might relate to genotoxicity remains unclear.

A reanalysis of data from Zhang et al. (2010) reaffirmed the lower levels of specific immune cell populations, specifically WBCs, lymphocytes, RBCs and platelets in the exposed participants with respect to the unexposed group (Mundt et al., 2017). However, when immune cell population levels were compared within the exposed group using a cutpoint at the median of 1.6 mg/m^3 (1.3 ppm), no difference was observed between the higher and lower exposed groups. Likewise, no association with formaldehyde modeled as a continuous variable and cell population levels was observed in regression analyses adjusted for sex and smoking. The 43 exposed participants were highly exposed, ranging from a TWA8 of 0.5 to 3.3 mg/m^3 (0.4 to 2.7 ppm) with one outlier at 6.9 mg/m^3 (5.6 ppm). Fifty percent of the exposed group was exposed to a TWA8 from 1.1 to 2.5 mg/m^3 (interquartile range). Therefore, the exposure levels in the study group did not include the breadth of exposure levels needed at lower formaldehyde levels to evaluate an exposure-response trend. The high formaldehyde exposure and the inadequate range of the concentrations limited the power of the study to detect a trend with exposure level of the expected magnitude based on those previously detected for benzene exposure (Rothman et al., 2017).

Changes in serum NK cells and B cells were not entirely consistent across studies, although the available data suggest that formaldehyde concentration may strongly influence the results,

similar to findings for CTLs (see Section 1.2.3). For example, while NK cell numbers were decreased at 0.36 and 1.6 mg/m^3 (Costa et al., 2013; Hosgood et al., 2013) NK cells were actually increased at 0.2 and 0.25 mg/m^3 (Jia et al., 2014; Aydın et al., 2013) and unchanged at 0.8 mg/m^3 (Jia et al., 2014). Although changes in B cell counts were supported by moderate evidence across several medium or high confidence studies conducted after several months of exposure, for example at 0.99 mg/m^3 (Ye et al., 2005) and 0.2–0.8 mg/m^3 (Jia et al., 2014), other *medium* or *high* confidence studies testing formaldehyde exposures for several years, for example at 0.25 mg/m^3 (Aydın et al., 2013) and 1.6 mg/m^3 (Hosgood et al., 2013) did not report B cell changes, or reported B cell decreases at lower formaldehyde levels (0.36-0.47 mg/m^3) (Costa et al., 2019; Costa et al., 2013). Looking across studies, the overall pattern of these responses across exposure levels and exposure durations is difficult to interpret.

Although infrequently studied, some limited mechanistic information suggests the potential for stimulation of the immune system at lower formaldehyde exposures, and decreases in blood cell numbers at higher exposure concentrations. In one study evaluating immunological markers in a cohort of plywood workers, exposure to 0.2–0.8 mg/m^3 formaldehyde was positively correlated with increased serum interleukin (IL)-10 and IL-4, alongside decreased IL-8 and interferon-gamma (IFN–γ); no significant changes in total lymphocyte or T cell numbers were observed in this study (Jia et al., 2014). These cytokine changes are consistent with observations of increased plasma IL-4 and decreased IFN-γ in a short-term rat study at ≥6.2 mg/m^3 that reported corresponding lymphocyte genotoxicity (Im et al., 2006). Workers with higher formaldehyde exposure (i.e., 1.8 mg/m^3) exhibited formaldehyde-associated aneuploidy and had decreased peripheral blood levels of various chemokines and cytokines, including IL-10 (Seow et al., 2015). These observations suggest the possibility of a shift in the functional activation of immune effector cells such as T lymphocytes and macrophages at formaldehyde concentrations below which overt changes in cell number become observable; however, studies specifically testing this possibility have not been performed.

While changes in subpopulations of peripheral leukocytes and circulating levels of cytokines may indicate the potential for some manner of dysfunction in the host immune system, direct observations of dysfunction would be most informative; however, only a few studies specifically examined the potential for events such as immunosuppression in either humans or experimental animals following formaldehyde exposure. In addition, while studies of immune function in the affected airways indicate a probable effect of formaldehyde exposure, studies evaluating immunosuppression at distal sites are inadequate (see Section 1.2.3). In the airways of exposed humans, indirect evidence of decreased immune capacity exists, including decreased resistance to URT infection at 0.9 mg/m^3 formaldehyde with chronic exposure (Lyapina et al., 2004), and an increased rate of LRT infection in infants exposed to 0.02 mg/m^3 during their first year of life (Roda et al., 2011). These observations in humans are consistent with the decreased bactericidal activity of leukocytes from the lungs of mice acutely exposed to ≥1 mg/m^3

formaldehyde (Jakab et al., 1992), and the enhanced malignancy and growth of lung tumors, in association with decreases in NK cell numbers and activity, formed by an injection of syngeneic melanoma cells in mice following exposure to 12 mg/m^3 (Kim et al., 2013a). Observations related to systemic immune dysfunction, including increased survival to Listeria monocytogenes infections and reduced melanoma tumor mass in B6C3F1 mice (Dean et al., 1984), and increased autoantibodies in exposed adults (Thrasher et al., 1990) are mixed and inconclusive. Thus, while it appears that formaldehyde exposure can suppress immune function in the airways, the pattern of effects across tissue compartments (i.e., URT, LRT, blood and lymphoid tissues) remains unclear.

Together, the evidence supports a decrease in peripheral blood WBC counts in formaldehyde-exposed humans (see Section 1.2.3), although some heterogeneity across studies has been reported in terms of the directionality and magnitude of changes in specific leukocyte subsets and in levels of soluble immunomodulatory molecules (see Section 1.2.3). Considerable heterogeneity has also been observed in relation to the formaldehyde concentration or exposure duration reported for the different observations, further complicating interpretation. Despite this variability, the available data suggest that formaldehyde exposure modifies immune system function across a range of concentrations and durations, with changes in specific leukocyte subpopulations becoming more robust and consistent following exposure to >0.5 mg/m^3 (see Section 1.2.3).

Relevance to LHP carcinogenesis

While many of the changes reported following formaldehyde exposure could create a more permissive environment favoring tumor growth and progression, evidence does not exist to determine whether these changes in immune cell populations or cytokine profiles significantly impact tumor immunosurveillance or cause chronic inflammation; therefore, any specific role for altered immune function in formaldehyde-associated leukemogenesis remains unclear. Changes in immune cell subpopulations, distribution, and activation have a complex relationship with carcinogenesis in terms of tumor suppressing or enhancing activity (Hanahan and Weinberg, 2011). For example, immune suppression is associated with a greater risk of hematopoietic cancers (Bassig et al., 2012), and chronically immunosuppressed human transplant recipients are at increased risk for developing myeloid neoplasms (Morton et al., 2014). Together, this evidence shows that the immune system can operate as a significant barrier to LHP carcinogenesis (Corthay, 2014). In addition, impaired tumor immunosurveillance could result from deficiencies in the development or function of cytotoxic T lymphocytes (CTLs), type 1 T-helper (T_H1) cells, or NK cells, which might lead to demonstrable increases in tumor incidence (Hanahan and Weinberg, 2011). Conversely, inflammatory immune effector cells (i.e., neutrophils, macrophages, type 2 T-helper [T_H2] cells, and T and B lymphocytes) can release growth factors and other tolerogenic signaling mediators, which permit tumor growth. The release of reactive oxygen species (ROS) from such cells can be actively mutagenic for nearby cancer cells and accelerate their genetic evolution toward heightened malignancy (Coussens and Werb, 2002). While NK cells play a prominent role in

infection and carcinogenesis in the airways (and likely elsewhere in the body), the studies and evidence reporting effects on these cells in any tissue system following formaldehyde exposure are considered weak. Overall, despite the potential for these associations, cell type-specific changes indicative of impaired immunosurveillance or enhanced tumor growth have not been conclusively demonstrated following formaldehyde exposure, particularly at lower levels.

The observed changes in soluble immune factors are similarly difficult to interpret. In addition to the evidence of increased IL-4 in the blood, multiple observations, primarily from allergen sensitization studies in rodents, suggest that IL-4 production in the lower respiratory tract (LRT) in response to antigen stimulation is further exacerbated by formaldehyde exposures ≥0.3 mg/m^3 (see Sections 1.2.2–1.2.3). Although the specific implications of cytokine changes for tumor development and progression is still emerging, IL-10 and IL-4 in particular are important cytokines in tumor immunology (Li et al., 2009), and the tendency of IL-4 and IL-10 to increase while IFN-γ decreases (see Section 1.2.3) is a pattern commonly observed in human cancer patients, including those diagnosed with some LHP cancer subtypes (Shurin et al., 1999). However, the relationships between cell signaling molecules and affected components of the immune system are complex, and an understanding of how these molecular changes might relate specifically to immune cell dysfunction, and further, to LHP carcinogenesis, is incomplete.

Evidence does not exist to describe how formaldehyde exposure might cause the observed systemic changes in immune system-related responses. While it is possible that these changes might result from disturbed bone marrow hematopoiesis resulting indirectly from formaldehyde exposure, studies specifically testing this possibility were not identified. Alternatively, it is possible that altered immune system responses are related to formaldehyde-induced toxicity at the URT. Interestingly, while peripheral blood CTL levels were generally decreased in individuals exposed to formaldehyde concentrations >0.5 mg/m^3, respiratory tract CTL levels (and total WBC counts) tended to increase in rodent studies, although the latter data are limited to short-term exposure at much higher formaldehyde levels (see Appendix A.5.6). It is possible that CTLs were preferentially recruited from the peripheral blood into the URT, thus explaining their depletion from the former and accumulation in the latter tissue; however, none of the identified human studies report WBC counts from both peripheral blood and POE tissue compartments, and the available animal data likewise cannot adequately inform this hypothesis.

Overall, while several studies indicate effects on hematopoietic cell populations and secreted factors, for which exposure concentration may be an important determinant, the impact of these changes on leukemogenesis cannot be clearly discerned.

Evidence of formaldehyde-induced oxidative stress

Similar to observations in the airways, inhaled formaldehyde has been associated with biomarkers of oxidative stress in distal tissues (see Section 1.2.3 and Appendix A.5.6).

Some human studies have evaluated changes in markers of oxidative stress in blood or urine in relation to formaldehyde exposure, and also have attempted to determine whether the

oxidation of lipid membrane components might be associated with the presence of formaldehyde-induced DNA damage. Two studies provide evidence of oxidative stress-related genotoxicity or mutagenicity, including elevations in malondialdehyde-deoxyguanosine (M1dG) adducts (i.e., exocyclic DNA adducts formed as byproducts of lipid peroxidation) in WBC DNA with exposure to an average formaldehyde concentration as low as 0.07 mg/m^3 (Bono et al., 2010). This finding is indirectly supported by an observed association between increases in malondialdehyde and p53 protein (a potential biomarker of carcinogenicity; see discussion of the potential for p53 to contribute to URT carcinogenesis in Section 1.2.5) in plasma with urinary formate levels (which may serve as an imprecise marker of formaldehyde exposure) among cosmetic workers (Attia et al., 2014). Additional evidence that formaldehyde exposure is associated with oxidative stress is provided by a study that reported increased urine levels of 15-F2t isoprostane (a sensitive, but nonspecific marker of oxidative stress) from formaldehyde-exposed workers (Romanazzi et al., 2013); although this marker is not specific to changes in a particular tissue, strong correlations between measurements from urine and plasma (Rodrigo et al., 2007; Morrow et al., 1995) suggest similarly elevated isoprostanes in the workers' blood. Somewhat in support of the observations in humans, several animal studies in two species observed increases in markers of oxidative stress following acute or short-term formaldehyde exposure to a range of formaldehyde concentrations including ≤1 mg/m^3; however, these studies had notable methodological limitations, and it is not clear whether these changes persist with long-term exposure (see Section 1.2.3). Suggestive evidence of elevated indicators of formaldehyde-induced oxidative stress and inflammation have been reported in bone marrow from exposed mice at ≥0.5 mg/m^3 formaldehyde; however, these animals were coexposed to methanol, drawing into question the validity of these findings (formalin was the formaldehyde source; (Yu et al., 2014; Ye et al., 2013b; Zhang et al., 2013b)). These limited studies also observed higher rates of DNA damage in bone marrow. Overall, together with the genotoxicity data, this evidence indicates the likely presence of DNA damage and, possibly coincidentally, the likely presence of elevated oxidative stress in circulating leukocytes, although the data are insufficient to describe this potential relationship in terms of duration or concentration of exposure.

Studies of susceptibility to DNA damage conferred by polymorphisms in genes coding for enzymes with activity that either increases or decreases oxidative damage observed greater genotoxicity associated with formaldehyde exposure and polymorphic variation in genes encoding the ROS-inducer, CYP2E1 (more damage associated with wildtype), and the detoxifying enzyme, GSTP1 (more damage associated with variant) (Costa et al., 2015), although another study using a different measure of DNA damage found a marginal increase in susceptibility among exposed with the wildtype GSTP1 allele compared to the variant genotype (Jiang et al., 2010). However, DNA damage in human PBLs was not increased to a greater degree in formaldehyde-exposed human cohorts with increased susceptibility to oxidative damage due to glutathione-S transferase (GSTM1

or GSTT1) null genotype (Santovito et al., 2011; Jiang et al., 2010; Costa et al., 2008); therefore, these results remain inconclusive.

Relevance to LHP carcinogenesis

Together, the available data suggest that oxidative stress may be elevated at distal sites following formaldehyde exposure in humans, rats, and mice; however, available studies of genetic susceptibility in exposed workers are not adequate to draw conclusions. Considered alongside the evidence of oxidative stress in the airways (Sections 1.2.1–1.2.2), the data reporting oxidative stress at distal sites suggest that formaldehyde exposure might increase the production of potentially harmful factors throughout the body. If sufficiently severe or sustained for a prolonged duration, oxidative stress could perturb the function of circulating leukocyte populations including HSPCs, increasing lipid, protein, and DNA oxidation, causing DNA strand breakage, as well as altering cellular energetics and signaling pathways (Mikhed et al., 2015). Regarding any potential role in LHP carcinogenesis, the impact of oxidative stress-induced DNA damage on gene or chromosomal changes could be similar to the damage caused by a variety of directly DNA-reactive compounds (Mchale et al., 2012; DeMarini et al., 2000). The available evidence is inadequate to determine what role formaldehyde-associated oxidative stress may play in LHP carcinogenesis, although impacts on leukocyte genotoxicity, increased HSPC mobilization, or immunomodulation are all plausible consequences of systemically elevated oxidative stress.

Data are not available to describe how formaldehyde might cause oxidative stress outside of the airways. Similar to changes in leukocyte cell numbers, this may be secondarily due to sustained airway inflammation, which could cause the release of factors from the inflamed tissue(s) into the circulation that result in increased oxidative stress; however, no studies have examined this possibility. In summary, the potential relationship of increased systemic oxidative stress to LHP carcinogenesis is unknown.

Evidence of formaldehyde-induced changes in the bone marrow niche

As noted above, there is some evidence of pancytopenia in formaldehyde-exposed humans that may indicate disturbance of or cytotoxicity in the bone marrow niche at higher environmental exposures. In F344 rats, bone marrow hyperplasia was elevated following chronic exposure to 18 mg/m^3 formaldehyde (Battelle, 1982). In two chronic rat bioassays (Kamata et al., 1997; Sellakumar et al., 1985) and a short-term (8-week) study of p53 deficient mice (Morgan et al., 2017), the authors evaluating nonrespiratory tissues did not provide details regarding nonneoplastic histopathology in tissues outside the URT, and the incidence of hematopoietic neoplasms did not appear to be elevated in any of these studies. In female B6C3F1 mice exposed similarly to the F344 rats above, hyperplasia was not observed in the bone marrow, spleen or lymph nodes (Battelle, 1982). Evaluations of changes in numbers of bone marrow megakaryocytes were likewise fairly equivocal in mice exposed to 0.5–20 mg/m^3 formaldehyde (see Appendix A.5.6).

Two studies in mice suggest that cell subpopulations in the bone marrow niche might be differentially affected by formaldehyde exposure. Specifically, in a 20-week study, a dose-dependent decrease in the ratio of immature to mature RBCs (PCE/NCE ratio) in the bone marrow was observed after exposure to 1 and 10 mg/m^3 formaldehyde for 2 hours per day (Liu et al., 2017); however, there was no corresponding change in micronucleus rate. A short-term, 2-week study indicated that *in vivo* formaldehyde exposure of 3 mg/m^3 caused a decreased formation of BFU-E (erythroid progenitor) and CFU-GM (granulocyte/monocyte progenitor) colonies in cultures from bone marrow or spleen (Zhao et al., 2020b). However, in both of these studies the formaldehyde source is presumed to have been formalin, which prevents interpretation of these results at systemic sites as reliable and highlights this as an area deserving of additional research.

As noted above, a dose-related increase in bone marrow DPXs was observed in BALB/c mice exposed to 0.5–3.0 mg/m^3 formaldehyde generated from evaporating formalin (Ye et al., 2013a). However, the presence of methanol in the formalin confounds interpretation of the potential for systemic formaldehyde effects, as the co-administered methanol could be rapidly absorbed, distributed to the bone marrow, and locally metabolized to formaldehyde (see Appendix A.2, A.4). Consistent with this hypothesized contribution of methanol, neither DPXs nor DNA mono adducts were elevated in rodent bone marrow exposed via paraformaldehyde (Leng et al., 2019; Lu et al., 2010a; Heck and Casanova, 2004; Casanova and Heck, 1987; Casanova-Schmitz et al., 1984a). While bone marrow has not been evaluated in exposed human cohorts, elevations in WBC DPX levels have been reported in some human workers chronically exposed to concentrations ≥0.5 mg/m^3 (Shaham et al., 2003; Shaham et al., 1997), but not consistently in others (Lin et al., 2013).

In general, the data relevant to potential formaldehyde-induced changes in the bone marrow niche were fairly weak and inconsistent across the available studies, although the minimal data available indicate that additional studies are warranted.

Relevance to LHP carcinogenesis

Bone marrow niches consist of bone marrow mesenchymal stem cells (BM-MSCs) and HSPC pairings under tight regulation by local input from the surrounding microenvironment, as well as long-distance cues from soluble signaling mediators (e.g., hormones, cytokines, eicosanoids) and the autonomic nervous system (Cristina Lo Celso1, 2011). Aberrant bone marrow stroma can lead to HSPC dysfunction including MDS (Cristina Lo Celso1, 2011), a precursor to AML. Therefore, altered stromal behavior could affect HSPC quiescence and mobilization as well as directly induce the expansion of leukemic clones over normal cells.

Although inhaled formaldehyde does not likely reach the bone marrow to elicit direct effects analogous to exposure in the URT (see Appendix A.2), formaldehyde-induced effects in the URT could indirectly affect the bone marrow microenvironment or "niche" in several ways, including inflammation or induction of systemic immune responses (see Section 1.2.3), oxidative

stress (see Sections 1.2.3), hormonal or cytokine changes that affect BM-MSC and HSPC interactions, and disrupted regulation of HSPC mobilization from the niche. However, evaluations of bone marrow following formaldehyde inhalation have been limited to histological or genotoxic endpoints in experimental systems, with no information available regarding either molecular changes in stromal cell function or HSPC activation, differentiation, or mobilization.

The sympathetic nervous system has some control over the mobilization and circulation rate of bone marrow progenitor cells including HSPCs (Elenkov et al., 2000). While formaldehyde exposure has been shown to activate the trigeminal nerve in the rodent URT via transient receptor potential channel stimulation at low concentrations ((Mcnamara et al., 2007); see Section 1.2.1), no studies have examined whether or how this might be indirectly related to regulation of HSPC mobilization or hematopoiesis; however, it is considered unrealistic that activation of neural pathways relaying irritant and pain information would convey excitatory or inhibitory signals to networks responsible for HSPC regulatory functions.

It is difficult to reconcile these disparate observations across the available data streams: the general lack of bone marrow toxicity in experimental model systems corresponds with no excess leukemia reported in chronic rodent bioassays, while the varied fluctuations in immune cell subpopulations, including some evidence of pancytopenia in the peripheral blood of chronically exposed humans (Section 1.2.3), is consistent with the evidence of leukemia induction in humans. It is possible that humans are more sensitive to the hematotoxic effects of formaldehyde than either rodents or nonhuman primates (Goldstein, 2011), as has been noted in the context of chromosomal damage resulting from direct leukemogens (e.g., benzene; (French et al., 2015; IARC, 2012; Mchale et al., 2012)). However, mechanism(s) responsible for any potential differential sensitivity remain to be elucidated. Based on the currently available data, no conclusions can be drawn regarding the potential involvement of formaldehyde exposure-induced indirect effects on the bone marrow niche in LHP carcinogenesis.

Evidence of formaldehyde-induced changes in gene expression or posttranscriptional regulation in peripheral blood leukocytes or bone marrow

Few studies have evaluated the effect of formaldehyde exposure on microRNA (miRNA) or messenger RNA (mRNA) levels from non-POE tissues in vivo, and none evaluated chronic exposures. In a small study where human volunteers (N = 21) were variably exposed to ≤1 mg/m^3 formaldehyde for 5 days, statistically significant changes in mRNA expression were observed in cells from either nasal biopsies or whole blood samples; however, study limitations prevent interpretation of the changes to be a result of formaldehyde exposure (Zeller et al., 2011). In F344 rats, significant changes in both miRNA and mRNA expression were reported in the nasal epithelium and circulating white cells following inhalation exposure to 2.5 mg/m^3 formaldehyde for ≤4 weeks, primarily involving pathways related to immune/inflammatory response, apoptosis, and proliferation; no significant changes were observed in miRNA samples from the bone marrow, and mRNA transcript levels were not evaluated (Rager et al., 2014). A majority of the reported

changes appeared to be tissue- and exposure duration-specific, and only expression of one transcript was consistently affected (miR-326 levels increased) in the WBCs across exposure conditions (Rager et al., 2014). As these endpoints have not been well-studied, conclusions cannot be made regarding the consistency and reproducibility of these data across studies.

Relevance to LHP carcinogenesis

Epigenetic mechanisms such as miRNA-mediated regulation of mRNA may play a role in the pathogenesis of LHP malignancies (Yendamuri and Calin, 2009). For example, differential miRNA expression profiles have been reported between normal and leukemia cells, and among LHP cancer subtypes such as AML and ALL (Marcucci et al., 2009; Mi et al., 2007). However, the bone marrow represents a heterogeneous population of cells, and in the context of variable and temporal responses induced following formaldehyde exposure, such gene expression array results can be difficult to assimilate and interpret (Weinberg, 2014).

Although the potential role of miR-326 in LHP carcinogenesis is unknown, increased serum miR-326 expression was associated with bone matrix turnover and positively correlated with lung cancer bone marrow metastasis (Valencia et al., 2013). Considering that WBCs are a highly heterogeneous population, of which only a small fraction is likely to contain target cells of interest in LHP carcinogenesis (i.e., HSPCs), the observation of altered miRNA and mRNA levels in WBCs from rats provides very limited evidence that supports the biological plausibility for other formaldehyde-induced effects, such as genotoxicity (Appendix A.4) in the peripheral blood cells of occupationally exposed humans. Additional studies examining potential epigenetic and transcriptional mechanisms related to LHP carcinogenesis in non-POE tissues following formaldehyde exposure are needed to confirm and expand the observations from this limited set of studies.

Discussion of mechanistic evidence relevant to LHP carcinogenesis.

While the mechanistic events evaluated in the context of formaldehyde-associated LHP cancer are similar to those described for well-described human leukemogens (IARC, 2012; Mchale et al., 2012), the specific mechanism(s) of LHP cancer induction are not understood, which complicates the construction of any simple, linear MOA (Mchale et al., 2012). Therefore, a network of plausible mechanistic events or pathways was discussed, including specific aspects of genotoxicity and mutagenicity, hematologic effects, oxidative stress, and changes in gene expression or regulation, consistent with previous analytical frameworks employed in the evaluation of LHP carcinogenesis (NRC, 2014b). The most pertinent evidence and conclusions for potential mechanistic events associated with formaldehyde induction of LHP cancers are summarized in Table 1-66.

It is possible that potential LHP target cells (e.g., HSPCs) are affected in the URT tissue, via direct interactions with formaldehyde, given observations that stem cell precursors can traverse between the URT and bone marrow. However, the concentrations of inhaled formaldehyde

reaching sites through which HSPCs might traverse (e.g., lymphatic URT tissue), as well as the population of HSPCs present in the URT at any one time, would both be expected to be quite low, although no specific data address these unknowns. Indirect toxicity to HSPCs in the URT also might result from inflammation or oxidative stress in these tissues. Furthermore, genotoxic effects on HSPCs, as well as immune cell toxicity and dysfunction, may occur in peripheral blood or bone marrow via indirect effects of formaldehyde-associated inflammation in the URT resulting in systemic oxidative stress and changes in gene expression or regulation. However, no studies of formaldehyde exposure investigating these hypotheses have been conducted.

Evidence from evaluation of respiratory tract and oral cells (nasal and buccal epithelium), and circulating leukocytes (e.g., HSPCs and PBLs) consistently demonstrates increased levels of Comet assay-detectable DNA damage, as well as MN, CAs, and SCEs associated with formaldehyde exposure from a variety of occupational cohorts. Some of the genotoxic endpoints observed in circulating blood cell progenitors from formaldehyde-exposed workers have also been specifically observed in patients with AML (Mchale et al., 2012; Bowen and Hannigan, 2006), while other endpoints observed in PBLs, such as MN and CA, are generally regarded as biomarkers associated with increased human risk for a variety of cancers, including LHP malignancies (Kirsch-Volders et al., 2014; Fenech et al., 2011; Bonassi et al., 2008; Bonassi et al., 2007; Bonassi et al., 2004b); see Section 1.2.5, *Evidence on Mode of Action for URT Cancers*). Genotoxicity to circulating PBLs may also serve as a surrogate biomarker of genotoxicity in HSPCs, which may play a more direct role in LHP carcinogenesis. No information from the available formaldehyde studies exists to evaluate this potential association.

Following formaldehyde exposure, the available evidence supports the following observations: (a) elevated levels or severity of DNA or chromosomal damage in circulating human blood cells, including in both myeloblasts and mature lymphocyte populations; (b) the specific nature of DNA damage in circulating human leukocytes exhibits aneugenic characteristics similar to damage reported in humans with or at increased risk for AML; and (c) that the human immune system is impacted, possibly as a function of formaldehyde concentration, in a complex manner. Formaldehyde exposure is associated with reductions in immune cell populations, although other lines of evidence indicate stimulation of some immune cell populations, which might reflect a complex concentration or duration dependence in the pattern of effects. The observations of DNA or chromosomal damage in exposed humans, including aneuploidy, and reductions in immune cell populations associated with comparable formaldehyde levels (≥0.5 mg/m^3) provide coherent evidence suggesting that these effects may be related.

Despite the internal consistency of many of the individual effects described above regarding formaldehyde-induced damage to target cells and biomarkers of genotoxicity in circulating mature PBLs in humans, there is a general lack of understanding regarding both how formaldehyde exposure might cause these changes, as well as how these mechanistic events may lead to LHP cancer. Regarding the latter, for example, any specific effects on the bone marrow niche have not

been studied in exposed humans, and the evidence from the available animal studies is generally inconclusive.

The relationships between leukocyte responses in peripheral blood and formaldehyde exposure are complex; studies observed changes in different cell populations, which were both increased and decreased across studies, although some tentative patterns could be discerned, particularly at exposure concentrations >0.5 mg/m^3. The mechanisms responsible for these observations are unclear, as is any specific contribution of these mechanistic events to LHP carcinogenesis. Likewise, although some evidence exists to support increased systemic oxidative stress associated with formaldehyde exposure, its role in targets of LHP cancers is also unclear, and any specific impacts on immune function or tumor immunosurveillance remain to be determined.

Alternative hypotheses

A hypothesized scenario that does not require bone marrow cytotoxicity is that HSPCs damaged in the URT tissues do not return to the bone marrow but form local neoplastic foci. However, there is no evidence supporting this possibility. Collections of neoplastic myeloid cells localized in extramedullary tissues (myeloid or granulocytic sarcomas occurring outside of the medulla of the bone), are associated with MDS and AML but are not commonly reported in human nasal tissue (Yamamoto et al., 2010b; Paydas et al., 2006; Prades et al., 2002). Myeloid sarcomas have not been specifically associated with formaldehyde exposure, although these lesions are frequently misclassified as NHLs in patients without concurrent MDS or AML (Yamamoto et al., 2010a). However, HSPCs do not travel through the nasopharynx-associated lymphoid tissue (Massberg et al., 2007), and may not be the target cell population responsible for nasal myeloid sarcoma. This observation could suggest that the nasal tissue does not provide a suitable niche microenvironment for sustaining neoplastic myeloid cell expansion (Granick et al., 2012; Wilson et al., 2009).

Inferences can be made by extending the proposed hypothesis of circulating or nasal-resident HSPCs as LHP cancer target cells to the spectrum of effects commonly associated with leukemias induced by exposure to other agents (U.S. EPA, 2005a). Although the results of this exercise cannot dismiss the biological plausibility of the events evaluated with specific data from the formaldehyde exposure database, it may illustrate that the identified set of mechanistic events are incomplete. For example, if HSPCs are exposed to the genotoxic activity of formaldehyde as they transit through the URT tissues, and then proceed back to the bone marrow to progressively become leukemogenic, then other genotoxic URT carcinogens could potentially have a similar effect and be associated with both URT and bone marrow cancers. The agents in which both nasopharyngeal cancer and leukemias have been associated with human exposures are tobacco smoke (IARC, 2012), which contains formaldehyde, and formaldehyde itself (IARC, 2012). Most agents associated with nasal cancer in humans have not also been associated with leukemia induction, despite displaying variable genotoxic activity, except for those agents that are also systemically available and hematotoxic (IARC, 2012). This suggests that genotoxicity and

distribution to the URT alone may not be sufficient to induce LHP carcinogenesis. It has been proposed (IARC, 2012) that well-studied human leukemogens (e.g., ionizing radiation, benzene, chemotherapeutics) induce hematotoxicity more frequently or to a greater extent than neoplasia, which would be consistent with DNA damage more frequently resulting in bone marrow cell death than progenitor transformation. However, this observation cannot rule out leukemogenesis driven by mechanisms other than genotoxicity-induced bone marrow cytotoxicity.

Gaps in understanding of formaldehyde exposure-related LHP carcinogenesis

As discussed in this section, there appears to be a lack of concordance between evidence from chronic rodent bioassays and human epidemiological evidence regarding incidence of LHP cancers. Moreover, contrary to the consistent evidence supporting genetic damage to circulating leukocytes in formaldehyde-exposed humans, few positive associations have been reported in rodent bioassays. This MOA discussion evaluated the mechanistic database pertinent to leukemogenesis based on the fundamental assumption that exogenous formaldehyde is not distributed appreciably beyond POE tissues. Differences in physiology between humans and rodents, as well as the relative insensitivity of rodent models to reflect the human pathogenesis of AML, may together contribute to the potential lack of concordance between the abundant human epidemiological data and the more limited results (e.g., most bioassays did not examine tissues relevant to LHP cancers in detail) from rodent bioassay data.

Conclusion

The available evidence supports some events that could contribute to plausible mechanistic pathways relating formaldehyde exposure to LHP carcinogenesis. However, the database was insufficient to support the evaluation or development of any specific MOA. Although this analysis represents an independent evaluation of all identified, pertinent, primary information, it is informative to note that the conclusions reached herein are consistent with those reported following previous reviews by authoritative scientific organizations, including IARC (2012), NTP (2014), and the NRC (2014b). Notably, there was widespread, general agreement that the available evidence is largely consistent and strong, particularly for genotoxicity in circulating blood cells. Both temporal and exposure-response relationships have been demonstrated in studies of humans, and mechanistic pathways exist that support a biologically plausible relationship between formaldehyde exposure and cancer, even though the mechanistic pathways explaining such systemic effects are unclear (NRC, 2014b). It is important to note that systemic delivery of formaldehyde is not a prerequisite for the observed mechanistic changes, as some of the reported systemic effects might result from direct interactions with formaldehyde in the URT, while others could plausibly result indirectly from events such as URT irritation, cytotoxicity, oxidative stress, and inflammation locally initiated at the POE. Further, the evidence for other effects at distal sites was compelling. This evidence included increased female reproductive and developmental toxicity and male reproductive toxicity, based on studies of experimental animals and workers exposed to

high formaldehyde levels, as well as LRT disease (i.e., current asthma symptoms and decreased asthma control in population-based epidemiology studies). It is plausible that these effects could result indirectly from events occurring in the URT. While the available mechanistic database has limitations, this does not detract from the strength of the association between formaldehyde exposure and myeloid leukemia in epidemiology studies.

Conclusions from MOA evaluation

Support for the hypothesized mode of action in experimental animal models

While evidence for the several identified mechanistic events ranges from strong and consistent to inadequate (see Table 1-66), the supporting evidence was drawn primarily from studies of exposed humans; no single MOA could be assembled and evaluated from the limited relevant experimental animal data available.

Relevance of the hypothesized mode of action to humans

Due to the paucity of pertinent mechanistic information, no single, stochastic MOA was identified for LHP cancers associated with formaldehyde exposure. However, evidence supporting the identified mechanistic events was obtained primarily from studies of exposed human cohorts, and thus the mechanistic events are all relevant or of presumed relevance to human LHP cancer risk (see Table 1-66).

Table 1-66. Summary conclusions regarding plausible mechanistic events associated with formaldehyde induction of lymphohematopoietic cancers

Hypothesized mechanistic event	Evidence informing mechanistic event	Human relevance	Weight-of-evidence conclusion and biological plausibility
2.1 Formaldehyde-induced DNA damage to peripheral blood leukocytes	HSPC aneuploidy and structural chromosome damage in myeloid progenitors (CFU-GMs) from human workers occupationally exposed to median levels of 1.6 mg/m^3 (Lan et al., 2015; Zhang et al., 2010). • ↑ Monosomy and polysomy in multiple chromosomes (especially monosomy 1, 5, 7) consistent with damage observed in patients with MDS or AML (Lan et al., 2015) • ↑ Breaks, deletions, and translocations in chromosome 5 ↑ genotoxicity in circulating PBLs from inhalation-exposed humans, including increases in strand breaks, MN, CA (see Appendix A.4; (Kirsch-Volders et al., 2014) NBUDs, or SCE induction at ≥0.14 mg/m^3 (Jiang et al., 2010), and DPXs at higher exposures (Lin et al., 2013; Shaham et al., 2003). • ↑ DPXs in PBLs from mice after inhalation of formaldehyde generated from formalin (Ye et al.,	Yes. Evidence comes primarily from exposed humans.	Strong and consistent human data exist associating formaldehyde exposure with various genotoxic outcomes in myeloid progenitors and PBLs, and exposure-response relationships demonstrated. Genotoxicity in circulating leukocytes shows concordance with similar endpoints in POE tissues. Aneugenic damage observed in CFU-GMs from formaldehyde-exposed human workers is associated with MDS or AML in humans. Together this evidence constitutes

Hypothesized mechanistic event	Evidence informing mechanistic event	Human relevance	Weight-of-evidence conclusion and biological plausibility
	2013b), although results may be confounded by methanol coexposure • No increase in DPXs in peripheral blood or bone marrow of monkeys or rats exposed via paraformaldehyde (Lai et al., 2016; Casanova and Heck, 1987) • DNA damage in human PBLs is consistently associated with genotoxicity in human POE tissues (e.g., exfoliated buccal and nasal epithelial cells) in studies evaluating both tissues after longer-term exposures (see Appendix A.4; see Section 1.2.5)		the strongest support for the biological plausibility for LHP induction resulting from formaldehyde exposure.
2.2 Evidence of formaldehyde-induced impacts other than genotoxicity on circulating blood cell populations, including inflammatory changes and/or immune system dysfunction	↓ CFU-GM colony formation in human workers occupationally exposed to median levels 1.6 mg/m^3 (Zhang et al., 2010), which may reflect not only altered bone marrow progenitor cell viability, but also immune dysfunction or altered activation. • Numerous published studies reporting divergent changes in various peripheral blood cell populations from formaldehyde-exposed humans (see Section 1.2.3; Appendix A.5.6), including: - ↑ Pancytopenia and consistent decreases in total WBCs ↓ or ↑ in some lymphocyte populations, with decreased CD8 T cells likely at concentration >0.5 mg/m^3. Fluctuations in immune cell numbers and immune/inflammation markers show a complex pattern with concentration, with decreases in blood cell number and decreased cytotoxic response generally at higher concentrations, some of which are consistent with observations in AML patients (Kim et al., 2015). Other studies indicate immune cell activation generally observed at lower concentrations ≤0.36 mg/m^3.	Yes. Most of the available data comes from human studies.	The evidence supporting changes in populations or function of circulating blood leukocytes following human exposure to formaldehyde is strong in terms of a frequency of alterations, but different patterns in changes are reported (e.g., specific direction of changes in various lymphocyte subpopulations, or in blood levels of soluble signaling mediators). LHP cancer risk increases with loss of normal immune function.

Hypothesized mechanistic event	Evidence informing mechanistic event	Human relevance	Weight-of-evidence conclusion and biological plausibility
2.3 Formaldehyde-induced systemic oxidative stress	• ↑ M1dG adducts in whole blood DNA from pathologists, compared to workers and students in other science labs (Bono et al., 2010), elevated plasma MDA and plasma p53 associated with each other and with urinary formate concentrations (an imprecise marker of formaldehyde exposure) among cosmetics workers (Attia et al., 2014), and ↑ 15-F2t isoprostane levels in the urine of formaldehyde-exposed workers (Romanazzi et al., 2013) • Inconclusive evidence for and against involvement by genes that regulate oxidative stress in formaldehyde associations with DNA damage risk in PBL in humans (see Appendix A.4) • ↓ GSH, ↑ ROS, ↑ MDA in bone marrow, peripheral blood mononuclear cells, liver, spleen, and testes (Ye et al., 2013b), although markers of oxidative stress were not correlated with DPXs and results may be confounded by methanol coexposure.	Yes. Some human data available, and results from experimental models are presumed relevant to humans.	Limited human and rodent evidence supports the association between formaldehyde exposure and induction of oxidative stress beyond the POE. While biologically plausible, the available evidence is inadequate to determine what role such oxidative stress may play in LHP carcinogenesis.
2.4 Formaldehyde-induced changes in the bone marrow niche	• ↑ Bone marrow hyperplasia in rats from one study (Kerns et al., 1983; Battelle, 1981), but unclear if other results were negative or null (Kamata et al., 1997; Sellakumar et al., 1985) due to imprecise reporting • Dose-related ↑ DPXs in the bone marrow of formalin-exposed mice (Ye et al., 2013b), although results may be confounded by methanol coexposure • HSPC mobilization and the BM-MSC niche is regulated by cytokines, hormones, and signals, which may be distributed through circulation as a result of inflammation although these effects have not been directly evaluated following formaldehyde exposure	Yes. Available data are from experimental models presumed relevant to humans.	The limited evidence available is currently inadequate to evaluate any effect on bone marrow or stromal cells following formaldehyde exposure, although such an effect appears consistent with current understanding of hematopoiesis.
2.5 Evidence of formaldehyde-induced changes in gene expression or posttranscriptional regulation in peripheral blood leukocytes or bone marrow	Limited study reported some statistically significant differences in mRNA expression in either nasal or whole blood samples from human volunteers associated with 5-day exposures up to 1 mg/m^3 formaldehyde; however, study limitations prevent interpretation that results were related to formaldehyde exposure (Zeller et al., 2011). In F344 rats, significant changes in both miRNA and mRNA expression were reported in the nasal epithelium and circulating WBCs following inhalation exposure to 2.5 mg/m^3 formaldehyde for 1 or 4 weeks; no changes were observed in miRNA expression in the bone marrow, and mRNA was not evaluated (Rager et al., 2014). • "Immune system/inflammation" markers were enriched in both nasal tissue and WBCs at both time points	Yes. Available data are from experimental models presumed relevant to humans.	Limited rodent evidence supports the association between formaldehyde exposure and epigenetic effects in circulating leukocytes; the available human evidence is inadequate. Insufficient evidence is available to determine what role epigenetics may play in LHP carcinogenesis.

Hypothesized mechanistic event	Evidence informing mechanistic event	Human relevance	Weight-of-evidence conclusion and biological plausibility
	• ↑ WBC miR-326 expression, associated with bone marrow metastasis in other models (Valencia et al., 2013)		

Abbreviations: HSPC = hematopoietic stem and progenitor cell; MN = micronuclei; CA = chromosomal aberration; CFU-GM = colony-forming unit, granulocytes and macrophages; MDS = myelodysplastic syndrome; AML = acute myeloid leukemia; PBL = peripheral blood lymphocytes; NBUD = nuclear budding ; SCE = sister chromatid exchange; DPX = DNA-protein crosslink; GSH = glutathione; ROS = reactive oxygen species; MDA = malondialdehyde.

Integrated Summary of Evidence for Lymphohematopoietic Cancers

The strength of the evidence from human studies is *robust* for myeloid leukemia (see *Lymphohematopoietic cancers in humans* above). The assessment of LHP cancers was based on epidemiology studies of groups with occupational formaldehyde levels either in specific work settings (e.g., cohort studies) or in case-control studies. Aneuploidy in chromosomes 1, 5, and 7 in circulating myeloid progenitor cells, considered a potential primary target for LHP carcinogenesis was associated with occupational formaldehyde exposure. The type of aneuploidies observed in the formaldehyde-exposed asymptomatic human workers are also found in patients with leukemia, specifically MDS and AML, as well as other worker cohorts at increased risk of developing leukemias, which provides support for the plausibility of an association between chronic formaldehyde exposure and leukemogenesis. Moreover, the strong and consistent evidence from a large set of studies that observed mutagenicity in circulating leukocytes of formaldehyde-exposed humans, specifically CAs, and MN formation, provides additional evidence of biological plausibility for these cancer types. Further support is provided by studies that observed perturbations to immune cell populations in peripheral blood associated with formaldehyde exposure. In particular, decreases in RBCs, WBCs, and platelets, along with a 20% decrease in CFU-GM colony formation in vitro were observed in the same exposed group (Zhang et al., 2010), suggesting both a decrease in the circulating numbers of mature RBCs and WBCs as well as possible decreases in the replicative capacity of myeloblasts.

Increased LHP cancers have not been observed in a well-reported chronic rodent bioassay involving inhalation exposure of both rats and mice to formaldehyde, nor in another rat bioassay that failed to report the incidence of non-nasal neoplastic lesions, although there are notable uncertainties in the available data (i.e., increased bone marrow hyperplasia in rats; slight but uncertain increases in lymphoma in mice; and a general lack of rigorous evaluation of non-respiratory tissues). Further, mechanistic changes related to leukemia have not been consistently reported in well-conducted rodent studies. Thus, there appears to be a lack of support for the human epidemiological evidence from rodent bioassays, although concordance across species is not necessarily expected (U.S. EPA, 2005a). The apparent lack of consistency in results raises

uncertainties about the currently available research results on these diseases, including how formaldehyde exposure-induced LHP cancers might arise without substantial distribution to target sites. Notably, the available animal evidence was judged as *indeterminate* and not *compelling evidence of no effect* (see assessment Preface), as there are important uncertainties that prevent such an interpretation. Thus, the animal evidence does not detract from the strength of the association between formaldehyde exposure and myeloid leukemia (and related mechanistic changes) in epidemiology studies (NRC, 2014b). Differences in physiology between humans and rodents, as well as the relative insensitivity of rodent models to reflect the human pathogenesis of myeloid leukemia, in particular, may together contribute to the potential lack of concordance between the abundant human epidemiological data and the limited results available from rodent bioassay data.

Taken together, based on the *robust* human evidence from studies of groups with occupational formaldehyde levels, the **evidence demonstrates** that formaldehyde inhalation causes myeloid leukemia in humans, given appropriate exposure circumstances. Separately, based on a limited number of epidemiological studies and potentially relevant mechanistic evidence in exposed humans, the integration of the evidence results in a judgment that the **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation might cause multiple myeloma and Hodgkin lymphoma, given appropriate exposure circumstances. While mechanisms for the induction of myeloid leukemia are yet to be elucidated, they do not appear to require direct interactions between formaldehyde and bone marrow constituents, and either are different in animals or the existing animal models tested thus far do not characterize the complex process leading to cancers in exposed humans.

Table 1-67. Evidence integration summary for effects of formaldehyde inhalation on LHP cancers

Evidence	Evidence judgment	Hazard determination
Myeloid Leukemia		
Human evidence	*Robust* for myeloid leukemia based on: *Human health effect studies:* • Consistent increases in risk across a set of *high* and *medium* confidence, independent studies with varied study designs and populations • Several of these studies demonstrated strong associations (1.5- to 3-fold increase in risk) and clear exposure-response relationships across multiple measures of increasing exposure • The studies possessed a temporal relationship consistent with causality (e.g., allowing time for induction, latency, mortality) *Biological plausibility* (also of potential relevance to LHP cancer types below): Evidence from *high* and *medium* confidence studies of exposed humans identifies relevant mechanistic changes for cancers of the blood such as myeloid leukemia, including impacts on peripheral immune cell populations (which seem to be affected in a complex manner), and elevated levels or severity of DNA or chromosomal damage in circulating myeloblasts and mature lymphocyte populations. The DNA damage exhibits aneugenic characteristics similar to that found in humans with, or at increased risk for, AML.	The **evidence demonstrates** that formaldehyde inhalation causes myeloid leukemia in humans, given appropriate exposure circumstances[a] This conclusion was primarily based on epidemiology studies of groups with occupational formaldehyde exposure. While evidence exists to suggest a lack of concordance between chronic rodent bioassays and human epidemiological evidence, notable uncertainties prevent an animal evidence judgment

Animal evidence	*Indeterminate* for *any LHP cancer type*, based on: *Animal health effect studies:* Overall, the available data do not provide evidence supporting the development of LHP cancers in a *high* confidence chronic bioassay of rats and mice, a second *medium* confidence rat bioassay, and two other *low* confidence, long-term exposure studies. *Biological plausibility:* Although some potentially relevant changes have been observed in mechanistic studies of exposed animals (e.g., inflammatory and immune changes in systemic tissues and bone marrow hyperplasia in rats), the evidence related to genotoxicity (i.e., in systemic tissues) or other more directly relevant changes were weak (e.g., only in *low* confidence studies) or not observed and, overall, the mechanistic data do not suggest a judgment other than *indeterminate* for LHP cancers in animals.	of *compelling evidence of no effect* *Potential susceptibilities:* There is no evidence to evaluate the potential risk to sensitive populations or lifestages
Other Inferences	• *Relevance to humans:* The evidence is from studies in humans. • *MOA:* No MOA exists to explain how formaldehyde might cause LHP cancers without systemic distribution (i.e., without direct interactions of inhaled formaldehyde with constituents in bone marrow tissue); however, given the mechanistic changes in exposed humans, it is reasonable to infer that an undefined MOA is likely to involve modulatory effects on circulating immune cells.	
Multiple myeloma		
Human evidence	*Slight* for multiple myeloma, based on: *Human health effect studies:* • Increases in risk associated with peak exposure metrics across one *high*, one *medium*, and two *low* confidence studies; no associations with other exposure metrics • Increases spanned an approximate 1.2- to 4-fold increase in risk, with the highest confidence evidence showing a 2-fold increase • Very limited evidence of an exposure-response relationship in one *high* confidence study • However, risks may have been driven by peak exposures as increases were limited to groups of people who experienced high peak exposures, and two *low* confidence studies reported inverse relationships with duration of exposure	The **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation might cause multiple myeloma given appropriate exposure circumstances[b]
Animal evidence	*Indeterminate* (for any LHP cancer type): see explanation for myeloid leukemia	
Other Inferences	• *Relevance to humans:* The evidence is from studies in humans. • *MOA:* No MOA exists to explain how formaldehyde might cause LHP cancers without systemic distribution	
Hodgkin lymphoma		
Human evidence	*Slight* for Hodgkin lymphoma, based on: *Human health effect studies:* • Significantly increased risk in the highest peak exposure group alongside an exposure-response relationship in one *medium* confidence study of industrial workers • An inconsistent pattern of risks across 1 *medium* and the *low* confidence studies, many with <5 exposed cases • The high survival rate for Hodgkin lymphoma may indicate that mortality data are not a good proxy for incidence.	The **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation might cause Hodgkin lymphoma given appropriate exposure circumstances[b]
Animal	*Indeterminate* (for any LHP cancer type): see explanation for myeloid leukemia	

evidence		
Other inferences	• *Relevance to humans:* The evidence is from studies in humans. • *MOA:* No MOA exists to explain how formaldehyde might cause LHP cancers without systemic distribution	
Lymphatic leukemia		
Human evidence	*Indeterminate* for lymphatic leukemia, based on: *Human health effect studies:* • A consistent pattern of null results across eight *high*, *medium*, and *low* confidence studies • The high survival rate for lymphatic leukemia may indicate that mortality data are not a good proxy for incidence.	There is **inadequate evidence** to determine whether formaldehyde inhalation may be capable of causing lymphatic leukemia in humans
Animal evidence	*Indeterminate* (for any LHP cancer type): see explanation for myeloid leukemia	
Other inferences	N/A: no signal exists across lines of evidence	

[a]The "appropriate exposure circumstances" are more fully evaluated and defined through dose-response analysis in Section 2.
[b]Given the uncertainty in this judgment and the available evidence, this assessment does not attempt to define what might be the "appropriate exposure circumstances" for developing this outcome.

1.4. SUMMARY AND EVALUATION

This section provides summaries of the available evidence on susceptible populations and life stages and on populations that may have heightened formaldehyde exposures compared to the general population (Section 1.4.1), the weight of evidence for effects other than cancer (Section 1.4.2), and the weight of evidence for carcinogenicity (Section 1.4.3).

1.4.1. Susceptible Populations and Lifestages

Susceptible populations and lifestages refers to groups of people who may be at increased risk for adverse health consequences following chemical exposures due to factors such as age, genetics, health status and disease, sex, lifestyle, and other coexposures. This discussion of susceptibility focuses on factors for which there are available formaldehyde exposure-specific data and on factors hypothesized to be important to formaldehyde. Vulnerable populations, defined as groups that may be at increased risk for adverse health consequences due to heightened formaldehyde exposures, are also discussed.

Lifestage

Embryos, fetuses, infants, children, and the elderly may have differing levels of maturity and functioning of cellular and organ systems, and metabolizing enzymes, as well as unique activity patterns that may influence the toxicodynamics of chemicals in the body. Embryonic, fetal, neonatal, and juvenile periods, as well as reproductive lifestages in both men and women, are often periods of increased susceptibility to negative health consequences following chemical exposures.

Developmental and reproductive effects

The Developmental and Reproductive Toxicity (Section 1.3.2) provides a detailed analysis of human and animal studies evaluating susceptibility to formaldehyde toxicity while in utero and during infancy, childhood, and reproductive lifestages. Overall, it was judged that the available **evidence indicates** that formaldehyde inhalation exposure likely causes developmental or reproductive toxicity in humans. This hazard conclusion was primarily based on *moderate* evidence from epidemiological studies of women that reported decreased fecundity and increased spontaneous abortion risk at occupational exposure levels as high as 1.2 mg/m^3 (Taskinen et al., 1999; John et al., 1994) as well as effects on fetal growth among three pregnancy cohorts observed at indoor formaldehyde concentrations >0.04 mg/m^3, and possibly lower (Franklin et al., 2019; Amiri and Turner-Henson, 2017; Chang et al., 2017).

Further research is needed to determine if the increased spontaneous abortion risk and decreased fecundity in occupationally exposed women is due to toxicity to the reproductive system or to the developing fetus. Additionally, there is a need for more targeted evaluation of the female reproductive system following inhalation exposure to formaldehyde, including an assessment of female reproductive function, such as would be assessed in a two-generation reproductive study in animals. Further assessment of both female reproductive toxicity and developmental toxicity would benefit from the use of paraformaldehyde instead of formalin to avoid possible confounding exposures to methanol.

Several animal studies raise the possibility that formaldehyde exposure might also cause toxicity to the developing nervous system; however, due to methodological limitations, these data were considered inconclusive (i.e., **evidence suggests**). Three publications from one laboratory (Sarsilmaz et al., 2007; Aslan et al., 2006; Songur et al., 2003) reported changes in brain structure and neuron numbers following developmental exposure to formaldehyde. However, two of these studies were evaluations of the same animals, and all three studies possessed notable methodological limitations and tested formaldehyde levels >7 mg/m^3, which introduces uncertainties (e.g., differences in toxicokinetics; irritant effects not experienced by humans) in relating these data to the potential for effects in exposed humans. The changes in brain structure and neuron number were not tested using similarly sensitive protocols in adult animals, although less rigorous evaluations failed to observe effects, highlighting additional data gaps. Only *low* confidence studies evaluated other potential neurodevelopmental effects (i.e., the evidence is *inadequate*).

Children

Lungs in children are underdeveloped at birth and are not fully functional until about 6 to 8 years of age (Bateson and Schwartz, 2008); therefore, children may be more susceptible to the respiratory effects of formaldehyde, compared to adults. In addition, formaldehyde exposure has been associated with airway inflammation (see Section 1.2.3), which could have a greater impact on

children's airways because they are narrower than adult airways (OEHHA, 2003). This is supported by studies of other chemicals suggesting that human sensitivity to sensory irritation may also be dependent on age (Shusterman, 2007; Hummel et al., 2003). The distribution of inhaled formaldehyde may be different for children compared with adults as well. For example, population variability in distribution is influenced by differences in physical characteristics of the URT, breathing patterns (e.g., oral versus nasal), and ventilation rate. However, studies suggest that extrathoracic absorption of highly reactive and soluble gases, such as formaldehyde, is similar between children and adults (Ginsberg et al., 2010; Ginsberg et al., 2005), as is overall uptake efficiency, average flux, and maximum flux levels over the entire nasal lining (Garcia et al., 2009). Garcia et al. (2009) did find that local flux between the seven individuals (five adults and two children) in his study varied by a factor of three to five, which is important as formaldehyde toxicity is likely to be mediated by its point-of-contact effects along the URT. Because this study only evaluated seven individuals who had normally shaped nasal cavities, it may not be generalizable to the entire population, including susceptible individuals. Notably, formaldehyde distribution to more distal parts of the airways could be substantial under conditions of higher activity and oral breathing, both of which occur with children.[30]

The expression of formaldehyde metabolizing enzymes may also be different in infants and children. The metabolism of formaldehyde is described in more detail in Appendix A2. Briefly, expression of glutathione-dependent formaldehyde dehydrogenase, also called alcohol dehydrogenase class III, ADH3, or ADH5, the primary enzyme in formaldehyde metabolism, is developmentally regulated and thus may alter the toxicokinetics of formaldehyde in early life (Reviewed in (Thompson et al., 2009; Hines and McCarver, 2002)). ADH3 is critical to the detoxification of formaldehyde, as it is involved in the pathway leading to formaldehyde's conversion to formate, a metabolite that is excreted from the body. Therefore, if the concentration or activity of ADH3 is reduced, more formaldehyde is likely to remain in the body to react with cellular macromolecules. ADH3 mRNA expression levels are significantly lower in premature neonates and infants up to 5 months old compared with adults. Benedetti et al. (2007) reported that ADH activity reached adult levels by 2.5 to 5 years of age. Thus, neonates and very young children, in particular, may have a decreased ability to metabolize formaldehyde, increasing their susceptibility to formaldehyde toxicity; however, enzyme activity levels for ADH3 specifically, and the potential for alternate metabolic pathways in children, are not known.

Some epidemiological studies have found that children have an increased sensitivity to formaldehyde exposure-induced respiratory effects. One study reported a relationship between increased residential formaldehyde exposure and decreased PEFR (both bedtime and morning) among children exposed to levels averaging 0.032 mg/m^3 (Krzyzanowski et al., 1990). In adults, an

[30]For example, in the case of ozone concentrations of 0.1 ppm, a moderately reactive gas, Ginsberg (2008) predicted a five-fold variation in the dose to the deep lung between quiet and heavy breathing conditions for an 8-year-old child.

association of smaller magnitude was observed, but only among smokers. Krzyzanowski et al. (1990) also reported an increase in the prevalence of physician-diagnosed asthma in children, but not in adults, who lived in homes with formaldehyde levels that were higher than 60 ppb (0.074 mg/m^3). Similarly, a study by Zhai et al. (2013) reported a higher prevalence of current asthma in children compared with adults at the same exposure levels in their homes. Although prevalence of current asthma (i.e., symptoms or use of medications in the past 12 months) does not appear to be increased among adults or children below exposure levels of approximately 0.05 mg/m^3, studies of the exacerbation of asthma symptoms (asthma control) among children suggest their greater susceptibility at lower average formaldehyde concentrations (e.g., 0.04 mg/m^3; (Dannemiller et al., 2013; Venn et al., 2003). Children younger than five years of age also may experience symptoms consistent with lower respiratory infections in association with residential formaldehyde levels lower than those at which older individuals experience these symptoms (Roda et al., 2011; Rumchev et al., 2002).

Children are also likely to be more susceptible than adults to the mutagenic effects of formaldehyde. EPA has concluded that early-life exposure to chemicals that are carcinogenic through a mutagenic MOA might present a higher risk of cancer than exposure during adulthood (U.S. EPA, 2005b). Because formaldehyde-induced carcinogenicity of the URT is attributable, at least in part, to a mutagenic MOA (see Section 1.2.5), it is expected that children are at heightened risk of URT cancers following formaldehyde exposure. In contrast, because it is unknown whether myeloid leukemia resulting from formaldehyde exposure involves a mutagenic MOA, no assumption about increased early-life susceptibility is made for this type of cancer.

Pregnant women

Because pregnant women have increased sensitivity to the development and exacerbation of atopic eczema (Kar et al., 2012; Cho et al., 2010; Weatherhead et al., 2007), it is likely that they also have heightened susceptibility to this form of dermatitis following exposure to formaldehyde. To date, however, no studies are available that specifically evaluate the prevalence of atopic eczema in pregnant women compared to other populations following exposure to formaldehyde. In one study, Matsunaga et al. (2008) found a two-fold higher risk for atopic eczema in pregnant women with formaldehyde exposures of approximately 0.06 mg/m^3 measured in their homes.

Later lifestages

In general, older adults may have greater susceptibility than younger adults to chemical exposures due to slower metabolisms and an increased incidence of altered health status (Benedetti et al., 2007; Ginsberg et al., 2005). One study (Bentayeb et al., 2015) indicated possible differential effects of formaldehyde exposure for elderly adults (>65 years old) compared with other age groups. Bentayeb et al. (2015) observed an elevated risk of decreased pulmonary function in nursing home residents at lower formaldehyde exposure levels than have been seen to cause effects in younger adults.

Health Status and Disease

Preexisting health conditions and diseases may predispose individuals to toxic effects following exposure to formaldehyde. Some epidemiological studies have suggested that asthmatics are more susceptible than nonasthmatics to declines in respiratory function following formaldehyde exposure. Krzyzanowski et al. (1990) found that asthmatic children showed a steeper decline in morning peak expiratory flow rate (PEFR) compared with nonasthmatic children at formaldehyde concentrations below 0.05 mg/m^3. Similarly, a study by Kriebel et al. (1993) reported a greater decrease in peak expiratory flow (PEF) in asthmatic, compared with nonasthmatic, medical students after formaldehyde exposures in an anatomy lab. However, this study (Kriebel et al., 1993) had a small sample size and the effect was not statistically significant.

Studies evaluating effect modification by existing allergies are inconsistent. Acute and short-term studies in two animal species demonstrate that formaldehyde increases responsiveness to allergens and bronchoconstrictors, particularly with prior sensitization, indicating that allergy status may modify an individual's sensitivity to bronchial hyperreactivity and other asthma symptoms due to formaldehyde exposure (Larsen et al., 2013; Riedel et al., 1996; Swiecichowski et al., 1993; Leikauf, 1992). However, studies of associations with eczema, prevalence of asthma or asthma control were inconsistent, reporting either an increased or decreased prevalence among groups with a positive atopy status in adults or children (Annesi-Maesano et al., 2012; Matsunaga et al., 2008; Venn et al., 2003; Smedje and Norback, 2001). The evidence, therefore, is inconclusive and additional research is needed to address the question of potential effect modification by atopy status. Separately, the swelling of the mucus membrane, which has been observed in humans exposed to <1 mg/m^3 formaldehyde (see Section 1.2.4), is expected to be highly influenced by the underlying respiratory status of the exposed individuals, such as allergy status or previous or current respiratory infections. Supporting this assumption, nasal lesions have been found to be more severe in formaldehyde-exposed rodents with prior nasal damage (Woutersen et al., 1989; Appelman et al., 1988), and similar observations have been made in exposed humans (Falk et al., 1994). Therefore, individuals with prior nasal damage might also have heightened subsceptibililty to the development of nasal cancer following formaldehyde exposure.

As discussed in Section 1.1.3, nasal anatomy and soluble factors in the URT play a major role in the uptake of a highly reactive gas like formaldehyde. There are considerable interindividual variations in nasal anatomy (ICRP, 1994). For example, the nasal volumes of 10 adult nonsmoking subjects between 18 and 50 years of age in a study in the United States varied between 15 and 60 mL (Santiago et al., 2001), and disease states can result in further variation (Singh et al., 1998). Therefore, population variability in the distribution of inhaled formaldehyde, and in the susceptibility to its health effects, could potentially be large.

To date, many other factors related to health, such as obesity, have not been investigated to determine if they affect susceptibility to formaldehyde-related adverse effects.

Sex

Males and females can differ greatly in body composition, organ function, and many other physiological parameters that may influence the toxicokinetics of chemicals and their metabolites in the body (Gochfeld, 2007; Gandhi et al., 2004). The human epidemiology data set does not support many specific sex susceptibilities for noncancer effects due to formaldehyde exposure. However, in general, data suggest that nonpregnant women, on a per kilogram body weight basis, may have slightly lower air intake than men, which would suggest that women may be less susceptible than men to inhaled pollutants like formaldehyde, but this has not been investigated to date.

Similar to age and allergy and respiratory infection status, studies of related chemicals suggest that human sensitivity to sensory irritation may also be dependent on sex (Shusterman, 2007; Hummel et al., 2003). It is likely that women may be more sensitive than men to the eye and URT irritant properties of formaldehyde. For example, a higher prevalence of burning or tearing eyes was observed among women compared to men in a study of residential exposure (Liu et al., 1991).

In contrast, several animal studies suggest that males may be more susceptible than females to histopathological lesions of the URT, although most studies only examined male animals. For example, one study in rats reported that males generally had more severe damage, including metaplasia, to the nasal respiratory and olfactory epithelium and larynx following formaldehyde exposure (Woutersen et al., 1987). Supportive findings of increased incidence or severity of lesions in males as compared to females was also reported in a second study of rats (Zwart et al., 1988), and in mouse studies of (Maronpot et al., 1986; Kerns et al., 1983). Male rats have a higher metabolic rate and oxygen demand than do female rats; therefore, these findings might reflect a greater inhaled dose of formaldehyde in males compared to females at similar exposure concentrations.

It is also concluded that the **evidence indicates** formaldehyde exposure likely causes sex-specific health effects related to reproduction, given the relevant exposure circumstances. Specifically, a coherent spectrum of male reproductive effects was observed in experimental animal studies following exposure to high levels of formaldehyde, with supporting evidence in a well-conducted human study. In addition, epidemiological studies identified decreased fecundity and increased spontaneous abortion risk in women occupationally exposed to formaldehyde. This evidence could reflect developmental effects, or changes in the female reproductive system.

Race

Race may be a modifying factor of formaldehyde toxicity, for example, if specific polymorphisms in metabolizing enzymes affecting chemical toxicokinetics are more prevalent in specific races. Additionally, lifestyle factors that modify toxicity may be more or less prevalent in specific races. The only study to evaluate the potential role of race in carcinogenicity (Hayes et al.,

1990) found significantly increased death rates from nasopharyngeal cancer and multiple myeloma in nonwhite embalmers and funeral directors; whereas no changes in death rates from nasopharyngeal cancer or in cases of multiple myeloma were found in white embalmers and funeral directors. Very few other studies have explored the role of race in formaldehyde susceptibility, preventing the interpretation and generalizability of this observation.

A more detailed description of the role of polymorphisms in susceptibility is provided below. Additional research is needed to confirm the findings in Hayes et al. (1990).

Genetic Polymorphisms

Genetic polymorphisms may affect the expression level of genes and resulting activity of important metabolizing enzymes, and this may lead to differential toxicity following chemical exposures. As discussed in Appendix A.2, the primary metabolizing enzyme of formaldehyde is ADH3 (referred to as ADH5 in recent papers). A secondary pathway involves mitochondrial aldehyde dehydrogenase 2 (ALDH2). Both ADH3 and ALDH2 are important in the detoxification of formaldehyde, converting it to formate, which is readily excreted from the body. ADH3 is also known to catalyze the NADP-dependent reduction of the endogenous nitrosylating agent S-nitrosoglutathione (GSNO) and, in this capacity, is referred to as S-nitrosoglutathione reductase (GSNOR) (Jensen et al., 1998). GSNOR participates in the oxidation of retinol and long-chain primary alcohols. It also contributes to nitric oxide (NO) signaling through its role in metabolizing GSNO an endogenous bronchodilator and reservoir of NO (Staab et al., 2008; Hess et al., 2005; Jensen et al., 1998), indicating ADH3's involvement in bronchial tone allergen-induced hyperresponsiveness (Gerard, 2005; Hess et al., 2005; Que et al., 2005).

Wu et al. (2007) found that carrying one or two copies of the minor allele rs1154404 for a single nucleotide polymorphism (SNP) of *ADH3* resulted in a decreased risk of asthma in Mexican children. For a different SNP (rs28730619), homozygotes for the minor allele had an increased risk of asthma. Although only speculative as their functional characteristics are unknown, these SNPs may affect the response of individuals to formaldehyde exposure by altering their metabolism. One study (Hedberg et al., 2001) identified four polymorphisms in the human *ADH3* gene promoter that resulted in reduced transcriptional activity. Because this would likely result in reduced levels of the ADH3 protein, individuals with this polymorphism may be at greater risk for formaldehyde toxicity compared with people with the wild-type gene. This is supported by a study in which deletion of the *ADH3* gene increased the sensitivity of mice to formaldehyde toxicity (Deltour et al., 1999).

Some studies have also suggested that CNS toxicity can result from reduced activity of the metabolizing enzymes responsible for clearing formaldehyde from relevant tissues (e.g., downregulated ALDH2 in Tan et al. (2018)). Therefore, it is plausible that individuals with polymorphisms in *ALDH2* or in other genes encoding detoxifying enzymes may be more susceptible to CNS toxicity caused by formaldehyde exposure compared to those with wild type alleles. This highlights another area of interest for future studies on potential susceptibility to inhaled formaldehyde exposure.

A few studies of genotoxicity among formaldehyde-exposed groups evaluated differences in response based on polymorphisms in genes coding for proteins involved in the metabolism of xenobiotics, including *CYP2E1*, glutathione-S-transferases (*GST*s), and *ADH3*. The X-ray repair cross-complementing gene 3 (*XRCC3*), which codes for a protein involved in DNA repair and chromosome stabilization, also was evaluated (Costa et al., 2015; Ladeira et al., 2013; Santovito et al., 2011; Jiang et al., 2010). The results of these studies were inconsistent and no conclusions regarding the impact of these genetic polymorphisms on susceptibility can be drawn. (e.g., Shen et al., 2016; Rager et al., 2014)

Studies of mice with knocked out *Aldh2* and *Aldh5*, which encode for enzymes that remove endogenous formaldehyde, have suggested that polymorphisms in *Aldh2* and *Aldh5*, may increase susceptibility to genotoxicity. These knockouts resulted in severely disrupted hematopoiesis and leukemia, including mutated and abnormal HSPCs, which is presumably linked to increased accumulation of endogenous formaldehyde (Dingler et al., 2020; Burgos-Barragan et al., 2017b; Pontel et al., 2015). Likewise, direct treatment of *Aldh5-/-* bone marrow cells with formaldehdye caused genotoxicity and reduced HSPC formation, effects which are further exacerbated by loss of *Fancd2* (this latter deficiency is associated with increased sensitivity to DNA damage) (García-Calderón et al., 2018; Burgos-Barragan et al., 2017b). As reviewed and tested by Dingler et al. (2020), genetic deficiencies in these Aldh family genes have been linked to bone marrow failure and related diseases in humans, including in children. Reduced ALDH2 or ALDH5 activity resulting in increased endogenous formaldeheyde in mice and humans might also contribute to postnatal lethality, stunted growth, cognitive effects (see Section 1.3.1) and various cancers arising from DNA damage or deficient repair (Dingler et al., 2020; Nakamura et al., 2020). While formaldehyde inhalation does not seem to cause appreciable changes in formaldehyde levels in nonrespiratory regions (see Appendix A.2), HSPCs expressing these enzymes are known to exist in many tissues. However, no studies in any species have specifically examined these possible linkages in relation to inhaled formaldehyde. Therefore, while genetic differences may alter susceptibility to the cytogenetic effects of formaldehyde, more definitive research is needed. A few in vitro studies have suggested that epigenetic changes or loss of function of important genes might increase susceptibility to formaldehyde toxicity (e.g., Shen et al., 2016; Rager et al., 2014). However, additional studies are needed to clarify these preliminary observations.

Lifestyle Factors

Lifestyle factors may increase or decrease exposure to formaldehyde and may also affect the resulting health effects following formaldehyde exposure. These lifestyle factors may vary by race, ethnicity, socio-economic status, or geographic location. To date, specific studies do not exist to address the role of lifestyle factors on formaldehyde toxicity.

Nutritional status

Because formaldehyde appears to cause inflammation, particularly in the airways, it is plausible that a diet rich in antioxidants would protect against inflammation and one that lacks sufficient antioxidants would result in greater inflammation. Additional research is needed to specifically evaluate possible modification of formaldehyde toxicity by nutritional status.

Smoking

Smoking is considered a lifestyle factor, but it also introduces coexposures to the many chemicals in cigarette smoke, including additional formaldehyde. Thus, it is difficult to disentangle potential indirect contributions of smoking to the health effects of formaldehyde exposure from the possible direct effects of the formaldehyde in tobacco smoke (see additional discussion below under "coexposures").

Exercise

The possibility that more extensive distribution of formaldehyde (e.g., to the LRT) may occur when people are breathing through the mouth during exercise has not been investigated. However, some controlled human exposure studies observed pulmonary function deficits when a longer exercise component (15 minutes) was included that were not observed by other studies with shorter periods or no exercise (Green et al., 1989; Green et al., 1987), and another study observed an increase in bronchial hyperresponsiveness with an exposure protocol using nose clips necessitating mouth-only breathing (Casset et al., 2006). Clearly, further research is warranted to understand the role of exercise in formaldehyde susceptibility.

Coexposures

Coexposures to other pollutants, such as those that produce similar metabolites and health effects to formaldehyde and those that are mutagens, may exacerbate the effects of formaldehyde exposure. In addition, constituents in the diet, such as methanol and caffeine, contribute to the generation of endogenous formaldehyde in nonrespiratory tissues (Summers et al., 2012; Riess et al., 2010; Hohnloser et al., 1980), which are promptly detoxified (Burgos-Barragan et al., 2017a). Yet, it is not expected that variation in endogenous formaldehyde levels at sites distal to the URT would affect relative sensitivity to the effects of inhaled formaldehyde. These findings are inconclusive, however, so additional research is needed to investigate the role of these coexposures.

As described in Section 1.2.3, tobacco smoke may increase the incidence of hypersensitivity responses in formaldehyde-exposed individuals. Effect modification by environmental tobacco smoke (i.e., stronger associations, or associations seen at lower formaldehyde exposures, with this coexposure) were reported in two studies that examined asthma prevalence stratified by environmental tobacco smoke exposure among children and adults (nonsmokers) (Palczynski et al., 1999; Krzyzanowski et al., 1990). Additional studies are needed to establish if this interaction is seen only in children, in adults and children, or in neither group. One residential study by

Krzyzanowski et al. (1990) indicated that smokers experienced a greater decline in morning PEFR compared to nonsmokers at formaldehyde concentrations above 0.050 mg/m^3. Smokers were not more responsive to formaldehyde exposures in most occupational studies that stratified by smoking behavior. Nonsmokers experienced 2- to 3.5-fold larger annual decreases in FEV_1, FEV_1/FVC, and FEF_{25-75} over 5 years (Alexandersson and Hedenstierna, 1989), as well as larger declines during a work shift (Alexandersson and Hedenstierna, 1989; Alexandersson et al., 1982). In contrast, current smokers had an approximately two-fold larger OR for airway obstruction, defined as an FEV_1/FVC <75%, compared with nonsmokers (Herbert et al., 1994). The magnitude of the difference associated with formaldehyde exposure may have reflected the existing difference in baseline pulmonary function values between smokers and nonsmokers.

Although not a chemical coexposure, humidity also appears to modify the effects of formaldehyde exposure. For example, formaldehyde exposure-induced bronchoconstriction in mice housed only in humid, but not dry, environments indicating that the bronchoconstrictive effects of formaldehyde may be impacted by humidity (Larsen et al., 2013). The effects of formaldehyde on mucus flow patterns also appear to vary based on humidity.

In addition, it is possible that exposure to nochemical stressors, such as poverty, violence, and other social factors, might make some populations more susceptible to formaldehyde-related health effects. However, at this time, studies evaluating the contribution of nonchemical stressors to formaldehyde susceptibility have not been published.

Additional research is needed to investigate whether coexposures to pollutants other than tobacco smoke and to nonchemical stressors confer additional susceptibility to formaldehyde toxicity.

Summary of Susceptible Populations and Lifestages

Epidemiological and toxicological studies, as a whole, identify reproductive or developmental toxicity as a human health hazard of formaldehyde exposure. At this time, it is not clear whether increased time-to-pregnancy (TTP) and spontaneous abortion rates seen in occupationally exposed women are due to reproductive system toxicity or to toxicity to the developing fetus.

Children also appear to be a susceptible population. Studies have indicated that they have an increased sensitivity to respiratory and immunological effects following formaldehyde exposure. In addition, younger age is likely to be associated with a higher risk of mutagenic effects and, therefore, to a higher risk of URT cancers. As age may be a modifying factor of the sensory irritant properties of formaldehyde, both children and the elderly may be at an either increased or decreased risk for sensory irritation.

Health status and disease are likely to be modifying factors of formaldehyde toxicity as well. Studies suggest that asthmatics are more susceptible than nonasthmatics to declines in respiratory function following formaldehyde exposure. Whether atopy and allergies can also influence the health effects of formaldehyde exposure remains to be determined; additional studies are needed to

confirm this relationship. Individuals with prior nasal damage might also have heightened subsceptibililty to the development of nasal cancer following formaldehyde exposure.

Study findings on the role of genetic susceptibility in formaldehyde toxicity are inconclusive. Therefore, gene-environment interaction studies are needed to investigate the effects of polymorphisms in genes that encode formaldehyde metabolizing enzymes, as well as receptors (e.g., TRPA1) or other proteins that appear to be key components of the MOA for certain human health effects of formaldehyde exposure.

Coexposures appear to increase susceptibility to health effects following formaldehyde exposure as well. There is some evidence that cigarette smoking increases sensitivity to formaldehyde toxicity; however, it is not clear if this increased sensitivity is due to the additional formaldehyde to which smokers are exposed, to exposures to other chemicals that are present in cigarette smoke, or to compromised respiratory systems.

Although other factors are hypothesized to confer increased susceptibility to formaldehyde toxicity, the available data are limited. Overall, the most extensive research on the health effects of inhaled formaldehyde and susceptible groups indicates a greater susceptibility among children to respiratory disease, manifested as reduced pulmonary function, increased prevalence of current asthma, and greater asthma severity (reduced asthma control). More research is needed to investigate the role of sex, race, nutrition, exercise, and other coexposures that may modulate susceptibility to formaldehyde toxicity. In addition, these susceptibility factors might interact with one another. For example, lifestage, pre-existing health conditions, genetic polymoprhisms and co-exposures to both chemical and nonchemical stressors could all contribute to heightened susceptibility to formaldehyde toxicity for some individuals.

Summary of Vulnerable Population

Groups that may receive disproportionally high levels of exposure to formaldehyde, and therefore might experience more frequent or severe formaldehyde-related health consequences, include people in occupations with workplace exposures. Some industries with the greatest potential for exposure include health services, business services, printing and publishing, chemical manufacturing, garment production, beauty salons, and furniture manufacturing (IARC, 1995). People who spend a significant amount of time in mobile homes and trailers, either as primary residences, classrooms, job sites or for other reasons, might also be vulnerable because these structures can have high formaldehyde levels (Murphy et al., 2013). Lastly, in addition to the potential of cigarette smoking to increase susceptibility to formaldeyde, it also can increase exposure to it (Fishbein, 1992). It should be noted that individuals who are both susceptible and highly exposed to formaldeyde are at the highest risk of suffering from formaldehyde-related health effects.

1.4.2. Summary of Evidence Integration Conclusions for Effects Other Than Cancer

Overall, the **evidence demonstrates** that inhalation of formaldehyde causes sensory irritation and respiratory pathology in humans, given appropriate exposure circumstances, based on studies of the general population with residential exposure, controlled human exposure studies, and occupational studies. The **evidence indicates** that inhalation of formaldehyde likely causes decrements in pulmonary function, and an increased frequency of current asthma symptoms and allergic responses, given appropriate exposure circumstances, based on studies of adults and children exposed in their homes or at school. In addition, the **evidence indicates** that inhalation of formaldehyde likely causes female reproductive or developmental toxicity, and reproductive toxicity in males, given appropriate exposure circumstances, based on studies involving residential and occupational exposure and toxicological studies. Lastly, while a number of studies reporting evidence of potential neurotoxic effects were available, including developmental neurotoxicity, multiple manifestations of behavioral toxicity, and an increased incidence of, or mortality from, the motor neuron disease, amyotrophic lateral sclerosis (ALS), due to limitations identified in the database (e.g., poor methodology; lack of consistency), the evidence integration analyses for these outcomes determined that the **evidence suggests**, but is not sufficient to infer, a human health hazard(s). The data on potential nervous system effects were considered insufficient for developing quantitative estimates of risk. Context on these decisions is provided below:

- Sensory Irritation:
    - The **evidence demonstrates** that inhalation of formaldehyde causes sensory irritation in humans, given appropriate exposure circumstances, based on *robust* human evidence from controlled human exposure studies testing responses to concentrations 0.1 mg/m^3 and above and observational epidemiology studies of residential populations with mean formaldehyde concentrations >0.05 mg/m^3 (range of 0.01 to approximately 1.0 mg/m^3), *robust* evidence for an effect in animals (this phenomenon is well described and accepted across a range of experimental species), as well as an established MOA based on mechanistic evidence in animals (the identified MOA is interpreted to be operant in humans). The irritant response occurs within minutes to hours depending on concentration, and severity is concentration dependent. Potentially large variations in sensitivity are expected, depending primarily on differences in nasal health (including allergy or inflammatory status) and physiology.
- Pulmonary Function:
    - The **evidence indicates** that long-term (chronic) inhalation of formaldehyde likely causes decrements in pulmonary function, given appropriate exposure circumstances, based on *moderate* human evidence primarily from observational epidemiology studies among occupational cohorts with long-term exposure to >0.2 mg/m^3 and a study of children and adults with residential exposure (mean, 0.03 mg/m^3, maximum 0.17 mg/m^3), as well as *slight* evidence for an effect in animals involving inflammatory airway changes in mechanistic studies (it is

expected that related mechanistic changes can occur in exposed humans, and some indirect confirmatory evidence from exposed humans exists). The evidence is *inadequate* to interpret whether acute or intermediate-term (hour-weeks) formaldehyde exposure might cause this effect. Variation in sensitivity is anticipated to depend on age and respiratory health.

- Respiratory Tract Pathology:

  - The **evidence demonstrates** that inhalation of formaldehyde causes increased respiratory tract pathology in humans, including hyperplasia and squamous metaplasia, given appropriate exposure circumstances, based on *robust* evidence from animal studies involving multiple species with increases in severity and frequency of lesions with increasing concentration or longer exposure duration. The primary support for this conclusion is based on rat bioassays of chronic exposure which consistently observed squamous metaplasia at formaldehyde exposure levels ≥2.5 mg/m^3. There is *moderate* human evidence from occupational epidemiology studies supported by more limited findings in mechanistic studies of exposed humans, and strong support for a plausible MOA based largely on mechanistic evidence in animals (supported by coherent findings in human studies). Variation in sensitivity may depend on differences in URT immunity and nasal structure or past injury, but few studies exist that specifically evaluate these possibilities.

- Immune-mediated Conditions, including Allergies and Asthma:

  - The **evidence indicates** that inhalation of formaldehyde likely causes increases in the prevalence of allergic conditions in humans**,** given appropriate exposure circumstances, based on *moderate* evidence of an enhanced immune hypersensitivity response to allergens (i.e., allergic rhinitis or rhinoconjunctivitis; eczema) in general population studies of adults and children at average exposures between 0.03 and <0.1 mg/m^3 formaldehyde, and *slight* evidence of effects relevant to immune-mediated respiratory conditions in animals from mechanistic studies of airway hyperresponsiveness and some more limited data relevant to systemic inflammatory changes in both human and animal mechanistic studies; however, the proposed, incomplete MOA(s) are not established and have not been experimentally verified.

  - The **evidence indicates** that inhalation of formaldehyde also likely causes increases in the prevalence of asthma symptoms in humans, given appropriate exposure circumstances, based on *moderate* evidence of an increased risk of prevalent current asthma in occupational settings (>0.1 mg/m^3) and population studies in adults and children, or poor asthma control in children at exposures above 0.05 mg/m^3 formaldehyde and *slight* evidence for effects in animals from mechanistic studies; however, an MOA explaining this association is not available. Specifically, regarding the animal evidence, although several events typically associated with asthma are not well supported by the available data, the animal mechanistic data support that formaldehyde inhalation induces bronchoconstriction with and without allergen sensitization and stimulates a number of immunological and neurological processes that would be expected to augment or drive asthmatic responses. Variation in

sensitivity is anticipated depending on respiratory health, age, and exposure to tobacco smoke.

- Developmental and Reproductive Toxicity:

  - The **evidence indicates** that inhalation of formaldehyde likely causes developmental or female reproductive toxicity in humans, based on moderate evidence in observational studies finding effects on fetal growth among pregnancy cohorts observed at indoor formaldehyde concentrations >0.04 mg/m^3, and possibly lower, as well as increases in TTP and spontaneous abortion risk among occupationally exposed women (average formaldehyde concentrations >0.1 mg/m^3); the evidence in animals is indeterminate, and a plausible, experimentally verified MOA explaining such effects without systemic distribution of formaldehyde is lacking.

  - The **evidence indicates** that inhalation of formaldehyde also likely causes reproductive toxicity in men, given appropriate exposure circumstances, based on *robust* evidence in animals that presents a coherent array of adverse effects in two species, and *slight* evidence from observational studies of occupational exposure. Uncertainties include a lack of well-conducted animal studies testing formaldehyde exposure levels below 6 mg/m^3 and no plausible, experimentally verified MOA explaining such effects without systemic distribution of formaldehyde; however, some support for indirect effects in rodents is provided by relevant mechanistic changes in male reproductive organs.

- Nervous System Effects

  - The **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation might cause an increase in incidence or mortality from the motor neuron disease, ALS, given the appropriate exposure circumstances, based on *slight* epidemiological evidence. No relevant animal studies (i.e., *indeterminate* evidence) or mechanistic information were identified, and additional studies are warranted.

  - Likewise, the **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation might cause increases in multiple manifestations of neurobehavioral toxicity, given appropriate exposure circumstances, based primarily on *slight* evidence of effects in animals of two species across several behavioral domains (i.e., neural sensitization; tests of learning and memory; and tests of motor-related behaviors), and supported by *slight* evidence in human observational and controlled exposure studies. An experimentally verified MOA explaining such effects without systemic distribution of formaldehyde is lacking; however, some mechanistic findings support the potential for indirect effects on relevant brain regions. Well-conducted studies of these potential effects are currently unavailable.

  - The **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation might cause developmental neurotoxicity, given appropriate exposure circumstances, based on *slight* evidence in animals for neuropathology and potentially supportive mechanistic findings in relevant brain regions. However, as neither an experimentally verified MOA nor relevant studies in children were identified, this is an area in need of further research.

1.4.3. Summary of Evidence Integration Conclusions for Carcinogenicity

"Formaldehyde Is Carcinogenic to Humans by the Inhalation Route of Exposure"[31]

Several lines of evidence support this conclusion. Specifically, the hazard descriptor ***carcinogenic to humans*** is independently substantiated by three lines of evidence, namely evidence integration judgments that the **evidence demonstrates** that formaldehyde inhalation causes nasopharyngeal cancer, sinonasal cancer and, myeloid leukemia, in exposed humans, given appropriate exposure circumstances.

These overall confidence conclusions, as well as the strength of the human and animal evidence (i.e., *robust, moderate, slight, indeterminate*), were based on the currently available evidence using the approaches described in the description of methods in the Preface of this report, which included a consideration of mechanistic evidence when drawing each conclusion. Note that, as the site-specific relationship of the animal data to the specific human cancer types involved additional considerations, the inference regarding the relevance of the animal data to each specific human cancer is presented herein as a component of the animal evidence judgments.

Evidence Integration Conclusion*: *Carcinogenic to Humans

Three separate evidence integration judgments independently substantiate this conclusion:

- Nasopharyngeal cancer—The **evidence demonstrates** that formaldehyde inhalation causes nasopharyngeal cancer (NPC) in humans. This is based primarily on observations of increased risk of NPC in groups exposed to occupational formaldehyde levels and nasal cancers in mice and several strains of rats, with strong, reliable, and consistent mechanistic evidence in both animals and humans (i.e., *robust* evidence for both the human and animal evidence, and strong mechanistic support for the human relevance of the animal data). The nasopharynx, although not typically specified in animal studies, is the region adjacent to the nasal cavity, where the animal evidence was predominantly observed (thus, the animal evidence is judged as *robust*). In addition, the evidence is sufficient to conclude that a mutagenic MOA of formaldehyde is operative in formaldehyde-induced nasopharyngeal carcinogenicity.

- Sinonasal cancer—The **evidence demonstrates** that formaldehyde inhalation causes sinonasal cancer (SNC) in humans. This is based primarily on observations of increased risk of SNC in groups exposed to occupational formaldehyde levels (i.e., *robust* human evidence) and supported by apical and mechanistic evidence for nasal cancers across multiple animal species. Some uncertainties remain in the interpretation of the animal nasal cavity data as wholly applicable to interpreting human sinonasal cancer (thus, the animal evidence is

[31]The hazard conclusion for cancer is consistent with those drawn by other expert review panels. Formaldehyde was classified as a known carcinogen by the NTP (2011) and a Group 1 carcinogen by IARC (2012, 2006), both based on evidence for nasal cancers in humans and animals and myeloid leukemia in humans, with supporting data on mechanisms of carcinogenesis. In addition, an expert committee convened by the NAS NRC confirmed the conclusions of the NTP 12th RoC and conducted an independent review of the literature through 2013, concluding that formaldehyde is a known carcinogen. The European Union and Health Canada concluded that formaldehyde is a genotoxic carcinogen with a cytotoxic MOA based on nasal cancer evidence (SCOEL, 2017; ECHA, 2012; Health Canada, 2006, 2001).

judged as *moderate*). While uncertainties remain, the evidence is sufficient to conclude that a mutagenic MOA of formaldehyde is operative in formaldehyde-induced sinonasal carcinogenicity.

- Myeloid leukemia—The **evidence demonstrates** that formaldehyde inhalation causes myeloid leukemia in humans, given appropriate exposure circumstances. This is based primarily on *robust* human evidence of an increased risk of the occurrence of myeloid leukemia in epidemiological studies among different populations exposed to occupational formaldehyde levels representing diverse exposure settings. The findings from the occupational cohorts are further supported by other studies of human occupational exposure providing strong and coherent mechanistic evidence that formaldehyde exposure is associated with the detection of additional endpoints relevant to LHP cancers, including an increased prevalence of multiple markers of genotoxicity in peripheral blood and myeloid progenitors. Indirect support is also provided by evidence of other systemic health effects (e.g., reproductive or developmental toxicity) and mechanistic evidence indicating changes in immune cell populations and markers of inflammation (e.g., oxidative stress) in the peripheral blood of exposed humans and animals, although the exact pattern of immune-related changes across studies and species was difficult to interpret. Notably, leukemia has not been observed in the two available rodent bioassays of chronic exposure, including one testing both sexes of rats and mice, and the evidence for genotoxicity in the peripheral tissues of exposed rodents is weak, providing *indeterminate* evidence of LHP cancers in animals. Taken together, it appears that mechanisms yet to be elucidated that do not involve direct interactions of formaldehyde in the bone marrow need to be considered, and that either the mechanistic pathways stimulated by formaldehyde are different in animals or that the existing animal models tested thus far do not characterize the disease process in humans for these cancers. The exact mechanism(s) leading to cancer formation outside of the respiratory tract are unknown.

The remaining evidence relevant to evaluating the potential for formaldehyde inhalation to cause cancer did not contribute to the overall hazard conclusion above, including formal evaluations of the following cancer types:

- Oropharyngeal/hypopharyngeal cancer—The available **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation might cause oropharyngeal/ hypopharyngeal cancer in humans, given appropriate exposure circumstances. This is based primarily on *slight* human evidence from epidemiological findings and potentially relevant mechanistic changes (e.g., in buccal cells) and supporting *slight* animal evidence of preneoplastic lesions and mechanistic changes. While cancer site concordance is not required for hazard determination (U.S. EPA, 2005a), given the known reactivity and distribution of inhaled formaldehyde, a lesser level of confidence in the applicability of the animal nasal findings is inferred for this cancer type as compared to NPC or SNC and the evidence overall is not interpreted to provide reasonable support for a MOA.

- Multiple myeloma—The available **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation might cause multiple myeloma, given the appropriate exposure circumstances. This is primarily based on *slight* human evidence from epidemiological findings. The animal evidence is *indeterminate*, and the available mechanistic information was not interpreted to be influential, indicating a need for additional study.

- Hodgkin lymphoma— The available **evidence suggests**, but is not sufficient to infer, that formaldehyde inhalation might cause Hodgkin lymphoma, given the appropriate exposure circumstances. This is primarily based on *slight* human evidence from epidemiological findings. The animal evidence is *indeterminate*, and the available mechanistic information was not interpreted to be influential, indicating a need for additional study.

- Laryngeal cancer— All the evidence related to laryngeal cancer was judged as *indeterminate*; thus, the **evidence** was **inadequate** to determine whether formaldehyde inhalation exposure may be capable of causing this cancer type.

- Lymphatic leukemia—All the evidence related to lymphatic leukemia was judged as *indeterminate*; thus, the **evidence** was **inadequate** to determine whether formaldehyde inhalation exposure may be capable of causing this cancer type.

2. DOSE-RESPONSE ANALYSIS

2.1. INHALATION REFERENCE CONCENTRATION FOR EFFECTS OTHER THAN CANCER

The reference concentration RfC (expressed in units of mg/m^3) is defined as an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a no-observed-adverse-effect level (NOAEL), lowest-observed-adverse-effect level (LOAEL), or the 95% lower bound on the benchmark concentration (BMCL), with uncertainty factors (UFs) generally applied to reflect limitations of the data used. The approach for deriving an overall RfC involves the following steps, the specific methods and considerations for which are outlined within each of the subsequent sections:

1) Identify studies and endpoints for each health effect that are sufficient (i.e., with one of the two strongest evidence integration judgments for hazard, namely of **evidence demonstrates** or **evidence indicates,** and *high* or *medium* confidence in the study methodological conduct, as well as data amenable for dose-response analysis), and calculate points of departure (PODs)

2) Derive candidate RfCs (cRfCs) by applying UFs to the PODs

3) Select organ- or system-specific RfCs (osRfCs) based on the cRfCs

4) Select an overall RfC based on the osRfCs

Candidate RfCs were derived from studies supporting several health hazards, including sensory irritation (eye irritation), pulmonary function (peak expiratory flow rate), allergies (rhinoconjunctivitis, atopic eczema), current asthma (i.e., symptoms or medication in the previous 12 months), degree of asthma control, respiratory tract pathology (squamous metaplasia), developmental toxicity (delayed pregnancy), and male reproductive toxicity (testes weight, serum testosterone). The rationale for the prioritization of specific endpoints selected for use in dose-response evaluation (e.g., squamous metaplasia rather than hyperplasia for respiratory tract pathology) is discussed in Chapter 1. The cRfCs for sensory irritation, pulmonary function, immune effects including allergies and current asthma, and female and developmental toxicity were derived using data from epidemiology studies, while the cRfCs for respiratory tract pathology and male reproductive toxicity were derived using data from experimental animals. cRfCs were not derived for nervous system effects, as the available evidence was deemed to be too uncertain, and thus insufficient, to support quantitative dose-response assessment. In this case, the primary sources of

uncertainty in the data included study-specific methodological limitations[32] and a lack of reproducibility across well-conducted studies within the databases for the individual outcomes evaluated, all in the context of an incomplete evidence base.

The studies most applicable to formaldehyde exposure settings in the general population were preferred, and the level of confidence in cRfCs was incorporated in the derivation of the osRfCs. An overall RfC for formaldehyde of 0.007 mg/m^3 was selected. This value is within the narrow range (0.006–0.009 mg/m^3) of the group of respiratory system-related RfCs (i.e., sensory irritation, pulmonary function, allergy-related conditions, and current asthma prevalence or degree of control), which together are interpreted with *high confidence* based on the confidence considerations outlined below. These osRfCs are based on PODs that are the lowest of those identified in population studies for formaldehyde hazards, and with the lowest composite uncertainty. Uncertainties in the overall RfC are discussed with the rationale for the RfC selection in Section 2.1.4.

While the RfC is interpreted to be a concentration associated with minimal risk over a lifetime of exposure, a few of the hazards or outcomes, including sensory irritation symptoms, or the degree of asthma control, could be relevant to a shorter exposure time frame. The applicability of the osRfC to shorter exposure periods is noted for the relevant hazards.

2.1.1. Choice of Studies and Endpoints and Calculation of PODs

Data sufficient to support dose-response analyses were available for all of the health systems for which the integration of all the evidence resulted in judgments of **evidence demonstrates** or **evidence indicates** that inhalation of formaldehyde can cause adverse human health effects. Rationales for study selection and the specifics of cRfC calculations, as well as the determination of confidence in the PODs, are detailed in this section.

Methods of Analysis

From among the body of evidence used for the hazard identification assessment, selection of the studies for dose-response assessment used information from the study confidence evaluations, with particular emphasis on conclusions regarding the characteristics of the study population and the accuracy of formaldehyde exposure, the severity of the observed effects, and the exposure levels analyzed (see Table 2-1 and Appendix A.5.1). Human studies were preferred over laboratory animal studies if quantitative measures of exposure were analyzed in relation to health endpoints. Epidemiological studies that evaluated groups most representative of the general

[32]For example, the reported formaldehyde exposure data in epidemiology studies demonstrating associations were generally not amenable to use in quantitative dose-response analysis. In the available animal studies, there were prominent methodological limitations including poor exposure quality; an inability to rule out nonspecific effects due to irritant or odorant responses, or due to conditions unlikely to be relevant to human exposure scenarios; and deficiencies in the reporting of quantitative results important to quantitative analyses (e.g., litter information).

population (i.e., residential or school-based study populations) were preferred if exposure-response analyses were presented. These criteria emphasize the use of *high* or *medium* confidence studies with appropriate study designs, complete reporting of results, and results that would not be reasonably explained by selection bias or information bias or altered by adjustment for confounding. Studies with risk estimates for multiple exposure levels or regression coefficients per unit of formaldehyde concentration were preferred because they provided information about the concentration-response trend. The presence of an exposure-response gradient and analyses of data at lower exposure levels were considered. In the absence of such information, a LOAEL or NOAEL was identified using a rationale specific to the exposure data presented in the study.

If there were no adequate studies of human exposure for exposure-response analysis, then studies of experimental animals were evaluated. Using similar criteria as described for human studies (above), the overall quality of the experimental animal studies was considered (e.g., preference was given to studies with less likelihood of bias, confounding, etc.). To a large extent, this comparison of studies within a given health domain was facilitated using the study evaluation categories described in the *Preface on assessment methods and organization* (e.g., *high* or *medium* confidence). In addition, experimental animal studies were preferred if they were from models that respond most like humans; tested the effects of formaldehyde inhalation exposure using paraformaldehyde as the test article; were of longer exposure duration and follow-up, evaluated across multiple exposure levels; and were adequately powered to detect effects at lower exposure levels. Table 2-1 shows the *high* and *medium* confidence studies for each hazard that included information possibly suitable to evaluate dose-response relationships and indicates for each study whether the study was used to develop a POD or the rationale for why the study was not suitable.

Once the preferred studies and effect(s) were identified within each health domain, PODs were derived for each chosen endpoint using a NOAEL, LOAEL, or BMCL. These PODs were then adjusted (POD_{ADJ}), if appropriate, to extrapolate from the estimated or measured exposures to a continuous exposure scenario. For laboratory animal studies, as applicable (U.S. EPA, 1994), this POD_{ADJ} was then converted to a human equivalent concentration (POD_{HEC}) using a mathematical calibration. Each of the following organ/health system discussions includes a description of confidence in the PODs derived from the individual studies.

Table 2-1. Eligible studies for POD derivation and rationale for decisions to not select specific studies

Reference	Endpoint	POD derived?	Rationale for decisions to not select
Sensory irritation			
Hanrahan et al. (1984)	Eye irritation: Prevalence	Yes	
Kulle et al. (1987)	Eye irritation: Prevalence	Yes	
Andersen and Molhave (1983)	Eye irritation: Prevalence	Yes	
Liu et al. (1991)	Eye irritation: Prevalence	No	Incomplete reporting of modeling results. Provided support for use of Hanrahan et al. (1984)
Mueller et al. (2013)	Eye irritation: Tear film break-up time, symptom score using visual analogue scale (VAS)	No	An exposure-response trend was not observed for either endpoint. Difficult to define an adverse response level cutoff for these endpoints
Lang et al. (2008)	Eye irritation: Conjunctival redness, blinking frequency, symptom score	No	Difficult to define an adverse response level cutoff for these endpoints and appeared to be less sensitive than symptom score
Pulmonary function			
Krzyzanowski et al. (1990)	PEFR	Yes	
Malaka and Kodama (1990)	FEV_1, $FEF_{25–75}$	No	Incomplete reporting of modeling results
Kriebel et al. (2001)	PEFR	No	Difficult to use modeling results because of covariance in model coefficients
Wallner et al. (2012)	FEF_{25-75}	No	Incomplete reporting of modeling results
Immune-mediated conditions: allergic conditions			
Annesi-Maesano et al. (2012)	Rhinoconjunctivitis prevalence: Children	Yes	
Matsunaga et al. (2008)	Allergic rhinitis, atopic eczema	Yes	
Yon et al. (2019)	Rhinitis prevalence	No	Minimal details provided on formaldehyde distribution
Neamtiu et al. (2019)	Allergy-like symptoms (eyes, nose and skin)	No	Provided support for use of Annesi-Maesano et al. (2012)
Garrett et al. (1999)	Atopy prevalence (SPTs): Children	No	Uncertain window of exposure with respect to test results
Palczynski et al. (1999)	Atopy prevalence (SPTs): Children	No	Uncertain window of exposure with respect to test results; too few individuals in third tertile
Immune-mediated conditions: current asthma			

Reference	Endpoint	POD derived?	Rationale for decisions to not select
Krzyzanowski et al. (1990)	Current asthma prevalence: Children	Yes	
Annesi-Maesano et al. (2012)	Current asthma prevalence: Children	Yes	
Matsunaga et al. (2008)	Current asthma prevalence: Adults	No	Definition of current asthma was narrow and resulted in ascertainment of fewer cases than would be expected
Palczynski et al. (1999)	Current asthma prevalence: Children and adults	No	Uncertainty regarding asthma definition (current, ever?); few cases in third tertile ($n \leq 5$)
Kim et al. (2011)	Current asthma prevalence: Children	No	Provided support for use of Annesi-Maesano et al. (2012)
Mi et al. (2006)	Current asthma prevalence: Children	No	Provided support for use of Annesi-Maesano et al. (2012)
Respiratory and immune-related conditions: asthma control			
Venn et al. (2003)	Asthma control: Children	Yes	
Dannemiller et al. (2013)	Asthma control: Children	Yes	
Respiratory pathology[a] in animal studies (exposure duration ≥52 weeks)			
Kerns et al. (1983)	Squamous metaplasia: Nasal turbinates, Fischer 344 rats	Yes	
Kerns et al. (1983)	Squamous metaplasia: Nasal turbinates, B6C3F1 mice	No	Compared to rats, mice are less susceptible to formaldehyde exposure-induced nasal pathology
Woutersen et al. (1989)	Squamous metaplasia: Nasal turbinates, Wistar rats	Yes	
Appelman et al. (1988)	Squamous metaplasia: Nasal turbinates, Wistar rats	No	Limited sample size (n = 10/group) and exposure duration (1 year), as compared to Kerns et al. (1983) (n = up to ~100/group; 24 months) and Woutersen et al. (1989) (n = 30/group; 28 months)
Kamata et al. (1997)	Squamous metaplasia: Nose and trachea, Fischer 344 rats	No	Uncertainty associated with methanol coexposure from formalin exposure, although a control group received methanol; small sample size at 28 months (i.e., no animals in the high exposure group survived; only n = 7 at 2.43 mg/m^3); metaplasia results pooled across scheduled sacrifices (12, 18, 24, and 28 months) and dead animals includes exposure durations that are less likely to reveal effects
Developmental toxicity (occupational cohort)			

Reference	Endpoint	POD derived?	Rationale for decisions to not select
Taskinen et al. (1999)	Time to pregnancy	Yes	
Taskinen et al. (1999)	Spontaneous abortion	No	Uncertain applicability of temporal window for exposure data with respect to reported spontaneous abortions
Franklin et al. (2019)	Birth weight, head circumference	No	Uncertainties in exposure distribution due to large % < LOD and impact on quantitative results
Chang et al. (2017)	Birth weight	No	Evidence of confounding by co-exposure; Log transformed formaldehyde concentration
Male reproductive toxicity in animal studies			
Ozen et al. (2002)	Relative testes weight, 13-week exposure	Yes	
Ozen et al. (2005)	Serum testosterone, Wistar rat, 13-week exposure	Yes	
Ozen et al. (2005)	Seminiferous tubule diameter, Wistar rats, 13-week exposure	No	Unclear usefulness of data for quantification: for example, as the results reflect randomly selected tubules, the tubules could be oversampled from individual animals within a group, and the mean and variability across the group of animals when using the animal as the experimental unit is unknown
Vosoughi et al. (2013); Vosoughi et al. (2012)	Seminiferous tubule diameter, NMRI mice, 10-day exposure	No	Short exposure duration
Vosoughi et al. (2013); Vosoughi et al. (2012)	Sperm abnormalities, NMRI mice, 10-day exposure	No	Short exposure duration
Vosoughi et al. (2013); Vosoughi et al. (2012)	Serum testosterone, NMRI mice, 10-day exposure	No	Short exposure duration
Vosoughi et al. (2013); Vosoughi et al. (2012)	Testes weight, NMRI mice, 10-day exposure	No	Short exposure duration
Sarsilmaz et al. (1999)	Leydig cell quantity or nuclear damage, Wistar rat, 4-week exposure	No	Short exposure duration
Sarsilmaz et al. (1999)	Testes weight (relative), Wistar rats, 4-week exposure	No	Short exposure duration; non-preferred metric (absolute testes weight preferred)
Sapmaz et al. (2018)	Seminiferous tubule measures, Sprague-Dawley rats, 4- and 13-week exposure	No	Short exposure duration (for 4-week experiment); single exposure level

Abbreviations: PEFR = peak expiratory flow rate; FEF = forced expiratory flow; FEV = forced expiratory volume; SPT = skin prick test; IUR = inhalation unit risk.

[a]Note: squamous metaplasia was the preferred endpoint for RfC derivation (see Section 1.2.4 for explanation). Hyperplasia and cell proliferation are considered in the context of the cancer IUR.

Sensory Irritation

The effects of formaldehyde on sensory irritation are thought to occur via direct interactions of formaldehyde with cellular macromolecules in the nasal mucosa and stimulation of the trigeminal nerve, mediated through cation channels, resulting in the rapid detection of a burning sensation. It is not clear if desensitization occurs over time or the concentrations or timeframes over which this might occur. Because of the rapid nature of the irritant response generated by inhalation of formaldehyde, the studies that were considered to be the most informative for derivation of a cRfC were those where the exposure assessment was concurrent with the outcome assessment.

Data from studies in humans involving residential populations with continuous exposure, as well as controlled human exposure studies evaluating acute effects were determined to be pertinent to the derivation of a cRfC. The studies of anatomy students and formaldehyde-exposed workers assessed exposure settings with high formaldehyde concentrations and with frequent peaks. Thus, average formaldehyde concentrations or TWAs, the exposure metrics used by these studies, could not capture the variation inherent in these types of settings. Therefore, prevalence of irritation symptoms might not necessarily have corresponded to the time frame of the exposure measurements.

Hanrahan et al. (1984) used 1-hour average formaldehyde measurements taken in two rooms in the mobile homes of a group including teenagers and adults and presented the predicted concentration-response for prevalence of "burning eyes" experienced by the participants since moving into the homes from a logistic regression model that adjusted for age, sex, and smoking. These data were used to derive a POD of 0.09 mg/m^3, the concentration corresponding to a benchmark response (BMR) of 10%. The mathematical expression for the exposure-response pattern and a $BMCL_{10}$ was determined from a graph of the predicted prevalence and upper and lower 95% confidence bounds for several concentrations between 100 and 800 ppb (0.12–0.98 mg/m^3).[33] The concentration corresponding to a 13% prevalence of "burning eyes" was calculated from the model (for model details see Appendix B.1.2). The 13% prevalence represents a 10% increase in irritation as a result of formaldehyde exposure in addition to an assumed background prevalence of 3% (in the absence of formaldehyde exposure). The background

[33]EPA estimates that 44% of the average measured concentrations were below 100 ppb. While it is not clear from the published report what the distribution of exposures below 100 ppb was, if it can reasonably be assumed that the formaldehyde concentrations were log-normally distributed with median of 160 ppb and a standard deviation of 30 ppb (based on the reported standard deviation from the outdoor measurements), then it would be expected that about 44% of the measured indoor samples were below 100 ppb, with 36% below 50 ppb. Given that the measured indoor levels were likely to have been more variable than the reported outdoor levels, the true indoor standard deviation would likely have been higher than 30 ppb and, consequently, the percentages below 100 ppb and below 50 ppb would have been greater.

prevalence of 3% was considered to be a reasonable estimate, but the impact of using alternative estimates (1 and 2%) was evaluated.

Liu et al. (1991) collected data on symptoms for a period during and 1 week prior to the exposure assessment using a sampling protocol that captured average formaldehyde concentrations in the (mobile) home (7-day mean concentration from two rooms). Although Liu et al. (1991) estimated an exposure-response relation using logistic regression, the regression coefficients estimated by the model were not reported. The range of 7-day average formaldehyde concentrations measured by Liu et al. (1991) was comparable to the air concentrations in the homes studied by Hanrahan et al. (1984) (10–460 ppb [0.012–0.57 mg/m^3]). Although a cRfC was not derived from Liu et al. (1991), the data could be used to check the estimated POD based on Hanrahan et al. (1984). The prevalence of 10% during the winter and 13.3% during the summer in the lowest exposure category (<7 ppm-hr/week) is close to the best estimate of 13% benchmark response estimated from Hanrahan et al. (1984), which occurred at a concentration of 0.19 mg/m^3. A cumulative exposure of 7 ppm-hr/week is approximately equal to 0.07 ppm (0.086 mg/m^3) assuming that participants were in their homes 60% of a 24-hour day, supporting the selection of the lower confidence limit of the $BMCL_{10}$ (0.087 mg/m^3) from the Hanrahan et al. (1984) results as the POD.

PODs were determined using two controlled human exposure studies of formaldehyde for which there was *medium* confidence that evaluated multiple levels of exposure (see study descriptions in Table 2-2). Kulle et al. (1993) evaluated results for participants exposed for 3 hours once a week to five concentration levels (including a clean air exposure), while Andersen and Molhave (1983) exposed subjects for 5-hour periods to four concentration levels with a 2-hour clean air exposure prior to each trial. The occurrence of irritation symptoms during the clean air exposure was not reported. The results of these studies were evaluated in BMD models to identify the concentration at which a 10% increase in symptoms at concentrations above the clean air exposure was observed (see Appendix B.1.2 for details of the models). Two sets of models were evaluated using the data from Andersen (1983) and estimates of 0 and 3% for prevalence of irritation during the clean air exposure. The benchmark concentration (BMC) of 0.37 mg/m^3 derived from the model using a baseline prevalence of 3% was selected.

The results from two other controlled human exposure studies were considered, but PODs were not derived. Blinking frequency, an objective measure of irritation evaluated by Lang et al. (2008) and Mueller et al. (2013), was highly variable in all exposure groups, and it was difficult to define a meaningful magnitude of change in these measures that would be considered to be minimally adverse for the selection of a POD. Further, increased blinking frequency was observed at a higher exposure level compared to eye irritation symptoms.

Table 2-2 presents the studies used to calculate a POD with the epidemiology data and sequence of calculations leading to the derivation of a POD for each data set with effects relating to sensory irritation.

Table 2-2. Summary of derivation of PODs for sensory irritation

Endpoint and reference	Population	Observed effects by exposure level[a]	POD_{ADJ} (mg/m^3)
Residential exposure			
Symptom prevalence Hanrahan et al. (1984)	Teenage and adult (M and F), *n* = 61	Third-degree polynomial model fit to ln prevalence odds using presented results of logistic regression analysis: upper 95% confidence bound for predicted prevalence between <0.123 and 0.98 mg/m^3, BMC_{10}: concentration where an increased prevalence of 10% over a 3% background prevalence is anticipated	BMC_{10}[b] 0.19 $BMCL_{10}$ 0.09 [c]
Controlled human exposure			
Symptom prevalence Kulle et al. (1987)	Nonsmoking, healthy, *n* = 10-19, mean age 26.3 yr (M and F)	Exposure and proportion responding *mg/m³*: 0	0.62	1.2	2.5	3.7 *%*: 5	0	26	53	100 trend, $p < 0.05$ Probit model BMC = 0.69 ppm	BMC_{10} 0.85 [c] BMC/2[d] 0.42
Symptom prevalence Andersen and Molhave (1983)	Healthy students, *n* = 16, age 30–33 years, 31.2% smokers (M and F)	Exposure and percentage responding (prevalence at the end of exposure) *mg/m³*: 0.3	0.5	1.0	2.0 *%*: 19	31	94	94 Assuming prevalence for clean air dose 0% Log-logistic model BMC = 0.26 mg/m^3 3% Log-logistic model BMC = 0.37 mg/m^3	BMC_{10} 0.37 [c] BMC/2[d] 0.19

[a]Concentrations reported in publication converted to mg/m^3.
[b]BMC_{10} benchmark concentration at 10% increase in prevalence overestimated 3% background prevalence. An increase of 10% was selected consistent with EPA guidelines (U.S. EPA, 2012) because the endpoint, burning eyes with mild to moderate severity, was considered a minimally adverse outcome.
[c]The POD was not adjusted for a 24-hour equivalent concentration because the timing of formaldehyde measurements was concluded to be appropriate to the time frame of reported symptoms.
[d]The BMD models did not account for the correlated measures between concentration levels (each participant was exposed to each concentration). Therefore, the 95% confidence limit for the BMC estimated by the model is too narrow to use as the POD. A factor of 2 was used to adjust the BMC to identify a lower estimate that approximates the BMDL.

Conclusion

The POD derived using the exposure-response model using prevalence data from the residential population in Hanrahan et al. (1984) is 0.09 mg/m^3. EPA placed *medium* confidence in the results of this study. The study by Hanrahan et al. (1984) is pertinent to the U.S. general population because: (1) the population was randomly selected from the general population in the study area; (2) the exposure levels were concluded to reflect the usual, relatively constant formaldehyde concentrations in the residences; and (3) exposed individuals included a range of ages (teenagers and adults), men and women, and some with chronic disease. Moreover, a significant proportion of the study population was estimated to be exposed to average

formaldehyde concentrations below 0.05 mg/m^3. The impact of potential confounding by the presence of coexposures is likely to be minimal. The regression model adjusted for age, sex and smoking, and the presence of smokers or gas appliances in the home, sources that might contribute to variability in concentrations, were not associated with indoor formaldehyde concentrations. Other emissions released from the same sources as formaldehyde that also might contribute to eye irritation, such as phenols from resins in floor or wall coverings or pinene and terpenes from wood products, were not analyzed. However, a strong exposure-response relationship with formaldehyde concentration was observed by this study, which argues against a large effect by residual confounding by other coexposures.

The PODs based on the two controlled human exposure studies were 0.19 and 0.42 mg/m^3 (Kulle et al., 1987; Andersen and Molhave, 1983), less than an order of magnitude greater than the BMCL estimated from residential exposure. There is less confidence in the PODs based on these studies because: (1) the study participants were young, healthy volunteers, not representative of the age distribution and health status in the general population; (2) the PODs are based on small sample size, more subject to random variation; and (3) formaldehyde concentrations were high, imposing substantial uncertainty regarding responses at the low tail of the exposure distribution. The utility of the PODs from these two controlled exposure studies may be greater for other, less than chronic, exposure durations (e.g., derivation of an acute RfC).

The exposure-response pattern presented in Hanrahan et al. (1984) is consistent with the overall pattern exhibited when all of the studies of exposure in mobile homes and controlled human exposure studies with dose-response data less than 1 mg/m^3 are graphed together (see Figure 1-3). Therefore, the POD estimated from Hanrahan et al. (1984) is supported by the set of epidemiology studies describing formaldehyde-related irritation in humans. Confidence in the POD is *medium*, reflecting uncertainty in the temporal relationship of the exposure measurements with respect to the assessment of irritation symptoms.

Pulmonary Function

The studies that estimated an exposure-response relation with formaldehyde concentration for effects on pulmonary function involved exposures to anatomy students (Kriebel et al., 2001), an occupational population (Malaka and Kodama, 1990), school children (Wallner et al., 2012), and a residential population (Krzyzanowski et al., 1990). A POD was derived from the analyses reported by Krzyzanowski et al. (1990), but not from the other studies that analyzed exposure-response relationships because important data were not available (see Table 2-1).

Declines in peak expiratory flow rate (PEFR) were associated with increases in 2-week average indoor residential formaldehyde concentrations, with greater declines observed in children (5–15 years of age) compared to adults (Krzyzanowski et al., 1990). This study of effects in a residential population used the most thorough exposure assessment protocol and repeated measurements of PEFR, thus enhancing the ability to detect an association at the lower concentrations found in the homes. Mean formaldehyde levels were 26 ppb (0.032 mg/m^3), and

more than 84% of the homes had concentrations 40 ppb (0.049 mg/m^3) and lower. A BMC_{10} of 0.033 mg/m^3 and $BMCL_{10}$ of 0.021 mg/m^3 were determined from the regression coefficient from a random effects model of PEFR among children reported by the study authors (for details, see Appendix B.1.2). Table 2-3 presents the study used to calculate a POD with the epidemiology data and sequence of calculations leading to the derivation of a POD relating to pulmonary function.

Table 2-3. Summary of derivation of PODs for pulmonary function

Endpoint and reference	Population	Results by exposure level[a]	BMC and BMCL (mg/m^3)	POD_{ADJ}[b] (mg/m^3)
PEFR Krzyzanowski et al. (1990) Residential, prevalence	202 households, 298 children aged 5–15 years, current asthma prevalence 15.8%; 613 adults and adolescents >15 yr, 24.4% current smokers, current asthma prevalence 12.9%	Random effects model; decreased PEFR, children -1.28 ± 0.46 L/minute-ppb (95% upper bound −2.04 L/minute-ppb) Formaldehyde concentrations: Mean 0.032 mg/m^3, maximum 0.172 mg/m^3	BMC_{10}[c] 0.033 $BMCL_{10}$ 0.021	0.02

[a]Concentrations reported in publication converted to mg/m^3.

[b]The POD was not adjusted for a 24-hour equivalent concentration because formaldehyde is present in all indoor environments and time-activity information for participants was not reported.

[c]BMC_{10} benchmark concentration associated with a 10% decrease in pulmonary function. A BMR of 10% reduction in PEFR was selected as a cut-off point for adversity, based on rationales articulated by the American Thoracic Society (ATS, 2000). The American Thoracic Society (ATS, 2000) recommended that "a small, transient loss of lung function, by itself, should not automatically be designated as adverse" and ATS cited EPA's 1989 review of ozone, which offered a graded classification of lung function changes in persons with asthma as "mild," "moderate," or "severe" for reductions of less than 10, 10–20, and more than 20%, respectively (U.S. EPA, 1989). ATS (2000) concluded that, in evaluating the adverse health effects of air pollution at the level of population health (compared to individual risk), "[a]ssuming that the relationship between the risk factor and the disease is causal, the committee considered that such a shift in the risk factor distribution, and hence the risk profile of the exposed population, should be considered adverse." This was specifically considered by ATS (2000) even when "[e]xposure to air pollution could shift the distribution toward lower levels without bringing any individual child to a level that is associated with clinically relevant consequences." A moderate adverse effect at functional decrements of 10–20% was considered the best indicator of adverse effects in the study population.

Conclusion

The adjusted POD estimated using the results of Krzyzanowski et al. (1990) (0.021 mg/m^3) was derived from the responses of a randomly selected population of adults and children continuously exposed to formaldehyde in their homes. In this large, population-based sample, the investigators observed a linear relationship between increased formaldehyde exposure and decreased peak expiratory flow rate (PEFR) among children exposed to average concentrations of 0.032 mg/m^3 (26 ppb), and a stronger response was observed among children with asthma. Krzyzanowski et al. (1990) adjusted for smoking and NO_2 levels in their analyses; thus, confounding

by these coexposures can be ruled out. Further, a strong exposure-response relationship with formaldehyde concentration was observed by this study, which argues against a large effect by residual confounding by other coexposures. This study was able to evaluate associations with relatively constant, low formaldehyde concentrations and used a high-quality exposure measurement protocol, thus, reducing uncertainties for low-dose extrapolation (0.012 to 0.172 mg/m^3 (Quackenboss et al., 1989c). Average formaldehyde concentrations in these studies were pertinent to those experienced by the general population (the authors reported that more than 84% of the homes had concentrations 40 ppb [0.049 mg/m^3] and lower). The POD is based on the findings among children and was derived from a regression model that adjusted for important potential confounders including asthma status, smoking status, socioeconomic status, NO_2 levels, episodes of acute respiratory illness, and the time of day. Thus, confidence in the POD is **high**.

Immune-mediated Conditions, Focusing on Allergies and Current Asthma

Allergic conditions and sensitization

Three *high* or *medium* confidence epidemiology studies in children or adults provide data on measures of allergy-related conditions needed to conduct an exposure-response analysis (Annesi-Maesano et al., 2012; Billionnet et al., 2011; Matsunaga et al., 2008). As discussed in Section 1.2.3 and depicted in Figure 1-8, the results for the studies of rhinoconjunctivitis and rhinitis are similar, with a stronger effect estimate seen in the only study examining atopic eczema. Because Billionnet et al. (2011), presented only a dichotomized exposure-response analysis, it is not considered further as a basis for quantitation; the other studies presented an exposure-response analysis using formaldehyde as three (Annesi-Maesano et al., 2012) or four groups (Matsunaga et al., 2008). NOAELs and LOAELs were identified in each of these studies based on the pattern of risk seen across the exposure groups; the PODs were based on NOAELs. The study by Annesi-Maesano et al. (2012) uses a relatively long exposure period (5 days), and is a very large study in a school-based sample of children in France (n = 6,683) with analysis presented by tertile. Matsunaga et al. (2008) used 24-hour personal samples in a study of 998 pregnant women in Japan. The primary limitation of the Matsunaga et al. (2008) study is that it is conducted only among adults, and so is less able to address the variability in susceptibility that would be anticipated within a population. Given their attributes, the confidence in both studies was considered *high*.

Two *medium* confidence epidemiology studies in children provide data on exposure and SPTs needed to conduct a quantitative analysis (Garrett et al., 1999; Palczynski et al., 1999). However, because of the limitations with respect to the timing of the exposure measure and the interpretation of SPTs, these studies are not considered further as a basis for quantitation.

Conclusion

For allergy-related conditions (rhinoconjunctivitis), EPA selected NOAEL and LOAEL values of 0.024 and 0.040 mg/m^3, respectively, in the Annesi-Maesano et al. (2012) study. Higher values (NOAEL = 0.046, LOAEL = 0.062) were selected based on the study in adults by Matsunaga et al. (2008). The classification of rhinoconjunctivitis by Annesi-Maesano et al. (2012) was the most sensitive and specific of the measures, and the narrower confidence intervals in this study reflected the larger sample size. No other pollutants (e.g., NO_X, $PM_{2.5}$, acetaldehyde, acrolein, ETS) analyzed by this study were associated with rhinoconjunctivitis.

Current asthma

Several residential and school-based exposure studies examined prevalence of current asthma in relation to formaldehyde exposure in adults and children in relatively low exposure settings (see Tables 1-15 and 1-16). As discussed in Section 1.2.3 and seen in Figure 1-9, the six *medium* or *high* confidence studies at exposures of ≤0.050 mg/m^3 do not indicate risk at these lower exposure levels. Several of the RR estimates from these individual studies at these exposure levels were limited by low statistical power. However, the consistency of the results, and the absence of an increased risk in the study by Annesi-Maesano et al. (2012), a large school-based study (n = 6,683) that used a 5-day sampling period for formaldehyde measurement, strengthens the basis for interpreting this set of studies as indicating an absence of risk of current asthma below 0.05 mg/m^3. Based on the study by Annesi-Maesano et al. (2012) and this collection of studies, EPA selected a NOAEL of 0.042 mg/m^3 for risk of current asthma.

Two *medium* confidence studies examined prevalence of current asthma in children in higher exposure residential settings (>0.05 mg/m^3) (Zhai et al., 2013; Krzyzanowski et al., 1990). Because Zhai et al. (2013) presented only a dichotomized exposure-response analysis, it is not considered further as a basis for quantitation. The Krzyzanowski et al. (1990) results for children (5–15 years of age) are based on a relatively large sample size, with a comprehensive exposure assessment protocol (i.e., three locations in the home; two 1-week periods covering two seasons). An increased prevalence of current asthma was seen in the highest exposure group in a categorical analysis. The exposure range in this group was 0.075–0.172 mg/m^3, but the study also notes that few values were above 0.11 mg/m^3. Based on this information, EPA selected a LOAEL based on the midpoint of this exposure category using a range estimated as 0.075 to 0.11 mg/m^3 (midpoint of 0.092 mg/m^3). The estimate for the middle category of exposure was selected as a NOAEL, although confidence in this NOAEL is lower, given the imprecision of the estimate (n with asthma = 1).

Two of the four *medium* confidence studies of prevalence of current asthma in adults in higher exposure residential settings (>0.05 mg/m^3) did not provide quantitative results (Zhai et al., 2013; Krzyzanowski et al., 1990). Of the remaining two studies, Billionnet et al. (2011), presented only a dichotomized exposure-response analysis, and so was not used for quantitation. The four-

level categorical analysis from Matsunaga et al. (2008) contributed to the evaluation of the NOAEL for studies with exposures <0.05 mg/m^3, but the width of the confidence interval for the highest exposure group (OR = 2.15; 95% CI 0.41–11.3, for exposures of 0.058–0.161 compared to <0.022 mg/m^3) precludes its interpretation as a LOAEL. Thus, none of the asthma studies in adults provide a basis for developing a POD.

The collection of occupational studies (see Table 1-17) provides a strong basis for inferences regarding asthma risk at relatively high exposures (e.g., 0.1 to >0.5 mg/m^3) (Fransman et al., 2003; Herbert et al., 1994; Malaka and Kodama, 1990). However, there would be considerable uncertainty in a POD derived from these studies, identified as a LOAEL, given the dichotomous analyses used to examine associations and the wide variability in exposure measures within each of these studies. Therefore, PODs were not determined using the occupational studies.

EPA identified two studies that examined degree of asthma control in children with asthma in relation to formaldehyde measures in the home (Dannemiller et al., 2013; Venn et al., 2003). Analysis was conducted using four categories of exposure in Venn et al. (2003), based on 3-day exposure measures taken in the home and daily symptom diaries kept for one month among children with persistent wheeze. Dannemiller et al. (2013) compared mean exposure levels (based on 30-minute samples) in two groups (those with very poor control and all others, based on a five-question survey about symptom control in the past 4 weeks). The larger sample size, longer sampling period, and more detailed exposure-response analysis makes Venn et al. (2003) a stronger basis for providing a POD. Additional adjustment of regression models for dampness or other exposures including visible mold, total VOCs, or NO_2, did not affect formaldehyde results, reducing the likelihood of residual confounding by coexposures. EPA selected a NOAEL of 0.027 mg/m^3 (median exposure in the third quartile; no or weak RRs seen below this value) and a LOAEL of 0.041 mg/m^3 (median exposure in top quartile, for which a two- to three-fold increased risk of symptoms was seen). Venn et al. (2003) did identify an exposure-response relationship for both nighttime symptoms of poor asthma control as OR = 1.40 (95% CI 1.06–1.98) and for daytime symptoms of poor asthma control as OR = 1.45 (95% CI 1.00–1.94). Using the reported OR per quartile exposure from the regression results, and the median exposure values for each quartile (personal communication to EPA (Venn, 2012)), EPA calculated the concentration associated with a 5% increase in prevalence of symptoms above the prevalence observed in the referent group (for details of BMCL calculations, see Appendix B.1.2). A BMR of 5% was selected because asthma attacks are overt effects, generally requiring the use of drugs to control symptoms (i.e., a frank or adverse effect) (U.S. EPA, 2012).

Table 2-4 presents the studies with the epidemiology data and sequence of calculations leading to the derivation of a POD for each data set with effects relating to allergies and asthma.

Table 2-4. Summary of derivation of PODs for allergies and current asthma based on observational epidemiology studies

Endpoint and reference	Population	Observed effects by exposure level	POD_{ADJ} (mg/m^3)
Allergy-related conditions			
Rhinoconjunctivitis (prevalence); school-based exposure (5 days) Annesi-Maesano et al. (2012)	Children (M and F) *N* = 6,683	Prevalence 12.1%, OR (95% CI) (adjusted) ≤0.0191 mg/m^3 1.0 (referent) >0.0191–0.0284 1.11 (0.94, 1.37) >0.0284– ~0.055 1.19 (1.03, 1.39) NOAEL selection: 0.024 mg/m^3, midpoint of second exposure category (corresponding to RR 1.11) LOAEL selection: 0.040 mg/m^3, midpoint of third exposure category (corresponding to RR 1.19)	NOAEL: 0.024 LOAEL: 0.040
Atopic eczema (prevalence); personal monitor-based exposure (24 hours) Matsunaga et al. (2008)	Adult women (pregnancy cohort) *N* = 998	Atopic eczema (5.7% prevalence) / Allergic rhinitis (14.0% prevalence) mg/m^3 *n* OR (95% CI) OR (95% CI) <0.022 298 1.0 (referent) 1.0 (referent) 0.023–0.033 299 1.03 (0.47, 2.29) 1.06 (0.65, 1.73) 0.034–0.057 301 1.11 (0.50, 2.42) 0.85 (0.51, 1.40) 0.058–0.161 100 2.36 (0.92, 6.09) 1.17 (0.60, 2.28) (trend *p*-value) (0.08) (0.91) 0.058 to 0.161 vs. <0.058 2.25 (1.01, 5.01) 1.22 (0.68, 2.20) per 0.0123 mg/m^3 1.16 (0.99, 1.35) [Stronger associations seen for atopic eczema in women with no family history of atopy] For atopic eczema NOAEL selection: 0.046 mg/m^3, midpoint for third exposure category (corresponding to RR 1.11); LOAEL selection: 0.062 mg/m^3, estimated median of fourth category (personal communication to EPA (Matsunaga, 2012)) (corresponding to RR 2.25) For rhinitis NOAEL selection: 0.062 mg/m^3, based on median of fourth exposure category	Atopic eczema NOAEL: 0.046 LOAEL: 0.062
Current asthma/degree of asthma control			
Current asthma (prevalence); school-based exposure (5 days) *Annesi-Maesano et al. (2012)*	Children (M and F) *N* = 6,683	Exposure (mg/m^3) *n*[a] OR (95% CI) ≤0.0191 2,200 1.0 (referent) >0.0191–0.0284 2,200 1.10 (0.85, 1.39) >0.0284– ~0.055 2,200 0.90 (0.78, 1.07) [a]Approximation, based on tertiles, with total *n* = 6,590 NOAEL selection: 0.042 mg/m^3, midpoint of third exposure category (corresponding to RR 0.90)	NOAEL: 0.042
Current asthma (prevalence); residence-based exposure (two 1-week periods) Krzyzanowski et al. (1990)	Children (M and F) *N* = 298	Exposure (mg/m^3) *N* Proportion with asthma <0.049 248 0.12 0.049–0.074 24 0.04 0.075–0.172 21 0.24 (trend *p*-value) (0.03) Only a few values were reported to be above 0.11 mg/m^3. NOAEL selection: 0.062 mg/m^3, midpoint of second exposure category LOAEL selection: 0.092 mg/m^3, based on report that only a few values were above 0.11 mg/m^3, so estimated midpoint of third category was based on range from 0.075 to 0.11, with midpoint of 0.092 mg/m^3	NOAEL: 0.062 LOAEL: 0.092

Endpoint and reference	Population	Observed effects by exposure level	POD_{ADJ} (mg/m^3)
Asthma control among people with asthma, residence-based exposure (3 days) Venn et al. (2003)	Children (M and F) *N* = 194	Exposure (mg/m^3) *N* Proportion OR (95% CI) Frequent nighttime symptoms <0.016 39 0.41 1.0 (referent) 0.016–0.022 35 0.49 1.40 (0.54, 3.62) 0.022–0.032 36 0.53 1.61 (0.62, 4.19 0.032–0.083 33 0.67 3.33 (1.23, 9.01) (trend *p*-value) (0.02) per quartile increase 1.45 (1.06, 1.98) Frequent daytime symptoms <0.016 37 0.62 1.0 (referent) 0.020–0.022 34 0.47 0.47 (0.47, 1.25) 0.022–0.032 37 0.73 2.00 (0.71, 5.65) 0.032–0.083 32 0.73 2.08 (0.71, 6.11) (trend *p*-value) (0.05) per quartile increase 1.40 (1.00, 1.94) NOAEL selection: 0.027 mg/m^3, median of third exposure category LOAEL selection: 0.041 mg/m^3, median of fourth exposure category (based on correspondence with Dr. Venn)	NOAEL: 0.027 LOAEL: 0.041 From regression results: $BMCL_5$: 0.013
Asthma control among people with asthma, residence-based exposure (30 minutes) Venn et al. (2003)	Children (M and F) *N* = 37	Geometric mean formaldehyde (mg/m^3) Very poor control (score <12, *n* = 6) 0.066 mg/m^3 All others (score ≥12, *n* = 31) 0.042 mg/m^3 *p* = 0.078	NOAEL: 0.042

Conclusion

For the analysis of prevalence of current asthma, EPA selected a NOAEL of 0.042 mg/m^3 using the data from Annesi-Maesano et al. (2012) (and supported by other studies examining exposures at <0.05 mg/m^3), and a NOAEL of 0.062 mg/m^3 based on the data for children in the study by Krzyzanowski et al. (1990). The NOAEL identified from Krzyzanowski et al. (1990) is considered to be less reliable because it was based on only one case and a small number of participants in the exposure group. A $BMCL_5$ of 0.013 mg/m^3 was also selected based on the data for degree of asthma control among children with asthma (Venn et al., 2003). All three studies were well conducted and are interpreted with *high* or *medium* confidence. The study by Annesi-Maesano et al. (2012) is a large study with a relatively long exposure measurement period, and is supported by a collection of several other smaller studies (with more imprecise effect estimates) at exposures of <0.050 mg/m^3, which also indicate no increased risk of current asthma at these lower levels (see Figure 1–9A). The analyses by Annesi-Maesano et al. (2012) were adjusted for age, gender, passive smoking, and paternal or maternal history of asthma or allergic disease; thus, minimal impact by confounding is likely. Therefore, both the study and the POD based on the NOAEL in Annesi-Maesano et al. (2012) is viewed with **high** confidence. In contrast, only two studies examined the outcome defined as degree of asthma control among people with asthma (Dannemiller et al., 2013; Venn et al., 2003), so the POD derivation based on that specific outcome (However, Venn et al. (2003) used a strong study design, observed an exposure-related trend in

response and adjusted the statistical analyses for key confounders, including other indoor exposures (e.g., visible mold, total VOCs, NO2, cotinine levels). Based on these considerations, confidence in the POD calculations is **medium**. The lower NOAEL for degree of asthma control in children with asthma compared with the NOAEL for increased prevalence of current asthma indicates a greater sensitivity of this more susceptible population.

Respiratory Tract Pathology

The PODs derived were based on exposure-response data from two studies on histopathological changes (squamous metaplasia[34]) observed in the nasal passages of F344 rats (Kerns et al., 1983) and Wistar rats (Woutersen et al., 1989). The four *medium* confidence occupational studies provide support for the larger evidence base from the experimental studies in animals (Ballarin et al., 1992; Boysen et al., 1990; Holmstrom et al., 1989c; Edling et al., 1988). However, there would be considerable uncertainty in a POD derived from these studies, identified as a LOAEL, given the dichotomous analyses used to examine associations and the wide variability in exposure concentrations within each of these studies (e.g., 0.1 to >0.5 mg/m^3). Therefore, PODs were not determined using the occupational studies.

Squamous metaplasia in F344 rat (Kerns et al., 1983)

The result of a 2-year bioassay in F344 rats was reported in Kerns et al. (1983) and the supporting Battelle report (Battelle, 1982). In this study male and female rats, with at least 20/sex/group, were exposed to 2.5, 6.9, and 17.6 mg/m^3 with interim sacrifices at 6, 12, and 18 months. While Kerns et al. (1983) reported squamous cell metaplasia after inhaled formaldehyde exposure, detailed information on lesion incidence by concentration, duration, and cross-section level was provided in the report (Battelle, 1982). The lesions occurred only in the most anterior region (cross-section Level I) at low concentrations but progressed to more distal parts of the nose (cross-section Levels II–V) at higher concentrations. Additionally, the incidence of squamous metaplasia increased with exposure duration. Section 1.2.4 discusses the incidence of squamous metaplasia in the first five nasal sagittal cross sections of the F344 rat, as reported by Kerns et al. (1983) and Battelle (1982).[35]

The POD presented below is based on Level 1. Extrapolation of the rat BMCL to the human is based on the available dosimetric simulations of formaldehyde flux[36] to the nasal lining in rats

[34]Although a cRfC for hyperplasia was not estimated (see Section 1.2.4 for rationale), a human POD_{ADJ} that can be estimated based on the basal cell hyperplasia end point is roughly two-fold greater than that obtained from the squamous metaplasia data from Woutersen et al. (1989) study. This estimate of hyperplasia provides context to the development of unit risk estimates for nasal cancer (see Section 2.2.1)

[35]The data for 27 and 30 mos represent incidence after 3 and 6 mos of nonexposure, respectively, following 24 mos of exposure.

[36]Flux (in units of mass/area-time) expresses the net transport of formaldehyde from the inspired air to the air-mucus interface of the nasal lining (prior to disposition within the tissue).

and humans. This assessment uses dosimetry derived from Kimbell et al. (2001b; 2001) and Overton et al. (2001) when extrapolating risk-related dose from the rat to the human (discussed in detail in Appendix B.1.3), and estimates the impact on the dosimetry modeling using Schroeter et al. (2014).[37] A POD based on lesions reported at Level 2 in Battelle (1982) can also be modeled. However, formaldehyde flux to the nasal lining on Level 2 was not available to EPA and could only be crudely estimated based on the locations of the nasal regions tabulated in Kimbell et al. (2001a), as elaborated further in Appendix B.1.3. For this reason, only the Level 1 data were used in calculating a cRfC.

In determining the BMR level for the POD, severity scores for the squamous metaplasia data in Battelle (1982) were examined, where provided.[38] The average severity score was in the range of minimal-to-mild at the lowest dose for both the 18- and 24-month durations for Level 1. This finding supports a BMR of 0.1 extra risk, representing a minimal level of adversity. The 24-month data for Level 1 cannot be modeled because the dose-response relationship rises too steeply (for example, the Weibull model fit rises so steeply that the error on the Weibull model power cannot be bounded). Therefore, the 18-month data, for which incidence rises more gradually, were chosen even though these data would be less preferred over the 24-month exposure data. To address the fact that the lesion incidences in Table 1-26 are substantially higher with the longer duration (i.e., 24-month) data, which suggest a lower POD associated with the 24-month exposure, a UF_S will be applied to the POD derived from the 18-month data.

Interspecies extrapolation of the rat BMCL level to humans was carried out in two steps. First, average flux values in the Level 1 region of the rat corresponding to the rat BMCL derived from the incidence of squamous metaplasia were estimated. Next, the exposure concentration at which any region in the human nose (see Appendix B.1.3) is exposed to this same level of formaldehyde flux at the inspiratory rate of 15 L/min was estimated from the flux tabulations in Kimbell et al. (2001a), table 3). These estimates are provided in the Table 2-5 below. The flux-based extrapolation results in a value similar to that obtained by applying the principle of ppm

[37]As discussed in the Appendix A.2, Schroeter et al. (2014) revised the dosimetry model of Kimbell et al. (2001b; 2001) used for the flux estimates presented in Table 2-5, to include endogenous formaldehyde production and to explicitly model formaldehyde pharmacokinetics in the respiratory mucosa. EPA estimated the extent to which the results in Table 2-5 change if flux estimates from Schroeter et al. (2014) are used. The average flux over nonsquamous regions of the rat nose is roughly one-third of that in the human based on the dosimetry in Schroeter et al. (2014) in which endogenous formaldehyde is taken into account compared to a ratio of roughly one-half based on the dosimetry in Kimbell et al. (2001b; 2001). Thus the POD is not altered appreciably (changing only by roughly a factor of 1.4) if the revised dosimetry model by Schroeter et al. (2014) is applied.

[38]The individual rat data generally allowed for assigning average severity scores for a given nasal level, concentration, and time point. In several cases (as with the 24-month, Level 2), the nasal level was not clear (i.e., the individual rat data could have come from Level 1, 2, or 3).

equivalence[39] (see table footnote). The benchmark dose model fits and such details and further elaboration of the human extrapolation are provided in Appendix B.1.3.

Table 2-5. Summary of derivation of POD for squamous metaplasia based on observations in F344 rats (Kerns et al., 1983)

Rat sagittal section	BMR	Rat $BMCL_{10}$ (mg/m^3)	Flux[a] ($pmol/mm^2$-h)	Human exposure conc (mg/m^3)	Adjusted[b] human exposure conc (mg/m^3)
Level 1	0.10	0.448	685	0.484	0.086[c]

[a]Approximate average flux over nasal lining at this level corresponding to the BMCL.
[b]Adjusted for continuous exposure, (6 hours/24 hours) × (5 days/7 days).
[c]If extrapolation is based on ppm equivalence instead, value increases by 1.14-fold.

Squamous metaplasia Wistar rats (Woutersen et al., 1989)

Woutersen et al. (1989) reported on the nasal histopathology for male Wistar rats exposed to 0.1, 1.2, and 12.1 mg/m^3 for 28 months. Incidence of squamous metaplasia was reported by concentration and cross-section level (i.e., Level 1–2, 3, 4, and 5–6), with Level 1 as the most anterior region. The dose-response data for this effect is provided in Table 1-26 and can be modeled.

Following the determination for squamous metaplasia in F344 rats (Kerns et al., 1983), the same minimal adversity was considered for this effect in Wistar rats and a BMR of 0.10 extra risk was used. A dosimetry model for flux to the nasal lining of the Wistar rat is not available. EPA (U.S. EPA, 2012) concluded that internal dose equivalency in the extrathoracic region for rats and humans is in general achieved through similar external exposure concentrations (i.e., even for highly soluble and reactive gases ppm equivalence is a more appropriate default method for extrapolation than an approach based on adjustment by the ratio of surface area to minute volume). This concept is supported by the analysis described above of data from the squamous metaplasia occurring at Level 1 of the F344 rat nose. In that analysis, the extrapolation was based on site-specific flux in the rat and human and differs from an extrapolation based on ppm equivalence by only a factor of 1.14. Level 1 in that study was in the anterior portion of the nose, and the section levels in the Woutersen et al. (1989) study (see Table 2-6) are even more anteriorly located in the nose; therefore, there is even stronger support in this case for using ppm equivalence as the basis for extrapolation across species. The benchmark dose model fits and such details are provided in the appendix; the summary results are in Table 2-6.

[39]Also, see further discussion below in the analysis of squamous metaplasia in Wistar rats. "PPM equivalence" refers to toxicological equivalence across species when exposures are expressed in "ppm" and are suffered over equal durations expressed in units of the species lifetime. This originates from general allometric principles, wherein tissue exposure is equivalent when scaled by $BW^{3/4}$ while inhalation rates scale as $BW^{3/4}$; these factors cancel each other out when exposure is expressed in ppm.

Table 2-6. Summary of derivation of PODs for squamous metaplasia based on studies in F344 and Wistar rats (Woutersen et al., 1989; Kerns et al., 1983)

Endpoint and reference	Species/ sex	Model	BMR	Rat BMC[a] (mg/m^3)	Rat BMCL[a] (mg/m^3)	Human POD^a_{ADJ} (mg/m^3)
Squamous metaplasia Kerns et al. (1983); Battelle (1982)	F344 rat, M and F	Log-probit	0.10[b]	0.576	0.448	0.086[c]
Squamous metaplasia Woutersen et al. (1989)	Wistar rat, M	Log-logistic	0.10[b]	1.00	0.526	0.094[d]

[a]POD_{ADJ} is the human equivalent of the rat BMCL duration adjusted (6/24) × (5/7) for continuous daily exposure.
[b]BMR = 0.10 because the severity of squamous metaplasia, as indicated by the severity scores, was considered minimally adverse.
[c]Human extrapolation was based on modeled estimates of regional formaldehyde tissue flux.
[d]Human extrapolation was based on ppm equivalence derived from pharmacokinetic principles.

Conclusion

Confidence is *high* in the two studies used to derive PODs, as both studies were well designed and executed with adequate reporting of data. Kerns et al. (1983; Battelle, 1982) was conducted under Good Laboratory Practice conditions, and the inhalation exposure protocols in both studies were adequately documented and well conducted. Confidence in the POD calculations based on Wouterson et al. (1989) is *medium*, while confidence based on Kerns et al. (1983) is *low*. Confidence is lower in the POD from Kerns et al. (1983) because the calculation involved an extrapolation well below the tested formaldehyde concentrations, the BMCL was based on the 18-month exposure although the response was greater in magnitude after 24 months, and the incidence at Level 1 in the nose was modeled rather than the incidence at Level 2 where concentrations were lower. Studies with various durations and in multiple species/strains have consistently reported histopathological effects after inhaled formaldehyde exposure. Squamous metaplasia was also observed in humans exposed to formaldehyde levels between 0.1 and 2.5 mg/m^3 (see Section 1.2.4).

Reproductive and Developmental Toxicity

Female reproductive or developmental toxicity

Of the epidemiology studies that evaluated effects on fecundity or spontaneous abortion, one study developed individual exposure estimates suitable for dose-response evaluation. Taskinen et al. (1999) presented risk estimates for increased TTP for index pregnancies of women in three exposure categories. The exposure assignments were made for jobs held beginning at least 6 months prior to the index pregnancy to evaluate TTP, the primary endpoint of interest. Taskinen et al. (1999) calculated a fecundity density ratio for the three exposure categories based on 8-hour

(time-weighted average) TWA (TWA8) formaldehyde concentrations composed of measured concentrations associated with specific work tasks and reported time spent conducting those tasks in the workplace. TTP was elevated in the high exposure group relative to the unexposed group. EPA selected the middle TWA8 exposure level as a NOAEL.

The mean TWA concentrations for each exposure category needed to be adjusted for background formaldehyde exposures experienced by the employees when they were not conducting work tasks with identified formaldehyde exposure. Notably, the mean exposure (18 ppb TWA8) and lowest reported concentration measured in a work area (10 ppb) in the "low exposed" category were less than the reported average ambient exposures for Finland (21.4 ppb) (Jurvelin et al., 2001). The investigators in Taskinen et al. (1999) appear to have assumed that, while the women were away from their "exposed" work area, their exposure to formaldehyde was zero, not accounting for background occupational exposures and ambient levels of formaldehyde. Therefore, EPA recalculated the mean TWA8 concentrations. These calculations are presented in Table 2-7.

Normally, exposures from occupational studies are adjusted to account for the daily breathing volume appropriate to an environmental (versus occupational) setting and for exposure every day of the year (U.S. EPA, 1994). However, with formaldehyde, there is potential for exposure outside of work from in-home and environmental sources of formaldehyde. Therefore, the POD represents exposure during an 8-hour workday.

Table 2-7. Adjusted time-weighted average formaldehyde exposures for Taskinen et al. (1999)

(A) Proportion of work shift corresponding to the exposure group mean task-level formaldehyde exposure (ppb) and the exposure group daily exposure index (8-hour time-weighted average, TWA8). (B) Recalculation of daily exposure index (TWA8) where background formaldehyde exposure is estimated for work time spent on tasks considered unrelated to occupational use of formaldehyde.

A

Exposure group (*n*)	Reported mean exposure (TWA8)		Measured average task-level concentrations (ppb)		Estimate of work time for formaldehyde-related tasks assuming mean exposure levels	
	Mean (ppb)	Range	Mean	Range	Percentage of work time[a]	Hours per 8-hr work shift
Low (119)	18	1–39	70	10–300	26%	2
Medium (77)	76	40–129	140	50–400	54%	4.3
High (39)	219	130–630	330	150–1,000	66%	5.3

[a]Calculated as mean exposure (ppb, TWA8) divided by mean task-level exposures for the exposure group.

B

Exposure group (*n*)	Estimate of formaldehyde exposure during formaldehyde-related work tasks		Estimate of formaldehyde xposure from background levels during the work shift		Alternative daily eExposure index (ppb, TWA8)
	Mean (mg/m^3)[a]	Percentage of work time in formaldehyde task	Background formaldehyde (ppb)	Percentage of time in tasks unrelated to formaldehyde	
Low (119)	0.086	26%	0.026	74%	0.042
Medium (77)	0.172	54%	0.026	46%	0.106
High (39)	0.406	66%	0.026	34%	0.278

[a]Converted from units of ppb reported in paper.

Taskinen et al. (1999) also presented ORs for previous spontaneous abortion by multiple exposure categories based on the work experience relevant to the index pregnancy. Although spontaneous abortion risk was estimated only for events that occurred at the same workplace as the index pregnancy, there is more uncertainty regarding the relevant time window of the exposure characterization for this outcome. A POD for spontaneous abortion was not identified from this data set or any of the other studies.

Table 2-8. Summary of derivation of PODs for reproductive toxicity in females

Endpoint and reference	Population	Observed effects by exposure level	POD (mg/m^3)
Time-to-Pregnancy in Females			
Occupational prevalence Taskinen et al. (1999)	Adult women, *n* = 602	**Time-to-Pregnancy by Formaldehyde Category** Fecundability density ratio (FDR)[a] Mean TWA8 (mg/m^3) / # / FDR[b] / 95% CI Not exposed / 367 / 1.00 / - 0.042 / 119 / 1.09 / 0.86–1.37 0.106 / 77 / 0.96 / 0.72–1.26 0.278 / 39 / 0.64 / 0.43–0.92 FDR = ratio of average incidence densities of pregnancies in exposed compared to employed unexposed women Discrete proportional hazards regression; adjusted for employment, smoking, alcohol consumption, irregular menstrual cycles and # children Comparison: index pregnancies that occurred when participants were not employed in exposed workplace	NOAEL = 0.106 LOAEL = 0.278

Abbreviations: TWA8 = 8-hour time-weighted average; FDR = false discovery rate; NOAEL = no-observed-adverse-effect level; LOAEL = lowest-observed-adverse-effect level.
[a]Concentrations converted to mg/m^3.
[b]TWA8 reported by authors was recalculated by EPA to account for background formaldehyde exposure while working in "nonexposed" work areas.

Conclusion

A POD was identified based on the findings of Taskinen et al. (1999). The study was well-conducted, a robust exposure assessment was used, and the data analysis was adjusted for other risk factors and workplace exposures that could be associated with developmental toxicity. However, because the study evaluated an occupational cohort, generalization to the entire general population is more uncertain; EPA places *medium* confidence in the study. Confidence in the candidate RfC derivation is low. Stratification by use of gloves (yes/no) indicated that women who did not use gloves had a lower FDR. The stronger association among this group implies that dermal absorption might have resulted in a greater response. Therefore, the level of certainty concerning the value of the NOAEL associated solely with inhalation exposure is lessened.

Male reproductive toxicity

Two studies reporting effects on the male reproductive system in rats were considered to be of sufficient quality for candidate reference value derivation (Ozen et al., 2005; Ozen et al., 2002). Both studies exposed the animals to paraformaldehyde via inhalation; thus, the interpretation of the results from these studies was not compromised by possible methanol coexposure as with the other studies that evaluated male reproductive toxicity endpoints. In Özen et al. (2002), statistically significant and dose-dependent decreases in testis weight (relative to

body weight) were observed after 4 and 13 weeks of formaldehyde exposure. Although absolute organ weights are preferred for this measure because testis weights are generally conserved when body weight is decreased, mean body weights were also significantly decreased with exposure; thus, this response pattern suggests that the organ weight decreases were likely due to a direct effect on the testis (note: in this case, decreased relative testis weight is likely an underestimate of the more appropriate decrease in absolute testis weight). Also of note, the effects increased with duration of treatment (to 8 and 10% of control at 13 weeks) and were associated with alterations in testicular zinc, copper, and iron levels (measured in the same study), thus, increasing confidence in the study results. Although the decreased testis weight data at 4 weeks were successfully modeled[40] (see Appendix B.1.3) to derive a $BMDL_{1SD}$ of 2.60 mg/m^3, this endpoint was not used to calculate a cRfC because a subacute endpoint was not considered an appropriate basis for a chronic RfC when data from longer-term exposure were available from the same study. For the decreased testis weight at week 13 (Ozen et al., 2002), a LOAEL of 12.3 mg/m^3 was adjusted for continuous exposure based upon the experimental paradigm to yield a POD_{ADJ} of 2.93 mg/m^3 (POD_{ADJ} = 12.3 mg/m^3 × 8 hr exposed per day/24 hrs per day × 5 days exposed per week/7 days per week).

In Özen et al. (2005), statistically significant dose-dependent decreases in serum testosterone levels (6 to 9% decreases from control values) were observed following 91 days of inhalation exposure. At the same exposure levels, significant decreases of 23 to 26% from control were noted in mean seminiferous tubule diameters, an effect that could have been directly related to testosterone decreases. For the decreased serum testosterone at day 91 (Ozen et al., 2005), a $BMCL_{1SD}$ of 0.208 mg/m^3 was calculated. This value was adjusted for continuous exposure based upon the experimental paradigm to yield a POD_{ADJ} of 0.050 mg/m^3 (POD_{ADJ} = 0.208 mg/m^3 × 8 hr exposed per day/24 hrs per day × 5 days exposed per week/7 days per week). EPA (U.S. EPA, 2012) indicates that for highly soluble and reactive gases that interact with tissue at the portal of entry or for gases with systemic penetration ppm equivalence is likely to be the most appropriate default method for extrapolation. Accordingly, the human equivalent concentration (HEC) was derived by adjusting the POD derived for the rat by the duration adjustment of (6/24) × (5/7) for continuous daily exposure.

Although the Özen et al. (2005; 2002) studies evaluated a small number of animals (seven and six male rats per group, respectively), the sample sizes were adequate to detect statistically significant effects and did not demonstrate excessive variability.

[40]Using this BMR, a BMC of 3.81 mg/m^3 was derived, and a POD_{ADJ} of 0.619 mg/m^3 was calculated, while this is lower than the POD_{ADJ} at 13 weeks of 2.93 mg/m^3, the uncertainty in extrapolating the 13-week LOAEL to a NOAEL would be expected to result in a comparably lower cRfC.

Conclusion

The confidence in the PODs derived from these studies is **low**, as the lowest formaldehyde concentration tested in Özen et al. (2002) was 12.2 mg/m^3, and in Özen et al. (2005) was 6.2 mg/m^3. Both Özen et al. (2005; 2002) studies were well conducted and interpreted with *high* confidence that exposed the animals to paraformaldehyde via inhalation, and the observed responses in each study were statistically significant, dose-dependent, and supported by the larger body of animal study data for formaldehyde. Nevertheless, the magnitude of the testis weight response in Özen et al. (2002) was greater than that of the testosterone decreases observed in Özen et al. (2005), and a number of other rodent studies in the formaldehyde database demonstrated similar testis (and epididymal) weight deficits, while specific evidence of treatment-related serum testosterone decreases is quite limited. Uncertainties associated with the Özen et al. (2002) study include the small sample size (7 male rats per test group), lack of reported information on absolute organ weight values, and no indication in the study report that exposure levels were confirmed analytically. Additionally, the data could not successfully be modeled, and thus it was necessary to use the study LOAEL to derive the RfC.

Table 2-9. Summary of derivation of PODs for reproductive toxicity in males

Endpoint and reference	Species/ sex	Model	BMR (mg/m^3)	BMC (mg/m^3)	BMCL (mg/m^3)	POD_{ADJ} (mg/m^3)
Ozen et al. (2002) Decreased relative testis weight (13 wk)	Rat/M	LOAEL	N/A	N/A	N/A	2.91
Ozen et al. (2005) Decreased serum testosterone (13 wk)	Rat/M	Exponential (M2)	1 SD	0.284	0.208	0.050

2.1.2. Derivation of Candidate Reference Concentrations

In this section, the PODs (either POD_{ADJ} or POD_{HEC}) calculated in Section 2.1.1 were used to derive candidate reference concentrations (cRfCs). These derivations are presented according to the specific uncertainty factors (UFs) applied (to reduce redundancy for similar decisions across health effects); the resultant cRfCs are then organized in a table and figure according to health effect. The text below explains the rationale for the UFs that are applied for each candidate RfC; the implementation of those decisions is most easily seen by looking at Table 2-10 that immediately follows the explanatory text.

Methods of Analysis

A series of five UFs were applied to each of the PODs developed for each endpoint/study, specifically addressing the following areas of uncertainty: interspecies uncertainty (UF_A) to account for animal-to-human extrapolation, and consisting of equal parts representing toxicokinetic and toxicodynamic differences; intraspecies uncertainty (UF_H) to account for variation in susceptibility

across the human population (see Section 1.4.1), and the possibility that the available data may not be representative of individuals who are most susceptible to the effect; LOAEL-to-NOAEL uncertainty (UF_L) to estimate an exposure level where effects are not expected when a POD is based on a LOAEL; subchronic-to-chronic uncertainty (UF_S) to account for the uncertainty in using subchronic studies to make inferences about lifetime exposure, and to consider whether lifetime exposure would have effects at lower levels (e.g., for studies other than subchronic studies); and database uncertainty (UF_D) to account for database deficiencies if an incomplete database raises concern that further studies might identify a more sensitive effect, organ system, or lifestage. The application of these UFs (i.e., assigning a value) was based on EPA's Review of the Reference Dose and Reference Concentration Processes (U.S. EPA, 2002) (Section 4.4.5).

UF_A interspecies uncertainty: animal-to-human variation

- For the 10 candidate RfCs derived from human epidemiology studies, an interspecies uncertainty factor (UF_A) was not applied.

- For the candidate RfCs for respiratory tract pathology (squamous metaplasia) and male reproductive toxicity from rat data, an HEC was estimated using either dosimetry modeling (Kerns et al., 1983, metaplasia) or an assumption of ppm equivalence derived from pharmacokinetic principles (Woutersen et al., 1989, respiratory pathology); (Ozen et al., 2005; Ozen et al., 2002, male reproductive toxicity).

    - A factor of 3 was then applied to account for residual uncertainties in interspecies extrapolation from the two candidate RfCs for respiratory pathology and the two cRfCs for reproductive toxicity in males derived from rat studies.

UF_H intraspecies uncertainty: Human variation

- As summarized in Section 1.4.1, populations or lifestages demonstrated to have potentially increased susceptibility to the health effects of inhaled formaldehyde exposure include pregnant women and children, persons with pre-existing health conditions (particularly respiratory conditions such as asthma), and smokers. The UF_H selections below explicitly considered the ability of the selected studies to quantitatively address these potential susceptibilities. This resulted in reduced UF_Hs for several endpoints with quantitative analyses for several potentially susceptible groups, namely children, pregnant women, and asthmatics. In addition, co-exposure to tobacco smoke was considered during the evaluation of the individual studies. Section 1.4.1 discusses several other possible scenarios that might result in increased susceptibility to inhaled formaldehyde but for which the currently available information is inconclusive. While they may have an impact, these potential susceptibility factors without specific experimental support were not considered quantitatively.

- For four candidate RfCs derived from human epidemiology studies, an intraspecies uncertainty factor (UF_H) of 3 (i.e., $10^{1/2}$) was used.

    - For Venn et al. (2003), a UF_H of 3 was used because the POD was based on the degree of asthma control in children with asthma, a highly sensitive group. (A UF_H of

1 was considered but not used because the number of individuals in the two higher exposure groups was relatively low (n = 31–35), and likely did not characterize all possible human variability.)

- For the POD for decreased peak expiratory flow rates (PEFRs) among children from Krzyzanowski et al. (1990), a UF_H of 3 was used with support from the model results reported by the authors. The authors of this study evaluated a model of the association of formaldehyde with PEFR that assessed differences between asthmatic and nonasthmatic children. Multiple observations in the study indicate that a UF_H of 3 applied to the endpoint can be expected to be protective of asthmatic children and other susceptible individuals. EPA used the published regression coefficients from the random effects model to calculate the predicted decrease in PEFR from the baseline level (i.e., formaldehyde concentration equal to zero) for each group (for details of the analysis see Appendix B.1.2). At the BMC (i.e., PEFR change of 10% in the entire group), the asthmatic children experienced a decrement in PEFR that was 1.5-fold greater than that of the nonasthmatic children. Further, at the BMCL (0.021 mg/m^3), which was selected as the POD, the decrease in PEFR among asthmatic children was 10.5% while that in nonasthmatic children was 7.2%. The authors also stated that other characteristics that could affect variability such as acute respiratory illness episodes during the observation period, environmental tobacco smoke in the home, or socioeconomic status (education level of head of household) did not increase sensitivity. All of these observations indicate that a UF_H of 3 can be expected to be protective of asthmatic children and other susceptible individuals.

- For rhinoconjunctivitis and current asthma prevalence among children (school exposure) from Annesi-Maesano et al. (2012), a UF_H of 3 was used for the POD. Although Annesi-Maesano et al. (2012) did not select the study population based on characteristics that increased susceptibility to formaldehyde's respiratory effects, childhood is a susceptible lifestage for asthma and allergy, and the sample size of 6,600 children was large enough to have characterized an adequate spectrum of human variability. However, a UF_H of 1 was not used because susceptibility among subsets of the study population was not specifically assessed.

- Matsunaga et al. (2008) was a study of pregnant women, a sensitive population for eczema prevalence and an UF_H of 3 was used for the POD. An UF_H of 1 was not applied because the study participants were adult women and no information was available for other sensitive lifestages, including children, a subgroup with a higher prevalence of eczema compared to adults.

- A UF_H of 10 was used for the POD for current asthma prevalence in children (Krzyzanowski et al., 1990), the five cRfCs derived from epidemiology studies of adults, and the four cRfCs derived from animal studies.

  - For current asthma prevalence among children with residential exposure (Krzyzanowski et al., 1990), a UF_H of 10 was used because susceptibility among subsets of the population was not specifically assessed, and the precision of the NOAEL was lower compared to Annesi-Maesano et al. (2012).

- For the cRfC for sensory irritation in adult (and teenage) populations (residential exposures) in Hanrahan et al. (1984), a UF_H of 10 was used. Although the study population in Hanrahan et al. (1984) comprised randomly selected households in mobile homes with individuals representing a range of age, sex, health behavior, occupational status, and health status, the identified PODs were not based on evaluation of differential susceptibility among subgroups with conditions or characteristics that may contribute to variation in response.

- For the two sensory irritation PODs derived from short-term controlled human exposure studies (Kulle et al., 1987; Andersen and Molhave, 1983), as well as the developmental toxicity POD based on reduced fecundity in reproductive-age women in an occupational cohort studied by Taskinen et al. (1999), a factor of 10 was applied to account for variation in the broader human population not represented by occupationally exposed groups or participants in controlled human exposure studies who met the eligibility criteria. Physiological differences that affect sensitivity may become less of a concern for exposure to acute, high concentrations of direct-acting irritants (such as formaldehyde) for the derivation of an acute RfC, which could justify application of a lessor UF_H as noted by the NRC (2001).

- For the four cRfCs based on studies in animals, a factor of 10 was applied to account for the limited variability in susceptibility factors encompassed by these typical studies of inbred laboratory animal populations.

UF_L LOAEL uncertainty: LOAEL-to-NOAEL extrapolation

- A LOAEL-to-NOAEL UF was not applied to the five PODs based on a NOAEL.

- For the eight PODs derived from BMD modeling, a factor was not applied in keeping with EPA guidelines (U.S. EPA, 2012). EPA selected a BMR of 10% to identify a POD based on specific studies for several effects: sensory irritation, pulmonary function, and respiratory pathology. A BMR of 5% was selected for the POD identified using the Venn et al. (2003) study for effects on degree of asthma control. A BMR of 1 standard deviation from the control mean was selected for male reproductive toxicity.

UF_S subchronic uncertainty: extrapolation to chronic exposure

- Three experimental studies in animals evaluated exposures of durations less than a lifetime (Ozen et al., 2005; Ozen et al., 2002; Kerns et al., 1983).

  - A factor of 10 was applied to the two PODs for male reproductive toxicity to approximate the potential effect of lifetime exposure, as these effects are not necessarily dependent on a specific exposure window and they are expected to worsen with continued exposure (Ozen et al., 2005; Ozen et al., 2002).

  - A factor of 3 was applied to the respiratory tract pathology POD from Kerns et al. (1983) because it was based on 18-month exposure data from that rodent study in lieu of the 24-month exposure data available in the same study. As discussed in Section 1.2.4, there are data to suggest that exposure concentration would be more important to the development of this lesion than duration, although the specifics of this relationship have not been defined. However, the lesion incidences for this

particular study were substantially higher with the longer duration data (i.e., 24-month versus 18-month), and thus a lower POD would be expected if the 24-month data could have been modeled. Thus, while use of the 18-month exposure duration is expected to reduce the uncertainty associated with extrapolating to lifetime exposure compared with a shorter duration such as 90 days, this reduction in extrapolation to lifetime was considered incomplete (see text in 2.1.1) and a factor of 3 was applied, consistent with EPA guidelines [a factor other than 10 may be used, depending on the duration of the studies and the nature of the response (U.S. EPA, 2002, 1998, 1994)].

- For one study in a human population, a UF_S of 3 was applied to the POD. Matsunaga et al. (2008) evaluated the occurrence of atopic eczema during the past 12 months in a group of pregnant women and analyzed this outcome in relation to formaldehyde concentrations measured in their homes, which is a less-than-lifetime window of vulnerability. However, this outcome may have been pre-existing in a portion of the study sample and the window of susceptibility may not have been sufficiently represented by the shorter exposure period (Cho et al., 2010). Therefore, a UF_S of 1 was not applied.

- For the remaining seven PODs derived from human studies, a UF_S of 1 was applied. Three studies were of sensory irritation, which is considered to be predominantly an acute response (Kulle et al., 1987; Hanrahan et al., 1984; Andersen and Molhave, 1983). Notably, the controlled exposure studies by Kulle et al. (1987) and Andersen and Molhave (1983) demonstrate formaldehyde-induced sensory irritation after only brief periods of exposure; thus, these studies would be relevant for estimating the sensory irritant effects resulting from acute formaldehyde exposure. Three studies that were used for PODs for pulmonary function, allergic conditions, current asthma, and asthma control evaluated these outcomes in children and considered an appropriate window of exposure (Annesi-Maesano et al., 2012; Venn et al., 2003; Krzyzanowski et al., 1990). The study of Taskinen et al. (1999) evaluated TTP, which in this review is categorized as a female reproductive or developmental endpoint and the exposure window was considered to be appropriate. Matsunaga et al. (2008) evaluated the occurrence of atopic eczema during the past 12 months in a group of pregnant women and analyzed this outcome in relation to formaldehyde concentrations measured in their homes, which is a less-than-lifetime window of vulnerability.

UF_D database uncertainty

- A factor to account for database deficiencies was not applied to any of the PODs (i.e., UF_D = 1). The formaldehyde database is not considered complete, as important questions remain regarding the potential for formaldehyde inhalation exposure to cause reproductive and developmental toxicity and nervous system effects (both of which demonstrate an incomplete evidence base with methodological limitations). An incomplete database can raise concern that further studies might identify a more sensitive effect, organ system, or lifestage (U.S. EPA, 2002, 1998, 1996, 1994, 1991). However, given the breadth of the literature on formaldehyde toxicity, and given the poor distribution of inhaled formaldehyde to distal sites, an expectation that additional data are unlikely to reveal systemic effects (i.e., by indirect MOAs) at lower exposure levels than those eliciting adverse respiratory system changes seems unlikely; thus, this assessment uses a database uncertainty factor (UF_D) of 1.

Summary of Candidate Reference Concentrations

Table 2-10 summarizes the application of UFs to each POD from the *medium* or *high* confidence studies identified in Section 2.1.1 to derive one or more cRfC(s) in each health effect system. Figure 2-1 presents graphically these cRfCs, UFs, and PODs, with each bar corresponding to one data set described in Table 2-10.

Table 2-10. Health effects and corresponding derivation of candidate RfCs

Endpoint (reference; population)	POD[a]	POD basis	UF_A	UF_H	UF_L	UF_S	UF_D	$UF_{COMPOSITE}$	cRfC (mg/m^3)
Sensory Irritation									
Eye irritation symptoms (Hanrahan et al., 1984); adult M + F, *n* = 61, residential, prevalence at POD 13%	0.087	$BMCL_{10}$	1	10	1	1	1	10	**0.009**
Eye irritation symptoms (Kulle et al., 1987); adult M + F, *n* = 10, controlled exposure	0.42	BMC/2	1	10	1	1	1	10	**0.04**
Eye irritation symptoms (Andersen and Molhave, 1983); adult M + F, *n* = 16, controlled exposure	0.19	BMC/2	1	10	1	1	1	10	**0.02**
Pulmonary Function									
Peak expiratory flow rate (Krzyzanowski et al., 1990); Children M + F, *n* = 298, residential	0.021	$BMCL_{10}$	1	3	1	1	1	3	**0.007**
Allergy-related Conditions									
Rhinoconjunctivitis prevalence (Annesi-Maesano et al., 2012); children M + F, *n* = 2,200 at POD, school-based exposure	0.024	NOAEL	1	3	1	1	1	3	**0.008**
Atopic eczema prevalence (Matsunaga et al., 2008); adult F (pregnant), *n* = 301 at POD, personal monitor-based exposure	0.046	NOAEL	1	3	1	3	1	10	**0.005**
Asthma									
Current asthma prevalence (Annesi-Maesano et al., 2012); children M + F, *n* = 2,200 at POD, school-based exposure	0.042	NOAEL	1	3	1	1	1	3	**0.01**
Current asthma prevalence (Krzyzanowski et al., 1990); children M + F, *n* = 24 at POD, residential	0.06	NOAEL	1	10	1	1	1	10	**0.006**
Asthma control (Venn et al., 2003); children with asthma M + F, *n* = 35 at POD, residential	0.013	$BMCL_5$	1	3	1	1	1	3	**0.004**

Endpoint (reference; population)	POD[a]	POD basis	UF_A	UF_H	UF_L	UF_S	UF_D	$UF_{COMPOSITE}$	cRfC (mg/m^3)
Respiratory Tract Pathology									
Squamous metaplasia: (Kerns et al., 1983; Battelle, 1982); adult F344 rat M + F, 18-month exposure	0.086	$BMCL_{10}$	3	10	1	3	1	100	0.0009
Squamous metaplasia: (Woutersen et al., 1989); adult Wistar rat, M + F, 28-month exposure	0.094	$BMCL_{10}$	3	10	1	1	1	30	**0.003**
Female Reproductive and/or Developmental Toxicity									
Delayed pregnancy (Taskinen et al., 1999); pregnant F, *n* = 77 at POD	0.106	NOAEL	1	10	1	1	1	10	**0.01**
Male Reproductive Toxicity									
Relative testis weight (Ozen et al., 2002); adult rat, M, 13-week exposure	2.91	LOAEL	3	10	10	10	1	3,000	**0.001**
Serum testosterone (Ozen et al., 2005); adult rat, M, 13-week exposure	0.05	BMCL1SD	3	10	1	10	1	300	**0.0002**

Abbreviations: cRfC = candidate reference concentration; UF = uncertainty factor; POD = point of departure; BMC = benchmark concentration; BMCL = benchmark concentration, lower confidence bound; NOAEL = no-observed-adverse-effect level; LOAEL = lowest-observed-adverse-effect level.

[a]POD may be adjusted (e.g., to continuous exposure; to a human equivalent concentration) (see Section 2.1.1).

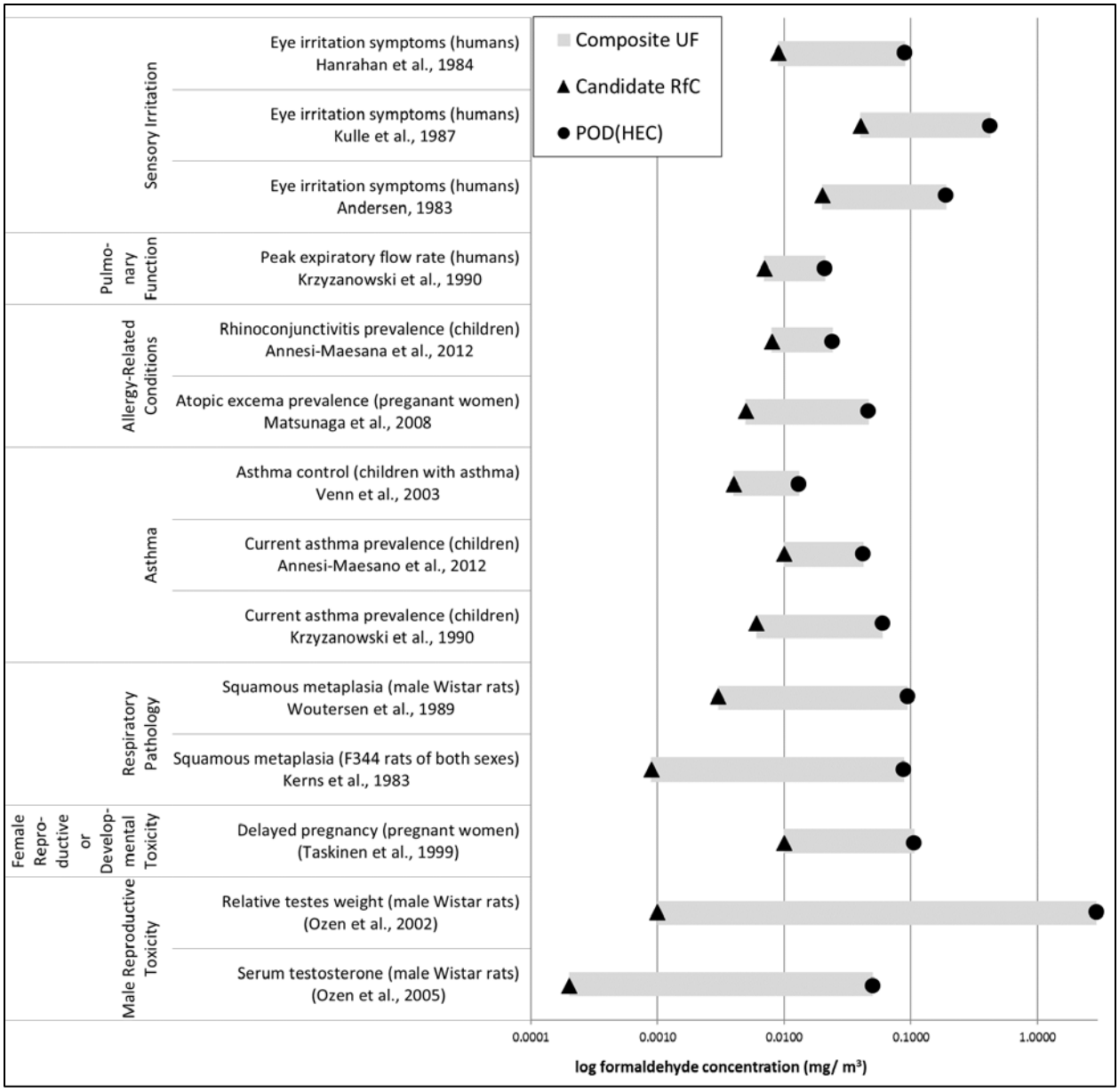


Figure 2-1. Candidate RfCs with corresponding POD and composite UF.

As the PODs reflect exact values, and the cRfCs are rounded to one significant figure, the $UF_{COMPOSITE}$ extrapolation between the two is not always exact.

2.1.3. Selection of Organ- or System-specific Reference Concentrations

This section distills the candidate values from Table 2-10 (i.e., the clusters of health effect-specific cRfCs) into a single value representing a level without an appreciable risk of deleterious effects on each particular organ or system during a lifetime. These organ- or system-specific RfCs (osRfCs) may be useful for subsequent cumulative risk assessments that consider the combined effect of multiple agents acting at a common site. In addition to the UFs applied, a set of three confidence descriptors are included with each osRfC to reflect confidence in the health hazard, in

the ability of the study to provide an accurate quantitative estimate, and in the completeness of the database of studies available to evaluate each hazard.

Methods of Analysis

EPA selected the osRfC for each specific organ or system using rationales specific to the data and studies for that health area, as described below. In general, studies of human populations with exposures that best represent that of the general population, and human or animal studies that evaluated long-term exposure were preferred, when available, unless a shorter window of susceptibility was appropriate. In addition, cRfCs with lower composite UFs were generally preferred. An osRfC was typically selected from cRfCs from higher confidence studies and higher confidence in the POD estimate used to derive the cRfC. osRfCs were sometimes derived using a method that combined two or more cRfCs.

Because the studies that are the basis of each of the osRfCs are interpreted to be representative of the sets of studies available for each of the health outcomes evaluated, the overall hazard descriptor for each database is presented. These descriptors represent the overall confidence in the findings from the sets of individual studies, as compared to the confidence in the individual *medium* or *high* confidence studies most amenable to estimating a cRfC.

An overall confidence level of *high*, *medium*, or *low* was also assigned to each osRfC based on the reliability of the associated POD. Confidence in the POD included considerations of the quality and variability of the exposure assessment in an epidemiology study or the exposure protocols in an animal study. Moreover, higher confidence was placed in the osRfC when the POD was identified close to the range of the observed data and the magnitude of exposure was relevant to those experienced in the general U.S. population.

In addition, a descriptor was included to describe the coverage and quality of studies that informed the hazard conclusion for that specific organ/system. The evidence base for different health effects varies in size, coverage of critical endpoints, and quality of the studies; this confidence level reflects database completeness for each of the organ systems.

Sensory Irritation

The osRfC for sensory irritation of 0.009 mg/m^3 is based on the cRfC for eye irritation derived using the results of Hanrahan et al. (1984). As described previously, the study population was more representative of the general population in terms of demographic characteristics and exposure levels, and the cRfC reflects more certainty compared to the cRfCs calculated from the two controlled human exposure studies. The POD is based on formaldehyde measurements in the participants' homes (1-hour sampling period in two rooms). The confidence in the POD and cRfC derivations is *medium* because of uncertainty related to the precise correspondence of the window of exposure with the period symptoms were experienced.

There is an extensive literature on this response to formaldehyde and the completeness of the database is considered to be *high*. Because sensory irritation is an immediate response to exposure, the osRfC is applicable to short-term as well as long-term exposure scenarios.

Pulmonary Function

Data from a study in a residential population exposed over multiple years was used to calculate a cRfC for pulmonary function of 0.007 mg/m^3 (Krzyzanowski et al., 1990). This value was chosen as the osRfC. The results from this study are generalizable to the general population, and a robust exposure assessment based on 2-week average measurements in multiple rooms and two different seasons. A strong exposure-response relationship with formaldehyde concentration was observed by this study, which reduces concern that residual confounding by unmeasured coexposures (smoking and NO_2 were controlled for) strongly influenced the association. Hence, confidence in the POD value is *high*. There is extensive information on this response to formaldehyde from multiple studies in diverse exposure settings, and the completeness of the database is considered to be *high*.

Allergy-related Conditions

The osRfC for allergy-related conditions is based on one study in children (Annesi-Maesano et al., 2012) and one study in adults (Matsunaga et al., 2008). Both PODs were based on NOAELs and are interpreted with *high* confidence. In particular, the large study of children (*n* = 6,683) by Annesi-Maesano et al. (2012) was able to address the variability in susceptibility that would be anticipated within a population. No other pollutants (e.g., NO_X, $PM_{2.5}$, acetaldehyde, acrolein, ETS) analyzed by this study were associated with rhinoconjunctivitis; thus confounding by coexposures is unlikely. EPA selected an osRfC of 0.008 mg/m^3, based on the overall greater strength of Annesi-Maesano et al. (2012). The completeness of the database relating formaldehyde exposure to allergic sensitization is considered to be **high**, based on the variety of endpoints, populations, and exposure scenarios considered in these studies.

Current Asthma/Degree of Asthma Control

There were three cRfCs developed for asthma based on the endpoints, current asthma, and degree of asthma control (Annesi-Maesano et al., 2012; Venn et al., 2003; Krzyzanowski et al., 1990). The POD based on Annesi-Maesano et al. (2012) was derived from a NOAEL using a large study with a relatively long exposure measurement period, supported by a collection of several other smaller studies. Although the effect estimates derived by Venn et al. (2003) were less precise because of relatively small group sizes, the POD derived from Venn et al. (2003) reflects the response among a susceptible population, asthmatic children. Venn et al. (2003) used a strong study design, observed an exposure-related trend in response and adjusted the statistical analyses for key confounders, including other indoor exposures (e.g., visible mold, total VOCs, NO2, cotinine levels). To account for the different uncertainties in the PODs from the three studies, the median of

the three PODs, 0.006 mg/m^3, was selected for the osRfC. The overall confidence in the PODs is *medium*. Two factors contribute to the determination that the completeness of the database relating formaldehyde exposure to prevalence of current asthma is *medium*. One factor is the relatively small number of studies examining asthma risk in relation to exposures between 0.05 and 0.1 mg/m^3, and limitations of these studies (e.g., low statistical power, incomplete reporting of study results and exposure measures). The second factor is the scarcity of data pertaining to asthma control among people with asthma.

Respiratory Tract Pathology

The osRfC for respiratory tract pathology is based on squamous metaplasia observed in anterior rodent nasal passages in two studies of long-term exposure. EPA could discern no particular basis to select either the Woutersen et al. (1989) study or Kerns et al. (1983; Battelle, 1982) study over the other on grounds of confidence in the study methods, or known differences in sensitivity between Wistar and F344 rats. In addition, the PODs were nearly identical and the cRfCs are very similar for the two data sets [i.e., cRfCs of 0.0009 for Kerns et al. (1983) and 0.003 for Woutersen et al. (1989), which are comparable given the limited precision of the calculations]. However, there was lower confidence in the derivation of the POD from Kerns et al. (1983), which involved an extrapolation well below the tested formaldehyde concentrations. In addition, the cRfC for Kerns et al. (1983) involved the application of a UF for exposure duration. While exposure duration is important to the development of this lesion, such effects appear to be more dependent on exposure concentration (see MOA discussion in Section 1.2.4). Thus, if a factor describing the concentration-duration relationship[41] were available for formaldehyde (and interpretable in the context of metaplasia), a data-defined UF could have been applied. Considering these uncertainties and the comparability of the cRfCs, to represent the results of both studies, the cRfC from Woutersen et al. (1989) was used to derive an osRfC of 0.003 mg/m^3 for the respiratory pathology endpoint. Because the POD basis for this value is from Woutersen et al. (1989), the confidence in the POD is considered *medium*. Completeness of the database for respiratory tract pathology is considered *high*, based primarily on the numerous well-conducted, long-term studies in experimental animals.

Female or Developmental Toxicity

Data from one study of women exposed to formaldehyde in the Finnish woodworking industry are available to derive a cRfC for effects on delayed pregnancy (Taskinen et al., 1999). This value was chosen as the osRfC. Although TTP is a sensitive measure of effects on the reproductive system, confidence in the POD is judged to be *low* because the outcome was evaluated in a healthy

[41]Studies of other irritants have, on average, identified a factor of ~1.8–1.9 for relationships between acute exposure and mortality (i.e., the observed mortality is more attributable to concentration, by 1.8- to 1.9-fold, than duration; see Section 1.2.4). A value for formaldehyde was not identified, nor were values for long-term exposure.

working population with relatively high exposure, and thus required substantial extrapolation. More complete assessments of developmental endpoints by epidemiology or toxicology studies were not available. Thus, the completeness of the database is considered *low*. The relevant period for exposure effects on TTP through unrecognized fetal losses or factors controlling the ability to conceive could range from the weeks just prior and after conception, to the entire period of prior exposure during the life of the individual because the mechanisms and events through which formaldehyde may cause this outcome are not known.

Male Reproductive Toxicity

The cRfC derived from Özen et al. (2002) was considered the stronger of the two candidates for male reproductive toxicity, and thus was chosen to represent the osRfC. The magnitude of the testes weight response in Özen et al. (2002) was greater than that of the testosterone decreases observed in Özen et al. (2005), and a number of other rodent studies in the formaldehyde database demonstrated similar testes (and epididymal) weight deficits, while specific evidence of treatment-related serum testosterone decreases is quite limited. The LOAEL from Özen et al. (2002) was used to derive the POD. The confidence in the POD derived from its results is *low*, given that the lowest formaldehyde concentration tested in this study was 12 mg/m^3. Confidence in the database is also considered *low* because while there are a number of published studies that evaluated reproductive toxicity in males, the interpretation of study results is complicated by their methodological limitations and exclusive use of formaldehyde concentrations above 6 mg/m^3, and data are lacking regarding functional endpoints.

2.1.4. Summary of Organ- or System-specific RfCs and RfC Selection

Table 2-11. Organ- or system-specific RfCs for formaldehyde inhalation

Health effect	Basis reference(s) [species]	UF_C	osRfC (mg/m^3)	Integrated hazard judgment	Confidence in POD estimate(s)[a]	Database completeness[b]
Sensory irritation	Hanrahan et al. (1984) [human]	10	0.009	**evidence demonstrates**	*medium*	*high*
Pulmonary function	Krzyzanowski et al. (1990) [human]	3	0.007	**evidence indicates (likely)**	*high*	*high*
Allergy-related conditions	Annesi-Maesano et al. (2012) [human]	3	0.008	**evidence indicates (likely)**	*high*	*high*

Health effect	Basis reference(s) [species]	UF_C	osRfC (mg/m^3)	Integrated hazard judgment	Confidence in POD estimate(s)[a]	Database completeness[b]
Asthma (prevalence of current asthma/degree of asthma control)	Annesi-Maesano et al. (2012); Venn et al. (2003); Krzyzanowski et al. (1990) [human]	10[c]	0.006	**evidence indicates (likely)**	*medium*	*medium*
Respiratory pathology	Woutersen et al. (1989); Kerns et al. (1983) [rat]	30[c]	0.003	**evidence demonstrates**	*medium*	*high*
Female or developmental toxicity	Taskinen et al. (1999) [human]	10	0.01	**evidence indicates (likely)**	*low*	*low*
Male reproductive toxicity	Ozen et al. (2002) [rat]	3,000	0.001	**evidence indicates (likely)**	*low*	*low*

Abbreviations: osRfC = organ- or system-specific reference concentration; UF = uncertainty factor; POD = point of departure.

[a]This reflects a judgment regarding how well the study-specific data are able to estimate a no-effect- or minimal-effect-level of response (e.g., a lower level of confidence would be applied to high-concentration studies that required extrapolation far below the lowest tested concentration to estimate a POD). A descriptor of **l***ow* means that the POD derived is expected to be less accurate.

[b]Although no UF_D was applied to any RfC, it is recognized that the evidence databases for the various health effects are not equal. This descriptor was added to emphasize the health areas where additional research could reduce existing uncertainties. A descriptor of *low* means the degree of certainty regarding the RfC is lower.

[c]These two osRFCs are based on multiple studies and candidate values, sometimes with different UF_Cs applied. The UF_C values shown in this table and Figure 2-2 reflect the candidate values selected to represent each osRfC [i.e., the UF_C applied to the POD from Krzyzanowski et al. (Krzyzanowski et al., 1990) for asthma and from Woutersen et al. (Woutersen et al., 1989) for respiratory pathology].

Selection of the Proposed Overall Reference Concentration

The following discussion outlines the selection of an overall RfC from among the osRfCs presented in Table 2-11. The overall RfC was chosen to reflect an estimate of continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The amount of risk between the RfC and the PODs from which the RfC is derived is not known.

Methods of Analysis

Choice of the overall RfC involves consideration of both the level of certainty in the estimated organ- or system-specific values, as well as the level of confidence in the observed effect(s) (see Figure 2-2). An overall confidence level is assigned to the RfC to reflect an interpretation regarding confidence in the collection of study/studies used to determine the

hazard(s) and derive the RfC, the RfC calculation itself, as well as the overall completeness of the database on the potential health effects of formaldehyde exposure.

Comparison

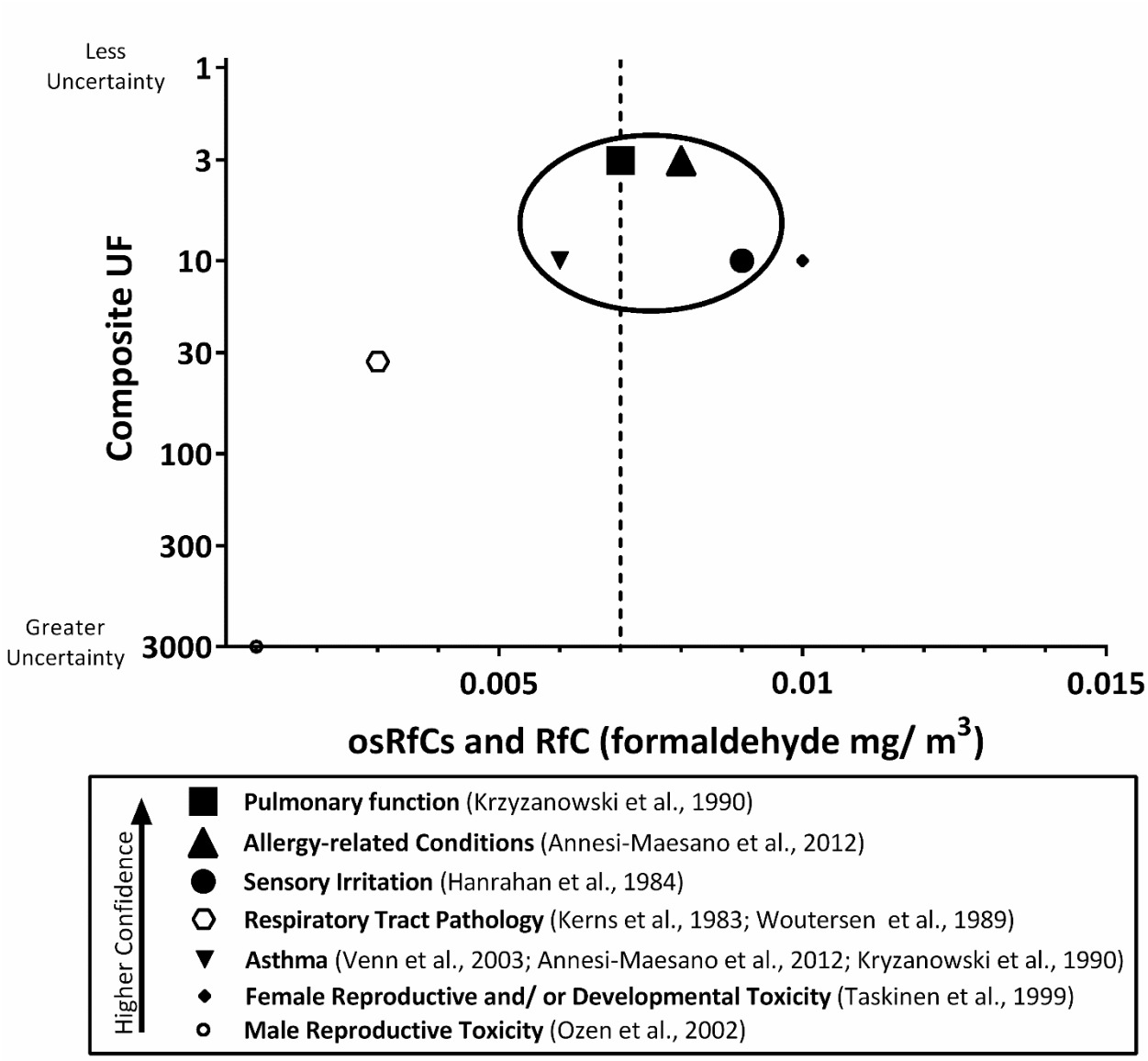


Figure 2-2. Organ- or system-specific RfC scatterplot.

Organ/system RfCs (osRfCs) that are represented by larger shapes and that are closer to the top of the graph are interpreted with higher confidence regarding the basis from which the value was derived (see Table-2-11), and with less uncertainty (i.e., lower UFs were applied). Size of the shape represents confidence in the study(ies) and health hazard (i.e., hazards with **evidence demonstrates** judgments are larger than those with **evidence indicates [likely]** judgments), POD estimate(s) (for the purposes of this graphic, confidence in the POD was given slightly greater weight than the others), and completeness of the available evidence database for each health outcome: larger shapes indicate higher confidence; solid shapes indicate studies in humans; hollow shapes indicate animal studies. For composite UF, if multiple studies served as the basis for an osRfC, the composite UF associated with the candidate value selected to

represent the osRfC was used (see Table 2-11). The dashed line represents the proposed overall RfC of 0.007 mg/m^3; the circled osRfCs indicate the cluster of effects selected as the basis for this value.

Choice of the Proposed Overall RfC

An overall RfC for formaldehyde of 0.007 mg/m^3 was selected. This value is within the narrow range (0.006–0.009 mg/m^3) of the group of respiratory system-related RfCs, which together are interpreted with **high confidence** (sensory irritation, pulmonary function, allergy-related conditions, and current asthma prevalence or degree of control) (see Figure 2-2). These osRfCs are based on PODs that are the lowest of those identified in population studies for formaldehyde hazards, and with the lowest composite uncertainty. The RfC for developmental toxicity, although only slightly higher than the range observed for the selected respiratory effects, is associated with less confidence in the POD. Likewise, the osRfCs for respiratory pathology and male reproductive effects were associated with a larger degree of uncertainty, as reflected by their position along the y-axis.

The RfC is an estimate of exposure that is likely to be without an appreciable risk of adverse health effects over a lifetime. As illustrated in Figure 2-3, the selected RfC is at the upper end of the range of outdoor formaldehyde levels recorded in some locations, and it would be expected that levels in indoor air would exceed this concentration in most situations. However, it is important to reiterate that this level is interpreted to be without appreciable risk. It is also important to note that the RfC does not provide information about the magnitude of the risk of respiratory-related effects that might occur at different concentrations above the RfC (e.g., at 0.02 or 0.03 mg/m^3). As illustrated in Figure 2-3, nearly all the study-specific findings of effects (e.g., LOAELs, BMCs) were not observed until formaldehyde levels were in the upper end of the range of average indoor air concentrations, with effects generally being observed at or above ~35–40 µg/m^3. One study that contributed to the RfC derivation involved an analysis of the degree of asthma control in children with current asthma, and the RfC is expected to apply to this susceptible subgroup in the population. Although current asthma symptoms and allergic conditions were not observed in studies of children with exposures less than the range of 0.02–0.05 mg/m^3, at 0.021 mg/m^3, a 10.5% decrease in PEFR among asthmatic children could be estimated (the regression model included a term for asthma status), based on a model using results of Krzyzanowski et al. (1990) (see Table 2-12). Thus, attributes that increase susceptibility in individuals are expected to play a role in increasing the advent of adverse responses to formaldehyde levels above the RfC (e.g., somewhere between 0.007 and 0.04 mg/m^3).

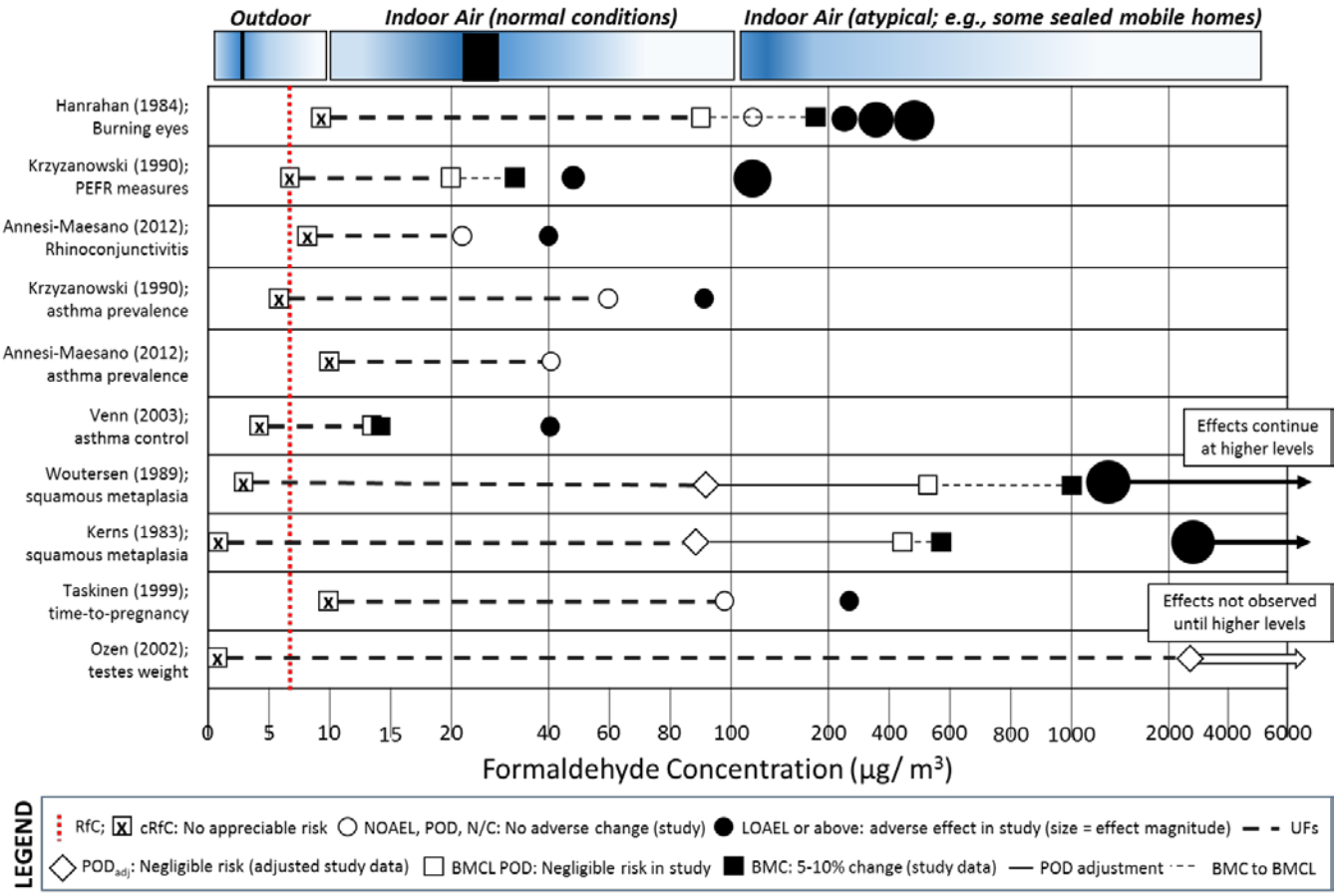


Figure 2-3. Illustration of noncancer toxicity value estimations.

This figure provides a representation of the estimates from studies supporting the osRfCs, including a summary of formaldehyde exposure data. Formaldehyde exposure estimates reflect approximates of the range (boxes), medians or means (black vertical bars), and more commonly reported estimates (gradations), based on the data discussed in Appendix A.1.2**.** Horizontal lines in the figure reflect the extrapolation process for arriving at points of departure (PODs) and toxicity values (unfilled symbols) in the context of the study-specific evidence for effects (filled symbols; effect magnitude estimated based on study figures, tables, or reported regressions; see previous sections). Note: The *x*-axis is intentionally not on a linear or log scale so as not to convey a false level of precision. Abbreviations: cRfC = candidate RfC; N/LOAEL = no-/lowest-observed-adverse-effect level; UFs = uncertainty factors; BMCL = benchmark concentration, lower confidence bound.

Although the RfC is designed to apply to exposures over a lifetime, the relevant window of exposure for some of the effects observed in the contributing studies may be less than lifetime. Sensory irritation is an immediate response to reactive compounds such as formaldehyde. The relevant window of exposure for effects on asthma outcomes also is less than lifetime, although the time frame for the control of asthma symptoms (i.e., a few weeks) is expected to be different than that for the prevalence of current asthma symptoms or a decrease in pulmonary function (i.e., the last 12 months). In addition, the relevant window of exposure for the osRfC for female reproductive or developmental outcomes is from conception to the end of the pregnancy.

The exposure paradigm used by controlled human exposure studies evaluates an immediate response (i.e., on the order of minutes to hours) to acute formaldehyde exposure and it may be appropriate to use the results from these studies to derive an acute RfC. The evidence base for formaldehyde included results from controlled human exposure studies of formaldehyde inhalation and sensory irritation endpoints, pulmonary function response among healthy or asthmatic individuals and hyperbronchoreactivity among allergic asthmatics in response to an allergen challenge. Two cRfCs for sensory irritation were derived from short-term controlled human exposure studies (Kulle et al., 1987; Andersen and Molhave, 1983), Generally, pulmonary function measures were not changed by acute exposure in several controlled human exposure studies of healthy or asthmatic volunteers, although small decrements were observed after longer exercise components (15 minutes). Two additional studies did not observe pulmonary function changes in response to acute formaldehyde inhalation, but did observe an early phase increase in airway reactivity in response to an allergen challenge indicating a potential exacerbation effect by formaldehyde inhalation on asthma symptoms (Ezratty et al., 2007; Casset et al., 2006). Casset et al. (2006) observed a statistically significant response at lower dust mite amounts with formaldehyde levels of 0.092 mg/m^3 and mouth breathing only, while Ezratty et al. (2007) observed an increase in a reactivity index in response to a grass allergen challenge ($p = 0.06$) using a higher formaldehyde concentration (0.5 mg/m^3).

Table 2-12. Proposed overall RfC for formaldehyde inhalation

Health effect(s) basis	RfC (mg/m^3)	Overall confidence
Sensory irritation, pulmonary function, allergy-related conditions, and degree of asthma control/prevalence of current asthma in human studies[a]	0.007	**High**

[a]Based on the following studies: Annesi-Maesano et al. (2012); Matsunaga et al. (2008); Venn et al. (2003); Krzyzanowski et al. (1990); Hanrahan et al. (1984).

Uncertainties in the Derivation of the Proposed Overall Reference Concentration

Research in experimental animals with regard to two health effects, respiratory tract pathology and male reproductive toxicity, indicates that the proposed overall RfC may not be protective against these hazards. Based on these effects, an alternative RfC of 0.001–0.003 mg/m^3 would be derived. However, the confidence in this alternative RfC would be low because uncertainties regarding these osRfCs are greater and the extrapolation from concentrations at which effects were observed in these experimental animal studies was much larger.

The potential for formaldehyde to adversely affect the nervous system, female and male reproduction, as well as development are not well studied, and the systemic effects of inhaled formaldehyde are not well understood. The potential for a localized, immunosuppressive effect in the respiratory tract, with implications for infectious diseases spread through inhalation, is another

understudied issue. Additional research in these areas would increase understanding of the spectrum of effects seen with formaldehyde exposure, formaldehyde concentrations that pose a hazard for specific types of effects, and MOAs for these effects.

Confidence Statement Regarding the Proposed Overall Reference Concentration

An overall confidence level of **high**, **medium**, or **low** is assigned to reflect the level of confidence in the study(ies) and hazard(s) used to derive the RfC, the overall database, and the RfC itself, as described in Section 4.3.9.2 of EPA's *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994). Overall confidence in the RfC is **high**; the RfC is based on a spectrum of adverse effects reported in multiple well-conducted studies involving different populations of exposed humans. Most of the study populations were exposed to formaldehyde levels in a residential or school setting, and some of the studies focused on sensitive individuals. An extensive literature database supports the hazard conclusions.

2.1.5. Previous IRIS Assessment: Reference Value

An inhalation RfC for formaldehyde has not previously been derived. In 1990, an oral reference dose (RfD) of 0.2 mg/kg-day was developed. This value was based on reduced weight gain and histopathology (primarily of the gastrointestinal system) in Wistar rats during a 2-year bioassay in which formaldehyde was administered in the drinking water (Til et al., 1989). A UF_C of 100 was applied to the NOAEL to account for inter- and intraspecies differences. This RfD was interpreted with **medium confidence**, based on *high* confidence in the principal study and *medium* confidence in the database.

2.2. INHALATION UNIT RISK ESTIMATE FOR CANCER

Unit risk estimates for cancer were derived from different data sets available from both epidemiological and experimental animal studies. Unit risk estimates could be derived for two of three cancer types for which the evidence supporting a human health hazard was sufficiently strong (**evidence demonstrates**): nasal cancers (i.e., nasopharyngeal cancer in human studies; nasal SCC in experimental animal studies) and myeloid leukemia. While the evidence supporting a human health hazard from sinonasal cancer from studies in occupational cohorts and experimental animals also was sufficiently strong to support the derivation of unit risk estimates, no adequate exposure-response data sets were available to derive unit risk estimates.

Section 2.2.1 focuses on the derivation of unit risk estimates for nasal cancers with an examination of sources of uncertainty, and Section 2.2.2 discusses the derivation of unit risk estimates for myeloid leukemia and examines sources of uncertainty. Section 2.2.3 presents a summary of the unit risk estimates obtained from the different data sets and selection of the preferred estimate. Section 2.2.4 describes adjustments to the preferred estimate for assumed early-life susceptibility for cancers with a mutagenic MOA. In addition, an approach to bound low-

dose cancer risks from formaldehyde exposure using DNA adduct concentrations in nasal epithelium and bone marrow from animal experiments and U.S. cancer incidence statistics (a "bottom-up" approach) is summarized to provide some perspective on the uncertainty in extrapolating from high-dose animal toxicology or human occupational data (Section 2.2.5). Finally, Section 2.2.6 provides a summary of the final adjusted unit risk estimate and uncertainties.

EPA concluded that the evidence for increased risks of NPC and myeloid leukemia was sufficiently strong to support the derivation of unit risk estimates. A judgment that the **evidence demonstrates that** formaldehyde inhalation causes NPC cancer was based on *robust* human evidence of increased risk in groups exposed to occupational formaldehyde levels, and *robust* animal evidence of nasal cancers in rats and mice that exhibits steeply increasing incidence at high formaldehyde levels. Strong mechanistic support is provided across species (primarily rats, but also mice, monkeys, and humans), including genotoxicity (sometimes at low formaldehyde levels in rats), epithelial damage or remodeling, and cellular proliferation that are consistent with neoplastic development in a regional, temporal, and dose-related fashion. A judgment that the **evidence demonstrates that** formaldehyde inhalation also causes myeloid leukemia was based on *robust* human evidence of increased risk in groups exposed to occupational formaldehyde levels. Supporting mechanistic evidence consistent with leukemia development is provided across numerous studies of peripheral blood isolated from exposed workers, including evidence of mutagenicity and other genotoxic damage in lymphocytes and myeloid progenitors, and perturbations to immune cell populations. The animal evidence is *inadequate* and, although notable uncertainties remain (see Section 1.3.3), the findings to date suggest either a lack of concordance across species or a lack of long-term studies in animal models that characterize the disease process in humans for leukemia. Leukemia was not increased in two well-conducted chronic bioassays of rats or mice, and the available animal data provide weak mechanistic support for LHP cancers. No MOA has been established to explain how formaldehyde inhalation can cause myeloid leukemia without systemic distribution (inhaled formaldehyde does not appear to be distributed to an appreciable extent beyond the URT to distal tissues).

EPA's standard approach for deriving an inhalation unit risk (IUR) estimate using results from epidemiology studies involves using a regression coefficient that describes the relationship between increases in cancer risk and increases in cumulative exposure, and estimating a (upper-bound) lifetime extra risk-per-unit exposure concentration through a life-table analysis. Cumulative exposure, which incorporates both average concentration and the duration of time over which exposure occurred, is generally the preferred metric for quantitative estimates of lifetime risk from environmental exposure to carcinogens, and thus cumulative exposure was chosen as the exposure metric for calculations in this assessment. The "true" exposure metric best describing the biologically relevant delivered dose of formaldehyde is unknown. Few epidemiological studies presented dose-response analyses based on cumulative measures of formaldehyde concentration that could support the derivation of unit risk estimates. A unit risk estimate was derived based on

dose-response modeling of mortality and cumulative formaldehyde exposure for nasopharyngeal cancer (NPC) in a human occupational cohort. Upper respiratory tract (URT) cancer risk was also extrapolated from the incidence of nasal squamous cell carcinoma (SCC) in experimental studies on F344 rats. Results from several approaches used to model these data are evaluated and compared, including biologically based dose-response (BBDR) modeling, statistical time-to-tumor modeling, and statistical benchmark dose modeling using data on DNA-protein crosslinks (DPXs) and formaldehyde flux as dose measures. Additional analyses and comparisons were conducted based on mechanistic hypotheses, including derivation of RfCs based solely on estimates of cell proliferation (i.e., one contributing MOA to formaldehyde exposure-induced nasal cancers; see MOA discussion in Section 1.2.5), and assessing impacts of endogenous formaldehyde concentration on dosimetric estimates.

Results from the follow-up of mortality from LHP cancer in the same occupational cohort were used to derive a unit risk estimate for myeloid leukemia. In this study (see Section 2.2.2), however, there is no apparent association between myeloid leukemia mortality and cumulative exposure. A clearer association is observed with peak exposure, though it is not statistically significant in the latest follow-up (in an earlier 1994 follow-up of that study, myeloid leukemia mortality was statistically significantly associated with peak exposure; see Section 1.3.3). Although multiple approaches for deriving a unit risk estimate for myeloid leukemia were explored, EPA did not develop an approach based on the peak exposure metric because EPA deemed the uncertainty associated with the peak exposure metric and the difficulties in translating risk from peak exposure to risk from chronic low-level exposure to be prohibitive.

Instead, EPA explored alternative approaches for deriving a unit risk estimate for myeloid leukemia based on cumulative exposure. Although an association between myeloid leukemia and cumulative formaldehyde exposure was not apparent in the key exposure-response study, there are indications that this may, at least in part, reflect a misclassification of myeloid leukemia deaths on death certificates. Percy et al. (1990; 1981) have reported that myeloid leukemia is often recorded as "leukemia" (not otherwise specified) on death certificates and hence underreported]. The approach described in the Toxicological Review is to estimate a unit risk for myeloid leukemia using the regression coefficient for myeloid and other/unspecified leukemias combined; this cancer grouping had a stronger association with cumulative exposure in the key exposure-response study than did myeloid leukemia alone and it captures the unclassified myeloid leukemias with the least inclusion of nonmyeloid leukemias. A comparison of the use of the different cancer groupings shows that they yield similar unit risk estimates (see Table 2-34).

An IUR estimate for cancer was estimated based on the unit risk estimate for NPC using the results from the occupational study for cumulative exposure. While the estimates for NPC and myeloid leukemia could be combined to derive an inhalation unit risk (IUR) for formaldehyde, there is considerable scientific uncertainty in the data used to estimate a unit risk for myeloid leukemia. Therefore, the unit risk estimate for myeloid leukemia is not included in the IUR calculation in this

draft assessment. A charge question will be provided for peer review asking for advice regarding the development of a unit risk estimate for myeloid leukemia and how, if at all, the unit risk estimate might inform the quantification of risk for cancer. Section 2.2.6 provides a summary and conclusions from the cancer exposure-response modeling, presenting the preferred unit risk estimate based on the extra risk of NPC associated with lifetime exposure to formaldehyde, calculated from the epidemiology studies. Because the MOA for formaldehyde's effect on nasal cancer risk was concluded to involve mutagenicity, the unit risk estimate was adjusted for assumed increased early-life susceptibility.

2.2.1. Unit Risk Estimates for Nasal Cancer

Derivation of Cancer Unit Risk Estimates Based on Human Data

Choice of epidemiology study

While several studies of cancer in workers exposed to formaldehyde evaluated exposure-response relationships, only a few reported risk estimates in relation to changes in formaldehyde concentration rather than duration of exposure, TSFE, probability of exposure, or exposure intensity score, measures which are not generally adequate for the derivation of cancer unit risk estimates. Beane Freeman et al. (2013) presented results of the follow-up of the large National Cancer Institute (NCI) retrospective cohort mortality study [originally described by Blair et al. (1986)] of workers at 10 U.S. plants producing or using formaldehyde. Marsh et al. (2007b; 2002) focused on pharyngeal cancer and, in particular, NPC mortality in sequential follow-up analyses of the Marsh et al. (1996) cohort study, which examined one of the 10 plants studied by NCI.

The quantitative analyses presented in this Toxicological Review are based on the NPC (Beane Freeman et al., 2013) results from the latest follow-up of the NCI cohort of industrial workers exposed to formaldehyde. The NCI cohort study is the largest of the three independent industrial worker cohort studies [the other two being Meyers et al. (2013) and Coggon et al. (2014)] and, more importantly, it is the only one with sufficient individual exposure data for exposure-response modeling. In addition, the NCI study is the only one of the three studies that used internal comparisons rather than standardized mortality ratios (SMRs), thus minimizing the potential impact of the healthy worker effect by addressing unmeasured confounding, which can bias effect estimates.

The NCI cohort consists of 25,619 workers (88% male) employed in any of the 10 plants prior to 1966. The most recent follow-up, based on 998,239 person-years of observation (through 2004) reported a total of 13,951 deaths (Beane Freeman et al., 2013). Beane Freeman et al. (2013) analyzed 10 deaths from NPC as well as deaths from other solid tumors. Some demographic details about the cohort are summarized in Table 2-13.

Table 2-13. Demographic details about the NCI industrial workers cohort[a]

Factor	Quantity
Number of workers	25,619
Person-years of follow-up	998,239
Percentage male	87.8%
Percentage white	92.7%
Percentage hourly workers	78.5%
Median duration of follow-up	42 yrs
Median (range) length of employment	2.6 yrs (<1 day–47.7 yrs)
Number of deaths	13,951
Number of cancer deaths	3,703

[a]Follow-up through December 31, 2004 (Beane Freeman et al., 2013).

A detailed exposure assessment was conducted for each worker in the NCI cohort, based on exposure estimates for different jobs held and tasks performed (Stewart et al., 1986). Exposure estimates were made using several different metrics—peak exposure, average intensity, cumulative exposure, and duration of exposure. Respirator use and exposures to formaldehyde-containing particulates and other chemicals were also considered. Some exposure details about the cohort are summarized in Table 2-14.

Table 2-14. Exposure details about the NCI industrial workers cohort[a]

Factor	Quantity
Percentage workers never exposed	10.5%
Median (range) formaldehyde TWA8 for exposed workers	0.3 (0.01–4.3) ppm
Median (range) cumulative exposure for exposed workers	0.6 (0.0–107.4) ppm × yrs
Number of workers who experienced peak exposures ≥4 ppm	6,255

[a]Follow-up through December 31, 2004 (Beane Freeman et al., 2013).

For NPC, RR estimates were increased in the highest exposure category for each of the exposure metrics (Beane Freeman et al., 2013), although these increases were generally not statistically significant, given the small number of deaths involved. A statistically significant trend was observed only for the peak exposure metric and only among the exposed person-years [two of the 10 deaths from this rare cancer were in the unexposed workers (Beane Freeman et al., 2013)]. The (log-linear) trend for cumulative exposure (as a continuous variable) approached statistical significance (p = 0.06 among exposed person-years only and p = 0.07 among all person-years).

With respect to the other solid cancers of interest, while Beane Freeman et al. (2013) reported results for cancers of the nose and nasal sinus, there were just five deaths for that endpoint. Marsh et al. (2002) reported some exposure-response results from their case-control study of all pharyngeal cancers in one of the industrial plants studied by the NCI, but they did not observe positive trends for cumulative or average exposure.

Exposure assessment and choice of exposure metric from the National Cancer Institute cohort

A detailed exposure assessment was conducted for the NCI cohort of industrial workers exposed to formaldehyde, and quantitative exposure estimates were generated for each worker (Stewart et al., 1986). Formaldehyde exposure estimates, including TWA8 concentration and categories of peak concentrations, were derived for each job, work area, and calendar year combination. A peak was defined as a short-duration exposure (typically <15 minutes) above the TWA, which could be related to either routine or nonroutine tasks (Beane Freeman et al., 2009). The frequency of peak exposures was also estimated, but these estimates were based on assumptions made by the assessors rather than direct measures or observations, making this metric highly uncertain. Cumulative exposures (in ppm × years) were estimated by multiplying the time a worker spent in a specific job by the TWA exposure for that job and summing over all the jobs held by the worker. Duration was the total time spent in jobs with formaldehyde exposure, and average intensity was the ratio of cumulative exposure to duration. Formaldehyde exposures after 1980 were not taken into account in the follow-up study, but this was considered to have a generally minimal impact on the results (Beane Freeman et al., 2013).

Some of the strongest exposure-response relationships in the NCI cohort studies (Beane Freeman et al., 2013) (e.g., for NPC) were observed for the peak exposure metric. It is not clear how to extrapolate RR estimates based on peak exposure estimates to meaningful estimates of lifetime extra risk of cancer from continuous exposure to low environmental levels. In addition, peak exposure level is a more subjective measure than the other metrics, it is not based on formaldehyde concentration measurements, and it is a categorical rather than continuous measure. Individual workers were assigned to peak exposure level categories based on their work histories and a matrix of job-, work area-, and calendar time-specific TWA8 formaldehyde measurements. Historical sampling records and sampling conducted by the investigators contributed to the development of this matrix. If a short-term (<15 minute) excursion above the TWA8 concentration for a job was observed, or expected based on industrial hygiene expertise, then that job was assigned to a peak exposure category: none, >0 to <0.5 ppm (>0 to 0.62 mg/m^3), 0.5 to <2.0 ppm (0.62 to <2.46 mg/m^3), 2.0 to <4.0 ppm (2.46 to 4.92 mg/m^3), or ≥4.0 ppm (≥4.92 mg/m^3). Individual workers may have experienced these peak concentrations rarely, intermittently, or routinely, and in jobs they held for a long time or only briefly. At a given time point, a worker's peak exposure estimate is the highest peak exposure category ever attained by the worker. As such, this exposure metric is not interpretable in terms of a lifetime exposure risk.

Similarly, the average exposure metric is not a measure of long-term exposure for chronic effects because it does not account for duration of exposure (e.g., exposure to a given exposure level for 1 year conveys the same amount of risk as exposure to the same level for 70 years). Likewise, duration of exposure does not account for the level of exposure and is not a useful metric for the calculation of risk estimates as a function of exposure level, such as the cancer unit risk estimate.

Cumulative exposure, which incorporates both average concentration and the duration of time over which exposure occurred, is generally the preferred metric for quantitative risk assessment of lifetime risk from environmental exposure to carcinogens, and cumulative exposure was chosen as the exposure metric for the risk estimate calculations for the cancer endpoints in this assessment. The "true" exposure metric best describing the biologically relevant delivered dose of formaldehyde is unknown.

Dose-response modeling of the National Cancer Institute cohort

The results of the internal analyses (i.e., comparing exposed workers to an internal referent group of other workers in the cohort) of Beane Freeman et al. (2013) for NPC using the cumulative exposure metric, with comparisons to the results using the peak exposure and average intensity metrics, are presented in Table 2-15. The relative risks (RRs; in this case, rate ratios) were estimated using log-linear Poisson regression models stratified by calendar year, age (in 5-year intervals), sex, and race (black/white) and adjusted for pay category (salary/wage). As shown by Callas et al. (1998), when age is well characterized and adjusted for, as it was in the Beane Freeman et al. (2013) study, the Poisson regression and Cox proportional hazards models yield essentially the same results. Beane Freeman et al. (2013) used a 15-year lag interval in estimating exposures to account for a latency period for the development of solid cancers, including NPCs. Lag intervals of 2–20 years were evaluated, and changing the interval had little impact on the RR estimates; thus, the interval of 15 years that was used in the previous follow-up analyses (Hauptmann et al., 2004) was retained. For all cancer types, the NCI investigators used the low-exposure category as the reference category to "minimize the impact of any unmeasured confounding variables since nonexposed workers may differ from exposed workers with respect to socioeconomic characteristics" (Hauptmann et al., 2004). Table 2-15 also presents the *p*-value for the (log-linear) trend of risk changing with exposure level for all workers and for only those workers exposed to formaldehyde. The strongest exposure-response relationship for NPC is observed for the peak exposure metric among exposed workers.

The log-linear trend analyses for the cumulative exposure metric approach statistical significance (p-trend = 0.07 for all person-years; p-trend = 0.06 for exposed person-years only). The fact that the two-sided p-values are not strictly <0.05 is not critical here, given that the hazard for NPC was established a priori in Chapter 1. The nonexposed person-years were included in the primary cancer risk analyses to use all the available exposure-response data. Furthermore, the data were stratified by pay category, which provided at least partial adjustment for socioeconomic characteristics. Final results for the exposed person-years only are also presented for comparison.

The log-linear trend tests conducted by Beane Freeman et al. (2013) used exposure as a continuous variable (except for peak exposure, for which categorical ranks were used) (general model form: $RR = e^{\beta X}$, where β represents the regression coefficient and X is exposure). Dr. Beane Freeman provided EPA with the β estimates (and their standard errors) from the trend tests for NPC and the cumulative exposure metric for all person-years and for exposed person-years only (personal communication to EPA from Laura Beane Freeman, NCI, to Jennifer Jinot, EPA, February 22, 2013). These estimates are presented in Table 2-16.

Table-2-15. Relative risk estimates for mortality from nasopharyngeal malignancies (ICD-8 code 147) by level of formaldehyde exposure for different exposure metrics

Rate ratio (number of deaths)				*p*-Trend	
				All person-years[a]	Exposed person-years[b]
Peak exposure (ppm)					
0	**>0 to <2.0[c]**	**2.0 to <4.0**	**≥4.0**		
4.39 (2)	1.0 (1)	– (0)	7.66 (7)	0.10	0.005
Average intensity (ppm)					
0	**>0 to <0.5[c]**	**0.5 to <1.0**	**≥1.0**		
6.79 (2)	1.0 (1)	2.44 (1)	11.54 (6)	0.16	0.09
Cumulative exposure (ppm × years)					
0	**>0 to <1.5[c]**	**1.5 to <5.5**	**≥5.5**		
1.87 (2)	1.0 (4)	0.86 (1)	2.94 (3)	0.07	0.06

[a]Likelihood ratio test (1 degree of freedom) of zero slope for formaldehyde exposure (continuous variable, except for peak exposure metric) among all (nonexposed and exposed) person-years.
[b]Likelihood ratio test (1 degree of freedom) of zero slope for formaldehyde exposure (continuous variable, except for peak exposure metric) among exposed person-years only.
[c]Reference category for all categories with the same exposure metric.
Source: Beane Freeman et al. (2013).

Table-2-16. Regression coefficients from NCI log-linear trend test models for NPC mortality from cumulative exposure to formaldehyde[a]

Person-years	β (per ppm × year)	Standard error (per ppm × year)
All	0.04311	0.01865
Exposed only	0.0439	0.01852

[a]Models stratified by calendar year, age, sex, and race and adjusted for pay category; cumulative exposures calculated using a 15-year lag interval.
Source: Personal communication to EPA from Laura Beane Freeman to Jennifer Jinot (February 22, 2013).

Prediction of lifetime extra risk of nasopharyngeal cancer mortality

The regression coefficients presented in Table 2-16 were used to predict the extra risk of NPC mortality from environmental exposure to formaldehyde.

$$\text{Extra risk} = (R_x - R_o) \div (1 - R_o), \quad (2\text{-}1)$$

where R_x is the lifetime risk in the exposed population and R_o is the lifetime risk in an unexposed population (i.e., the background risk). Extra risk estimates were calculated using the β regression coefficients and a life-table program that accounts for competing causes of death.[42] U.S. age-specific 2010 all-cause mortality rates and 2000–2010[43] NPC (ICD-10 C11.0-C11.9) mortality rates for all race and sex groups combined[44] were used to specify the all-cause and cause-specific background mortality rates in the life-table program. Risks were computed up to age 85 because cause-specific mortality (and incidence) rates for ages above 85 years are less reliable. Conversions between occupational formaldehyde exposures and continuous environmental exposures were made to account for differences in the number of days exposed per year (240 versus 365) and in the amount of air inhaled per day (10 versus 20 m^3). An adjustment was also made for the 15-year lag period. The reported standard errors for the regression coefficients were used to compute the one-sided 95% upper confidence limits (UCLs) for the extra risks based on a normal approximation.

Point estimates and one-sided 95% UCLs for the extra risk of NPC mortality associated with varying levels of continuous exposure to formaldehyde are presented in Table 2-17. The model predicts extra risk estimates that are fairly linear for exposures below about 0.001 to 0.01 ppm but not for exposures above 0.01 ppm.

Table 2-17. Extra risk estimates for nasopharyngeal cancer mortality from various levels of continuous exposure to formaldehyde

Exposure concentration (ppm)	Extra risk	95% UCL on extra risk
0.0001	1.24×10^{-7}	2.12×10^{-7}
0.001	1.24×10^{-6}	2.13×10^{-6}
0.01	1.28×10^{-5}	2.25×10^{-5}
0.1	1.79×10^{-4}	4.12×10^{-4}
1	2.67×10^{-1}	8.74×10^{-1}
10	9.83×10^{-1}	9.87×10^{-1}

[42]This program is an adaptation of the approach that was previously used in BEIR IV, "Health Risks of Radon and Other Internally Deposited Alpha Emitters." National Academy Press, Washington, DC, 1988, pp. 131–134. A spreadsheet illustrating the life table used for the extra risk calculation for the derivation of the LEC_{0005} for NPC incidence is presented in Appendix B.2.1.

[43]Typically, 5-year ranges are used as the basis for population cause-specific disease and mortality rates; a larger range is used here to get better stability in the rates because NPC is a rare cancer.

[44]Centers for Disease Control and Prevention, National Center for Health Statistics. Underlying Cause of Death on CDC WONDER Online Database. Accessed at http://wonder.cdc.gov/ucd-icd10.html on September 19, 2013.

Consistent with EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), the same data and methodology were also used to estimate the exposure level (effective concentration [ECx]) and the associated (one-sided) 95% lower confidence limit (LECx) corresponding to an extra risk of 0.05% (x = 0.0005). Although EPA guidelines emphasize the use of exposure levels associated with a 10% extra risk level for the POD for low-dose extrapolation, that would not be appropriate in this instance. A 10% extra risk level is very high for responses generally observed in epidemiology studies; thus, a 1% extra risk level is typically used for epidemiological data to avoid upward extrapolation. However, NPC has a very low background mortality rate (e.g., lifetime background risk is about 0.00019); therefore, even a 1% extra risk (i.e., 0.01) would be a large increase relative to the background risk. This is consistent with the fact that, even with a large cohort followed for a long time, only 10 NPC deaths were observed in the NCI follow-up through 2004.[45] The 1% level of risk is associated with RR estimates that are substantially higher than those observed in the epidemiology study. Based on the life-table program, the RR estimate for an extra risk of 1% for NPC mortality is 53, an upward extrapolation. Even 0.1% yields an RR estimate on the high end of the observable range of the epidemiology study (RR = 6.2). A 0.05% extra risk level yields an RR estimate of 3.6, which better corresponds to the RRs in the range of the data. Thus, 0.05% extra risk was selected for determination of the POD, and, consistent with EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), the LEC value corresponding to that risk level was used as the POD.

Because formaldehyde is a mutagenic carcinogen and the weight of evidence supports the conclusion that formaldehyde carcinogenicity for URT cancers can be attributed, at least in part, to a mutagenic MOA (see Section 1.2.5), a linear low-dose extrapolation was performed in accordance with EPA's carcinogen risk assessment guidelines (U.S. EPA, 2005a). The EC_{0005}, LEC_{0005}, and IUR estimates for NPC mortality are presented in Table 2-18.

Table 2-18. EC_{0005}, LEC_{0005}, and inhalation unit risk estimates for nasopharyngeal cancer mortality from formaldehyde exposure based on the Beane Freeman et al. (2013) log-linear trend analyses for cumulative exposure

Person-years	EC_{0005} (ppm)	LEC_{0005} (ppm)	Unit risk[a] (per ppm)	Unit risk (per mg/m^3)
All	0.191	0.112	4.5×10^{-3}	3.7×10^{-3}
Exposed only	0.187	0.111	4.5×10^{-3}	3.7×10^{-3}

[a]Unit risk = $0.0005/LEC_{0005}$.

[45]Eleven NPCs were reported on death certificates and included in NCI's SMR analyses, but one of these cases was apparently misclassified on the death certificate, so only 10 cases were used to estimate the RRs in the internal comparison analyses (Beane Freeman et al., 2013).

Prediction of lifetime extra risk of nasopharyngeal cancer incidence

EPA cancer risk estimates are typically derived to represent a plausible upper bound on increased risk of cancer incidence, as from experimental animal incidence data. Cancer data from epidemiology studies are more often mortality data, as is the case in the NCI study. For cancers with low survival rates, mortality-based estimates are reasonable approximations of cancer incidence risk. However, for NPC, the survival rate is substantial (51% at 5 years in the 1990s in the United States, according to Lee and Ko (2005) and incidence-based risks are preferred because EPA is concerned with cancer occurrence, not just cancer mortality.

Therefore, an additional calculation was done using the same regression coefficients provided by Dr. Beane Freeman (see Table 2-16) but with age-specific NPC incidence rates from NCI's Surveillance, Epidemiology, and End Results (SEER) Program in place of the NPC mortality rates in the life-table program. SEER collects cancer incidence data from a variety of geographical areas in the United States. The incidence data used here are from SEER-18, a registry covering about 27.8% of the U.S. population, which was the most current SEER registry at the time this analysis was done. SEER-18 age-specific background incidence rates for NPC (ICD-10 C11.0-C11.9) for 2000–2010 were obtained from the SEER public-use database (www.seer.cancer.gov) using NCI's SEER*Stat software (www.seer.cancer.gov/seerstat). The incidence-based calculation relies on the reasonable assumptions that NPC incidence and mortality have the same exposure-response relationship for formaldehyde exposure and that the incidence data are for first occurrences of NPC or that relapses provide a negligible contribution. The calculation, as presented in the life-table spreadsheet in Appendix B.2.1, also takes advantage of the fact that NPC incidence rates are negligible compared with the all-cause mortality rates and thus no special adjustment to the population at risk to account for live individuals who have been diagnosed with NPC is necessary.

The resulting EC_{0005}, LEC_{0005}, and IUR estimates for NPC incidence are presented in Table 2-19. The unit risk estimate for cancer incidence is two-fold higher than the corresponding mortality-based estimate, for all person-years, reflecting the high survival rates for NPC.

Table 2-19. EC_{0005}, LEC_{0005}, and inhalation unit risk estimates for nasopharyngeal cancer incidence from formaldehyde exposure based on the Beane Freeman et al. (2013) log-linear trend analyses for cumulative exposure

Person-years	EC_{0005} (ppm)	LEC_{0005} (ppm)	Unit risk[a] (per ppm)	Unit risk (per mg/m^3)
All	0.0942	0.0550	9.1×10^{-3}	7.4×10^{-3}
Exposed only	0.0925	0.0546	9.2×10^{-3}	7.5×10^{-3}

[a]Unit risk = $0.0005/LEC_{0005}$.

The preferred estimate for the inhalation cancer unit risk for NPC is the estimate of **9.1×10^{-3} per ppm (7.4×10^{-3} per mg/m^3)** derived using incidence rates for the cause-specific

background rates, for all person-years. The results from the exposed person-years are essentially identical.

Because NPC is a rare cancer in the United States, with a relatively low number of cases occurring per year, a rough calculation was done to ensure that the unit risk estimate derived for NPC incidence is not implausible in comparison to actual case numbers. For example, assuming an average constant lifetime formaldehyde exposure level of 5 ppb for the U.S. population, the IUR estimate for NPC equates to a lifetime extra risk estimate of 4.6×10^{-5}. Assuming an average lifetime of 75 years (this is not EPA's default average lifetime of 70 years but rather a value more representative of actual demographic data) and a U.S. population of 300,000,000, this lifetime extra risk estimate suggests a crude upper-bound estimate of 180 incident cases of NPC attributable to formaldehyde exposure per year. Alternatively, assuming an average constant lifetime formaldehyde exposure level of 20 ppb, the calculation suggests a crude upper-bound estimate of 730 incident cases of NPC per year. Both upper-bound estimates, using different assumed lifetime exposure levels, are well below the estimated 2,300 total incident NPC cases per year calculated from the SEER NPC incidence rate of 0.75/100,000.[46,47]

Derivation of Cancer Unit Risk Estimates Based on Squamous Cell Carcinoma in the Respiratory Tract Using Animal Data

In this section, dose-response analyses of cancer risk based on nasal tumor data from laboratory bioassays using F344 rats are presented. The Agency takes the position that human data, if adequate data are available, provide a more appropriate basis for estimating human cancer risk than do rodent data (U.S. EPA, 2005a), primarily because uncertainties in extrapolating quantitative risks from rodents to humans are avoided; therefore, the epidemiology-derived estimates presented in the previous section are the preferred unit risk estimates for nasal cancers.

Nonetheless, it is useful to compare human health risk estimates from available epidemiology data with estimates extrapolated from animal studies. Furthermore, a large body of mechanistic data on cell replication, DPX and DNA monoadduct formation, and dosimetry modeling of formaldehyde flux to local tissue exist for formaldehyde that can potentially inform the shape of the dose-response curve. This information, as well as data on the incidence of hyperplasia, facilitates the interpretation and extrapolation of nasal squamous cell carcinoma (SCC) incidence

[46]The crude NPC (ICD-10 C11.0-C11.9) incidence rate from 2000-2010 SEER-18 data was obtained from the SEER public-use database (www.seer.cancer.gov) using NCI's SEER*Stat software (www.seer.cancer.gov/seerstat). This value is similar to a published NPC incidence rate for the United States of 0.7/100,000 person-years (Lee and Ko, 2005). The age-adjusted NPC incidence rate from SEER was also 0.75/100,000.

[47]With the application of age-dependent adjustment factors (see Section 2.2.4), the lifetime unit risk estimate for NPC would increase by a factor of 1.42, and the crude upper-bound estimates of the incident cases per year attributable to formaldehyde exposure would similarly increase by a factor of 1.42. The resulting adjusted upper-bound estimates of 260 and 1,030 for 5- and 20-ppb exposure levels, respectively, are still well below the estimated total number of 2,300 incident cases per year in the United States.

results from F344 rat bioassays within the context of formaldehyde's reactivity and MOAs. The estimates derived from animal data incorporate this information into the modeling.

This section describes the data and modeling approaches available; presents PODs from the considered models at benchmark response rates in the range of the available data; presents results from a biologically based model for extrapolation to human exposure scenarios; evaluates uncertainties in the dose-response models and discusses the use of any of the models for extrapolating below the POD, including implications for low-dose risk; and presents candidate IURs and RfCs derivable from the modeled PODs.

Multiple approaches, including conventional multistage Weibull time-to-tumor modeling and a biologically based clonal expansion model of cancer, are used to model the incidence of nasal SCC in F344 rats. Use of the biologically based modeling allowed the use of various data, including mechanistic information, in an integrated manner. For a given benchmark response level, PODs and their corresponding HECs are remarkably similar across multiple models and dose metrics (formaldehyde inhaled exposure concentrations, formaldehyde inhaled flux to tissue, DNA-protein crosslink [DPX] concentrations).

A clonal expansion model (Conolly et al., 2004), as well as possible variations of this model, developed for extrapolation of the rat nasal cancer risk to human exposure scenarios are carefully evaluated. Predictions using these models for humans are found to be not robust at any exposure concentration. Furthermore, a key model inference in Conolly et al. (2003), (Conolly et al., 2004) that formaldehyde-induced mutagenicity, modeled as proportional to DPX concentration, is not relevant to its carcinogenicity is found to be extremely uncertain. Accordingly, the clonal expansion modeling of the rat data is employed to derive multiple PODs and corresponding HECs but it is not used for extrapolating to human exposure scenarios. Unit risks derived by straight line extrapolation from a POD as well as candidate RfCs (cRfCs) derived from benchmark modeling of data on cell proliferation and basal hyperplasia observed in F344 rats and Wistar rats, respectively, are also presented, with the cRfC interpreted as the concentration below which nasal cancers arising from increased cell proliferation due to formaldehyde-induced cytotoxicity are unlikely to occur. The assessment presents arguments from the literature that protection against these putative precursor events is sufficient to prevent a cancer response. However, the proven genotoxicity and mutagenicity of the chemical and the observation of human cytogenetic effects in human occupational exposures provide strong support for preferring the linear extrapolation from the POD to the origin. An additional contribution to uncertainty in the low dose-response comes from the potential for endogenous formaldehyde levels in respiratory tissue to reduce the uptake of the inhaled gas at low doses, as demonstrated in modeling efforts by Schroeter et al. (2014) and Campbell Jr et al. (2020) (discussed further in the context of toxicokinetics in Section 1.1.3). Candidate unit risks based on a point of departure at the 0.005 extra risk are found to be comparable to that derived from analysis of the NCI occupational epidemiology data on nasopharyngeal cancers (NPCs).

Animal nasal tumor incidence

An increased incidence of nasal SCC was seen in two long-term bioassays using F344 rats (Bermudez, 2004; Monticello et al., 1996; Kerns et al., 1983). As shown in Table 2-20 and in Chapter 1 (SCC incidence in rats exposed to formaldehyde in long-term studies), the incidences are similar between the two studies even though they were conducted 13 years apart, and the incidence is similar between males and females in Kerns et al. (1983) (there were only male rats in Monticello et al. (1996)). Therefore, it appears appropriate to combine these studies for greater power in dose-response analysis. No other long-term studies have been conducted on F344 rats (see Table 2-20). These two studies, when combined (see Table 2-20), provide a well-defined spread of concentrations with at least 90 animals per group from each study, whereas other chronic rat studies were either single concentration or had a relatively small number of animals per group. Thus, although other studies in laboratory animals exist, the two studies (Monticello et al., 1996; Kerns et al., 1983) combined provide the most robust data for analyses. The table shows only the grouped incidence; however, the individual animal incidence data were available and used in the assessment.

Table -2-20. F344 rat nasal cancer data

Formaldehyde exposure levels	Incidence of SCC tumors	References
0, 0.7, 2.0, 6.01, 9.93, and 14.96 ppm (0, 0.86, 2.5, 7.4, 12.2, and 18.4 mg/m^3)	0/341, 0/107, 0/353, 3/343, 22/103, 162/386 (time-to-tumor characteristics shown in Fig. 1)	Bermudez (2004); Monticello et al. (1996); Kerns et al. (1983) (combined bioassays)

Mechanistic information

In addition, two types of mechanistic data are used in the dose-response modeling. These include site-specific measurements of DNA-protein crosslinks (DPX) formed by formaldehyde in the F344 rat and rhesus monkey, and site-specific measurements of changes in cell labeling induced by inhalation exposure to formaldehyde in the F344 rat.

Formaldehyde is a direct-acting mutagen, and DPXs serve as a surrogate marker for the tissue dose associated with this mutagenic potential. The modeling uses physiologically based pharmacokinetic (PBPK) models that have been developed based on the DPX data in Table 2-21 to calculate DPX levels as a function of local formaldehyde flux, and to predict DPX levels in the human. As discussed in Chapter 1 and Appendix C.3, exposure to inhaled formaldehyde induces dose-related changes in rates of cell division as inferred from cell labeling studies in the formaldehyde-exposed F344 rat. In turn, regenerative increases in cell proliferation increase the probability of errors in DNA replication.

Computational fluid dynamic modeling

The ability to use mechanistic data in dose-response modeling is further facilitated by the availability of computational fluid dynamic (CFD) modeling of airflow in the rat, monkey, and human respiratory passages. The CFD modeling is useful on multiple accounts.

Formaldehyde-induced squamous cell carcinomas (SCCs) and other lesions that occur in the rat and monkey nasal passages and in the monkey LRT are seen to be distributed in localized patterns that differ across species. The anatomy of the respiratory tract, in particular the nasal passages, and the pattern of airflow, show large regional differences across species (see Appendix A). On this basis, several authors have argued that regional dose would be the main determinant of interspecies differences in tumor incidence for a highly reactive and water soluble chemical such as formaldehyde (Bogdanffy et al., 1999; Monticello et al., 1996; Monticello and Morgan, 1994; Morgan et al., 1991), thus motivating the use of modeling local formaldehyde flux in the nasal region of each species.

Kimbell et al. (1993), Kepler et al. (1998), and Subramaniam et al. (1998) developed anatomically realistic finite-element representations of the noses of F344 rats, rhesus monkeys, and humans, and used them in physical and computational models (Kimbell et al., 2001a; Kimbell et al., 2001b). The nasal dosimetry modeling by Kimbell et al. (2001a; 2001b) was revised by Schroeter et al. (2014) to include air:tissue partitioning and air and tissue phase diffusivity; production of endogenous formaldehyde in the respiratory mucosa as a zero-order process; clearance of formaldehyde in the form of a saturable pathway for enzymatic metabolism, a first-order pathway for nonenzymatic reactions, and a pseudo first-order pathway to include its binding to DNA to form DPX.

This assessment uses dosimetry derived from (Kimbell et al., 2001a; Kimbell et al., 2001b) when extrapolating risk-related dose from the rat to the human (discussed in detail in Appendix B.2), and estimates the impact on the point of departure of using an alternate dosimetry model developed by Schroeter et al. (2014). Furthermore, DPX levels and cell labeling data are characterized as a function of regional formaldehyde flux to further inform the interpretation of cancer incidence results. These are tabulated in Table 2-21 and used in the different dose-response methods presented in this assessment (see Appendix B.2 for additional details).

Table-2-21. Dosimetric and mechanistic information supporting dose-response assessment based on rat nasal tumors

Data or information	Formaldehyde exposure	Notes	Study references
FA dosimetry in anatomically realistic representations of the F344 rat and human nasal passages and in an idealized representation of the human lower respiratory tract	Inhaled concentrations of 0, 0.7, 2, 6, 10, or 15 ppm (0, 0.9, 2.5, 7.4, 12.3, or 18.5 mg/m^3) at various steady-state inhalation rates	Fluid dynamic models of local FA flux to tissue	Subramaniam et al. (2008); Kimbell et al. (2001a); Kimbell et al. (2001b); Overton et al. (2001); Kimbell et al. (1997b); Kimbell et al. (1993). See Appendix B.2
DPX[a] in F344 rat (2 studies) and in rhesus monkey	Rat study 1 (1989): 0.3, 0.7, 2.0, 6.0, 10.0 ppm (0.4, 0.9, 2.5, 7.4, 12.3 mg/m^3) for 6 hours. Rat study 2 (1994): 0.7, 2.0, 6.0, 15.0 ppm (0.9, 2.5, 7.4, 18.5 mg/m^3) for 3 hours. DPX measured over whole nose in study 1, and over two regions ("low" and "high" tumor sites) in study 2. Monkey study: 0.7, 2.0, 6.0 ppm (0.9, 2.5, 7.4 mg/m^3) for 6 hours	DPX lesions observed at all exposure concentrations (0.3 ppm–15 ppm/0.37 mg/m^3–18.5 mg/m^3). DPX tracheal and lung lesions in monkeys at 6.0 ppm (7.4 mg/m^3). Data used in PBPK model for FA and DPX	Conolly et al. (2000); Casanova et al. (1994); Casanova et al. (1991); Casanova et al. (1989)
Cell labeling index[b]; F344 rats. Labeling study with two phases	0, 0.7, 2, 6, 10, or 15 ppm (0, 0.9, 2.5, 7.4, 12.3, or 18.5 mg/m^3). Phase 1 exposure duration: 1, 4, and 9 days and 6 weeks. Phase 2 exposure duration: 13, 26, 52, and 78 weeks	Phase 1 used injection labeling with a 2-hour pulse of tritiated thymidine; Phase 2 used osmotic mini pump tritiated thymidine labeling with a 120-hour release time	Phase 1: Monticello et al. (1991). Phase 2: Monticello et al. (1996); Data analyzed in Appendix B.

Abbreviations: FA = formaldehyde exposure; DPX = DNA-protein crosslink; PBPK = physiologically based pharmacokinetic.

[a]Note that these studies do not present DPX measurements on control animals.

[b]These data were used as input for modeling the nasal tumors observed in F344 rats and for benchmark modeling of cell proliferation as a precursor response by authors from the same laboratory as this study (Conolly et al., 2003; Schlosser et al., 2003). Many other studies (see below on "uncertainty in dose-response estimates" and Appendix B.2) inform the effect of formaldehyde on cell proliferation and are brought to bear upon the discussion of uncertainties in modeling the dose-response. However, Monticello et al. (1996) is the only study that followed long-term exposure to formaldehyde.

Dose-response modeling of nasal SCC incidence in the rat

EPA used multiple dose-response models of the observed tumor incidence in F344 rats (Monticello et al., 1996; Kerns et al., 1983). These are briefly described below. Dose metrics derived from PBPK modeling or CFD modeling are included in all these approaches.

Time-to-tumor modeling without using mechanistic data

Because higher exposures were associated with both earlier tumor occurrence and increased mortality in the rats, methods that can reflect the influence of competing risks and intercurrent mortality on site-specific tumor incidence rates are preferred. For this reason, EPA used the multistage Weibull time-to-tumor model (Portier and Bailer, 1989; Krewski et al., 1983), which (a) models the replicate animal data, (b) includes the exact time of observation of the tumors and therefore gives appropriate weight to the amount of time each animal was on study without a tumor, and (c) acknowledges earlier tumor incidence with increasing dose level.

The model has the following form: $P(d) = 1 - \exp[-(q_0 + q_1 d + q_2 d^2 + ... + q_k d^k) \times (t - t_0)^z]$, where $p(d)$ represents the lifetime risk (probability) of cancer at dose d (i.e., human equivalent exposure in this case); parameters $q_i \geq 0$, for i = 0, 1, ..., k; t is the time at which the tumor was observed; and z is a parameter estimated in fitting the model, which characterizes the change in response with age. The parameter t_0 represents the time between when a potentially fatal tumor becomes observable and when it causes death.

A further consideration is the distinction between tumor types as being either fatal or incidental to adjust for competing risks. Incidental tumors are those tumors thought not to have caused the death of an animal (such as those observed during interim or terminal sacrifices), while fatal tumors are thought to have resulted in animal death. For these data, nasal tumors observed with early deaths other than interim sacrifices were considered to be fatal.

The data used in this analysis were obtained from the appendix in Conolly et al. (2003) and combined the nasal squamous carcinoma data of Kerns et al. (1983) and Monticello et al. (1996) along with results from an additional 94 animals not previously examined in the Monticello et al. (1996) study. The dose-response analyses, estimation of parameters, plots of model fits for fatal and incidental tumors, and model selection criteria are detailed in Appendix B.2.2.

Modeling of the grouped incidence data

This assessment also presents results from statistical modeling of the same data by Schlosser et al. (2003) in Table 2-22. These authors did not carry out a time-to-tumor analysis of the individual animal data but applied a Kaplan-Meier survival adjustment of the grouped incidence data. The best fit in Schlosser et al. (2003) was obtained with the polynomial and Weibull models for the tumor incidence data with a nonzero intercept (threshold) on the dose axis. See Schlosser et al. (2003) for further details.

Biologically based dose-response modeling

A biologically based time-to-tumor dose-response (BBDR) model for modeling the formaldehyde-induced rat nasal tumors is available (Conolly et al., 2003; CIIT, 1999). This model consists of interfacing dosimetry models for formaldehyde and formaldehyde-induced DPX in the rat nasal passages (Kimbell et al., 2001a; Kimbell et al., 2001b; Conolly et al., 2000) with a two-stage clonal expansion (TSCE) model for predicting the probability of occurrence of nasal SCC (Conolly et al., 2003). The term "BBDR modeling" is used here to collectively refer to various toxicokinetic and toxicodynamic dose-response modeling components.

The cancer modeling in the BBDR approach is based on an approximation of the Moolgavkar, Venzon, and Knudson stochastic TSCE model of cancer (Moolgavkar et al., 1988; Moolgavkar and Knudson, 1981; Moolgavkar and Venzon, 1979), which accounts for growth of a pool of normal cells, mutation of normal cells to initiated cells, clonal expansion of initiated cells, and mutation of initiated cells to fully malignant cells. The molecular dose associated with formaldehyde's direct mutagenic action was represented in this approach by the DPX formed by formaldehyde. Formaldehyde-induced changes in cell replication and DPX concentrations, derived from the data indicated in Table 2-21, were considered a function of local formaldehyde flux (pmol/mm^2-hour) to each region of nasal tissue as predicted by CFD modeling on anatomically accurate representations of the nasal passages of a single F344 rat (see Appendix B.2). The TSCE model was calibrated with the observed tumor incidence data to estimate various unknown parameters as indicated below. DPX tissue concentrations in Conolly et al. (2003) were calculated using a physiologically based pharmacokinetic model developed in Conolly et al. (2000).

Conolly et al. (2003) characterized the dose-response for cell replication rates as a J-shaped curve, indicating that cell division rates decreased below that determined for the unexposed case at low-exposure concentrations. In addition, these authors also used a hockey stick-shaped curve such that the dose-response for cell division rates remained unchanged from the baseline, rising only at 6 ppm (7.4 mg/m^3) and higher exposure concentrations. This resulted in more conservative estimates of risk when used in the clonal expansion model for cancer.

In addition to the data from the two tumor bioassays, Conolly et al. (2003) included historical control data on 7,684 animals obtained from the National Toxicology Program (NTP) F344 rat inhalation and oral bioassays. The resulting model predicts the probability of a nasal SCC in the F344 rat as a function of age and exposure to formaldehyde. The fit to the tumor incidence data is shown in Figure 2-4 as indicated by the long, dashed line. (For later reference in Appendices B.2, this figure compares the fit to the data obtained by the modeling in Conolly et al. (2003) with that obtained by EPA's reimplementation of this model under identical conditions, inputs, and assumptions in Subramaniam et al. (2007), as indicated by the dash-dot line). The reader is referred to the original papers for further details regarding the methodology.

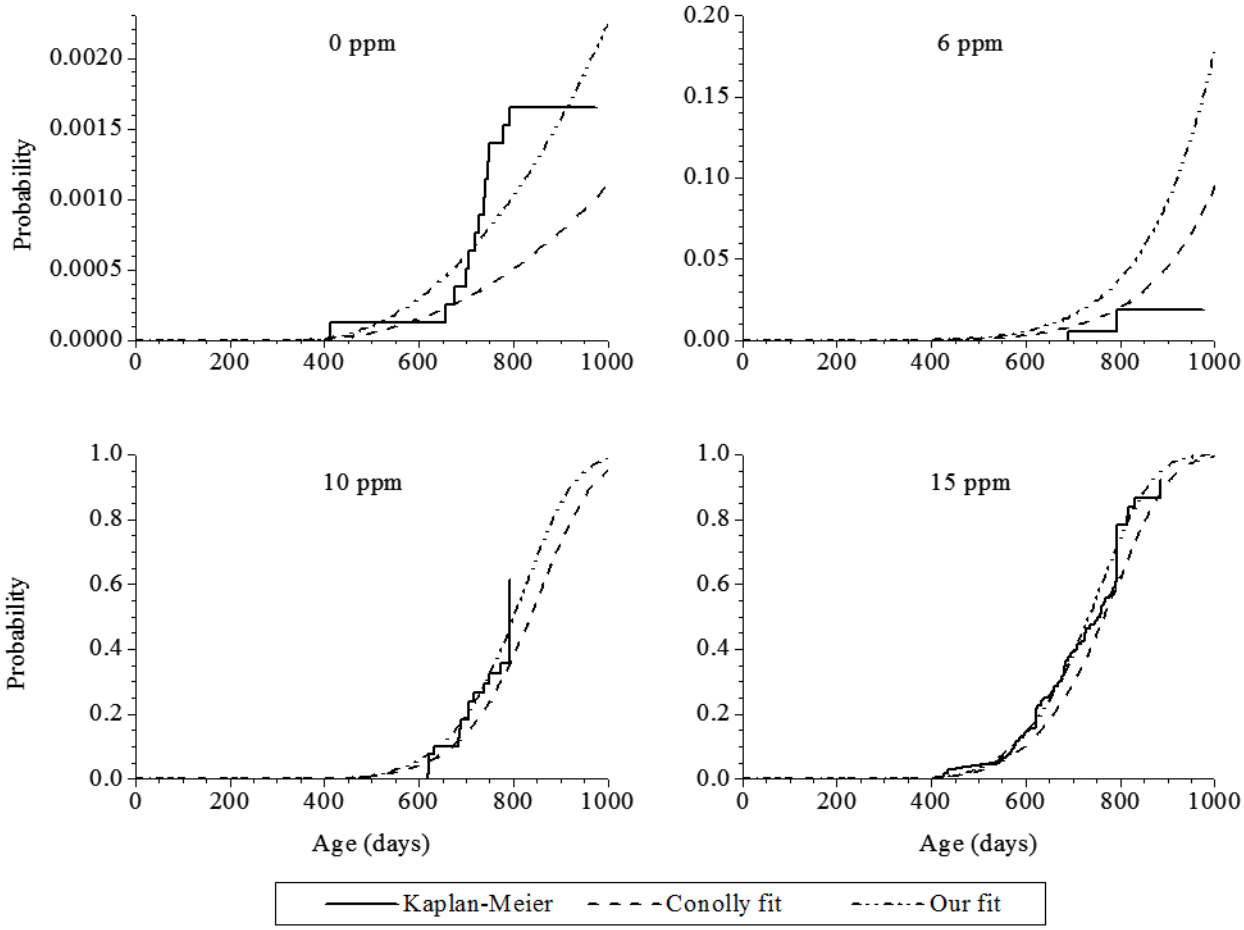


Figure 2-4. Fit to the rat tumor incidence data using the model and assumptions in Conolly et al. (2003).

Fitted curves obtained by Conolly et al. (2003) is compared with EPA reproduction of these results under identical conditions, inputs, and assumptions; there were minor residual differences among the implementations (see Subramaniam et al., 2007). The tumor incidence data are shown here by the Kaplan-Meier adjusted probabilities.

The BBDR modeling approach affords a convenient way to integrate multiple types of mechanistic information in modeling the time-to-tumor data, and visually it appears to fit these data well (as shown in Figure 2-4). Further clarification pertaining to the structure and calibration of the models in Conolly et al. (2004, 2003) that are key to understanding model assumptions is provided in Appendix B.2.

Benchmark modeling of cancer incidence and human equivalents within the range of the data

Benchmark concentrations (BMCs) and the corresponding 95% lower confidence bounds (BMCLs) were calculated at a benchmark response level (BMR) at the lowest end of the range of the observed data (U.S. EPA, 2012). BMCs and BMCLs at the BMRs of 0.005 and 0.01 extra risk were

determined with the BBDR models. These were compared with values determined at the BMRs of 0.05 or 0.1 extra risk level to facilitate comparison with other chemicals. A BMR of 0.005 is lower than the lowest observed tumor response (0.0085), when corrected for survival, from the combined data from the Kerns et al. (1983) and Monticello et al. (1996) bioassays. Using this lower value is considered appropriate because the BBDR modeling incorporates information on regenerative cell proliferation, derived from cell labeling data, which may be considered a precursor response. The BBDR models (model 1 & model 2 below) used for this purpose provided good fits to the time-to-tumor incidence data, similar to the fit shown in Figure 2-4, and are based on the Conolly et al. (2003) model with the following modifications.

Model 1 is based on the more conservative model in Conolly et al. (2003), where the parameters governing the kinetics of normal and initiated cells were derived as hockey stick-shaped functions of flux, with a critical modification. Conolly et al. (2003) added historical control animals from *all* NTP studies to the data from the concurrent controls, whereas model 1 includes NTP historical data from only the inhalation route of exposure. This is because the incidence rate of nasal SCC is very different between these two categories of NTP historical studies, and the generally accepted practice is to not include studies from other routes of exposure when using historical controls (see Subramaniam et al. (2008; 2007) for an explanation of this issue). Model 1 is the same as Model E in Table III of Subramaniam et al. (2007).

Model 2 makes major modifications to Conolly et al. (2003) in regards model structure as well as values for input parameters. First, the shape of the dose-response for the division rates of normal (N) cells as a function of formaldehyde flux, α_N(flux) [an input to the TSCE model], was monotone increasing without a threshold in dose, and obtained by fitting the 13-week cell replication data in Monticello et al. (1996). (See *modeling of cell replication data* in Appendix B.2.2 for a discussion pertaining to using the 13-week data.) The raw replicate animal data from this study was provided to EPA by the Hamner Institutes for Health Research. Second, the dose-response for the division rates of initiated (I) cells, α_I(flux), was assumed to be a sigmoidal-shaped curve, increasing monotonically with flux from a background value up to an asymptotic value, and constrained by $\alpha_I(\text{flux} = 0) \geq \alpha_N(\text{flux} = 0)$. The death rate of initiated cells was given by the assumption, $\beta_I(\text{flux}) = \kappa \cdot \alpha_I(\text{flux})$, where κ is an estimated constant. This model is discussed in detail as "model 15" in Appendix B.2.2. Furthermore, as in model 1, only the historical controls from inhalation studies were added to the concurrent controls.

Weekly averaged DPX concentrations as calculated by the PBPK model described in Subramaniam et al. (2007), a variant of the PBPK model in Conolly et al. (2000), were used. The model fits to the observed tumor incidence data, parameter values, and respective comparisons with Conolly et al. (2003) are provided in Appendix B.2.2. The results based on these models are included in Table 2-22, and details pertaining to the model structure are provided in Appendix B.2.2.

The BMCs mentioned above and their corresponding BMCLs were then converted to their equivalent concentrations in humans (HECs) based on formaldehyde flux to the nasal tissue obtained using CFD modeling in the rat and human (Kimbell et al., 2001b). The average mass flux of formaldehyde (pmol/mm^2-hour) to the entire surface of the airway lining, but excluding surface lined by nonmucus-coated squamous tissue which is thought not to absorb formaldehyde, was used for the extrapolation (see the Section, *Computational fluid dynamic modeling*, above, also in Section 2.2.1). The HEC corresponding to a particular benchmark level in the rat was then calculated by assuming that continuous lifetime exposure to a given steady-state flux of formaldehyde, expressed in pmol/mm^2-hour, leads to equivalent risk of nasal cancer across species. This extrapolation included a multiplication by (6/24) × (5/7) to adjust the laboratory exposure regimen for continuous exposure.

Schlosser et al. (2003) also calculated benchmark levels and corresponding HECs using DPX as the relevant dose metric expressed as pmol of formaldehyde equivalents covalently bound to DNA per unit volume of nasal tissue. These calculations used CFD and PBPK models to calculate formaldehyde flux and DPX concentrations in the rat and human. The assumption in using DPX data to calculate the HEC was that lifetime exposure to the same DPX concentration for a given duration each day leads to equivalent risk across species. These were exposures that resulted in the same steady-state DPX concentrations as the weekly time-weighted averaged DPX values in rats at the rat benchmark exposure concentrations.

The benchmark levels in the rat and the HECs obtained using the above methods and dose metrics are shown in Table 2-22.

Table 2-22. Benchmark concentrations and human equivalents using formaldehyde flux and DPX as dose metrics

Models	Rat benchmark conc (ppm)						Human equivalent conc[a] (ppm)					
		Extra risk						Extra risk				
		0.005[b]	0.01	0.05	0.1	Dose metric[c]		0.005[b]	0.01	0.05	0.1
Weibull[d] with threshold (Schlosser et al., 2003)	BMC BMCL		5.91 5.58	6.12 5.94	6.40 6.22	Flux	BMC BMCL		0.75 0.71	0.78 0.76	0.82 0.79
						DPX	BMC BMCL		0.76 0.71	0.79 0.76	0.84 0.81
Multistage Weibull time-to-tumor[e, g]	BMC BMCL		4.28 3.57	5.93 5.52	6.84 6.41	Flux	BMC BMCL		0.35 0.30	0.49 0.46	0.57 0.53
Rat BBDR model 1	BMC BMCL	4.99[f] 4.95	5.37[f] 5.19			Flux	BMC BMCL	0.42 0.41	0.45 0.43		
Rat BBDR model 2	BMC BMCL	5.41 5.25	5.75 5.59			Flux	BMC BMCL	0.45 0.44	0.48 0.46		

Abbreviations: BMC = benchmark concentration; BMCL = benchmark concentration; BBDR = biologically based dose-response; TWA = time=weighted average; DPX = DNA-protein crosslink; CFD = computational fluid dynamic; PBPK = physiologically based pharmacokinetic.

[a]Human benchmark levels were continuous environmental exposures that would result in steady-state flux (or DPX) levels in humans equal to the average flux (or weekly TWA DPX) levels in rats at the rat BMCs adjusted for 6 hours/day and 5 days/week. Values derived using flux as dose metric decrease by a factor of 1.4 if flux estimates based on Schroeter et al. (2014) are used instead of Kimbell et al. (2001a).

[b]The BMR of 0.005 was used only with the BBDR modeling because these models incorporate precursor response data related to cellular proliferation (see discussion in surrounding text). Because benchmark concentrations at 0.005 and 0.010 extra risk levels were reported when BBDR modeling was used, they were not calculated at the 0.05 and 0.1 levels.

[c]Flux and DPX levels were computed by CFD and PBPK modeling, respectively.

[d]*p*-value for Weibull model fit = 0.90, best fit obtained with a positive intercept on dose axis.

[e]$P(d,t) = 1 - \exp[-(q_0 + q_1 d + q_2 d^2 + \ldots + q_k d^k)x\, t^z]$. q_0, q_1, q_2, q_3, $q_4 = 0$, $q_5 = 2.9 \times 10^{-22}$, z = 8.1. Curve passes through origin. Fit was judged by comparing fitted curve to Kaplan-Meir survival estimates since goodness-of-fit *p*-value was not provided by software package.

[f]Roughly similar result was obtained with model in Conolly et al. (2003). BMC_{005} = 4.84 ppm and BMC_{01} = 5.48 ppm for their hockey-stick model as discerned from Figure 5 of their paper. BMCL values could not be estimated since confidence bounds were not reported.

As discussed in Section 1.1.3, Toxicokinetics of Formaldehyde, Schroeter et al. (2014) revised the dosimetry model of Kimbell et al. (2001b; 2001), used for the flux estimates in the table above, to include endogenous formaldehyde production and to explicitly model formaldehyde pharmacokinetics in the respiratory mucosa. EPA estimated the extent to which the results in the above table change if flux estimates from Schroeter et al. (2014) are used. The average flux over nonsquamous regions of the rat nose is roughly one-third[48] of that in the human, based on the dosimetry in Schroeter et al. (2014) in which endogenous formaldehyde is taken into account

[48]0.33 at 0.1 ppm, 0.32 at 1 ppm.

compared to a ratio of roughly one-half based on the dosimetry in Kimbell et al. (2001a). Thus, wherever flux is used as the dose metric, the benchmark concentrations calculated in the above table are not altered appreciably if the revised dosimetry model by Schroeter et al. (2014) is applied, decreasing only by roughly a factor of 1.4.[49]

Benchmark modeling of precursor lesion data in the rat: cell proliferation and hyperplasia

Benchmark concentrations based on signatures of increased cell proliferation are useful in that increased regenerative cell proliferation is assumed to be a contributory MOA—a factor that can lead to a greater likelihood that DNA damage becomes heritable mutations before it is repaired. Significantly increased cell proliferation as well as hyperplasia (increased cellular proliferation that is identified to be pathologically "abnormal" in tissues) has been observed in response to exposure to formaldehyde as described earlier in Section 1.2.4.

Cell proliferation

Schlosser et al. (2003) used cell proliferation to represent an adverse response and modeled the dose-response for unit length labeling index measurements in F344 rats. They reported benchmark concentrations and 95% lower confidence bounds corresponding to 1%, 5%, and 10% increase in this index over the mean level for controls using dose-response functions that allowed for a threshold in dose.[50] The corresponding HECs spanned a tight range of 0.44–0.47 ppm (0.54–0.58 mg/m^3) (see Table 8 of their paper.)

The data used in their modeling were constructed using a cellular labeling index over several locations on the F344 rat nose, as reported by Monticello et al. (1996). The data from Monticello et al. (1996) represent the longest duration cell proliferation study available, which included measurements across a range of study time points and nasal regions. Due to methodological constraints intrinsic to all the available cellular labeling studies, including Monticello et al. (1996), these data are based on DNA labeling of actively proliferating cells only during the last day of exposure (see Appendix A.5.6 for additional discussion). Schlosser et al. (2003) averaged the data collected from several nasal sites after weighting by exposure time. This introduces some uncertainty because time-weighted averaging underweights early exposures (e.g., 12–13 weeks of exposure) that may have contributed significantly to carcinogenesis (see Section, *Uncertainty-variability in cell replication dose-response of normal cells*, later in this section for further discussion); for instance, the few studies that investigated latent effects in rats (i.e., Wistar) did observe an increased tumor incidence at 1 to ≥2 years following high-level formaldehyde exposure lasting only ~13 weeks (Woutersen et al., 1989; Feron et al., 1988). Similarly, additional methodological uncertainties that are difficult to address experimentally

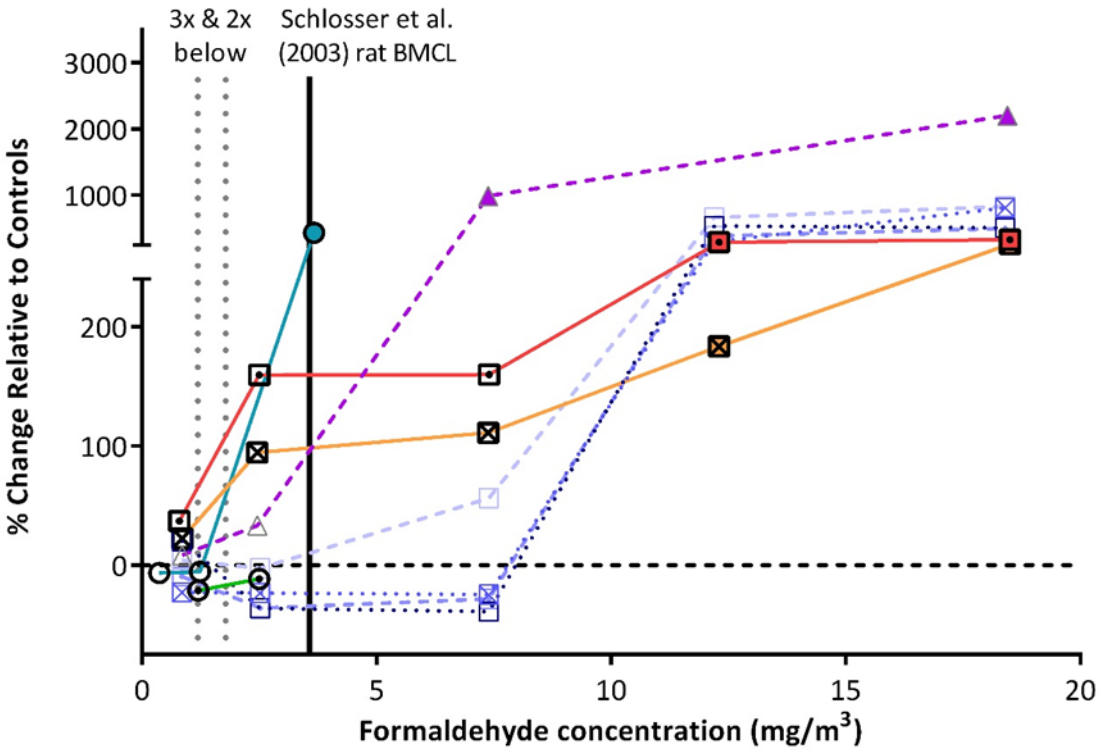
[49]This is an approximate estimate for resting inspiration. The various components of the BBDR modeling were not recalibrated or rerun in light of the revised flux estimates for both species.

[50]They also modeled with functions that were constrained to pass through the origin but do not report BMCL values.

include large site-to-site variation in the labeling (i.e., ≥10-fold); differences in the number of cells across nasal sites; and the possibility that histologic changes and thickening of epithelium that occur at later times for the higher doses likely affect the replication rate. These issues are discussed further and several other plausible dose-response curves for cell replication from Monticello et al. (1996) are developed (see Appendix B.2).

Other well-conducted studies of cellular proliferation using similar labeling methods help estimate the potential impact of these uncertainties in the benchmark concentrations calculated by Schlosser et al. (2003). In general, data from other studies investigating shorter-term formaldehyde exposure durations, as well as the data for shorter duration exposures in Monticello et al. (1996), routinely indicate proliferative effects at lower formaldehyde exposure levels within similar nasal regions[51] (see Appendix A.5.6 for comparisons across various durations of exposure). As discussed in the Appendix, it appears reasonable to assume that all formaldehyde exposures longer than 12 weeks are equally relevant to potential cancer development. The data available from *medium* and *high* confidence studies longer than 12 weeks, including multiple measures in Monticello et al. (1996), are arrayed in Figure 2-5, below, and point to a two- to-three-fold range of observed values below the benchmark concentration estimated by Schlosser et al. (2003) as represented by the dotted vertical lines in the figure. This comparison partly elucidates the uncertainty in the HEC values derived by Schlosser et al. (2003) to understand the cumulative effects of chronic formaldehyde exposure on cellular proliferation.

[51]As the regions analyzed varied across studies, comparisons in Appendix A.5.6 and in Figure 2-5 compare proliferation observed in locations as near to the anterior lateral meatus as possible, as this region was most commonly reported across studies and is a region at which tumors have commonly been observed (see Section 1.2.5, URT cancer in experimental animals).



	Study	High/Med	Strain	Exposure	Nasal region shown	Labeling	Metric
	Andersen et al., 2010	H	F344	13wk	ALM (L2)	3d BrdU	ULLI
	Meng et al., 2010	H	F344	13wk	ALM (note: p<0.01)	3d BrdU	LI
	Wilmer et al., 1989	H	Wistar	13wk	NT/MT	18h thym.	LI
	Zwart et al., 1988	H	Wistar	13wk	NT/MT/ALM (L2; NC in L3)	18h thym.	turnover
	Monticello et al., 1996	M	F344	12wk	ALM (note: no statistics)	18h thym.	ULLI
	Monticello et al., 1996	M	F344	6mos	ALM (note: no statistics)	18h thym.	ULLI
	Monticello et al., 1996	M	F344	1yr	ALM (note: no statistics)	18h thym.	ULLI
	Monticello et al., 1996	M	F344	18mos	ALM (note: no statistics)	18h thym.	ULLI
	Casanova et al., 1994	M	F344	12wk	LM (less in M/PM)	3h ^{14}C	^{14}C incorp.

Figure 2-5. Cellular proliferation measured by DNA labeling in studies ≥12 weeks.

Data from *high* and *medium* confidence studies (High/Med; H/M) exposing rats to formaldehyde for at least 12 weeks (wk), and up to 18 months (mos), were normalized to percentage change from controls to compare across the different metrics of proliferation reported (e.g., labeling index [LI]; unit length labeling index [ULLI]; incorporation of radiolabeled carbon). The regions compared typically included the lateral meatus (LM) in anterior regions (e.g., L1; L2; anterior LM), although one comparison was in related structures (i.e., nasoturbinates [NT] and maxilloturbinates [MT] in Wilmer et al. (1989). The DNA labeling procedures included bromodeoxyuridine (BrdU), thymidine (thym.), and radiolabel. Filled shapes represent statistical significance ($p \leq 0.05$), as reported by the study authors. The vertical lines represent the rat BMDL01, as reported by Schlosser et al. (2003) and estimates which are two- and three-fold lower than the Schlosser et al. (2003) rat BMDL. References: Andersen et al. (2010); Meng et al. (2010); Monticello et al. (1996); Casanova et al. (1994); Wilmer et al. (1989); Zwart et al. (1988).

Hyperplasia

EPA modeled the incidence of basal hyperplasia reported by Woutersen et al. (1989) in a 28-month bioassay using Wistar rats. These animals were exposed to 0, 0.1, 1.0, and 9.8 ppm (0, 0.123, 1.23, and 12.05 mg/m^3) formaldehyde and the observed incidences of hyperplasia were 0/26, 1/26, 2/28, and 14/26. The BMC and BMCL at the benchmark response of 0.1 extra risk were 1.68 and 1.108 ppm (2.07, and 1.36 mg/m^3), respectively. The HEC corresponding to the BMCL is 0.1609 ppm (0.198 mg/m^3) when adjusted for continuous human lifetime exposure, which is roughly three times lower than the HEC derived from the time-weighted averaged labeling index by Schlosser et al. (2003). It is useful to note that this value is roughly comparable to the LEC_{0005} derived from EPA's modeling of the NPC risk from the NCI epidemiology data.

Extrapolation using a biologically based dose-response model

In the case of formaldehyde, there are multiple options available for extrapolating to human exposure scenarios which are typically at lower concentrations than the various HECs calculated above. Subsequent to their BBDR modeling (Conolly et al. (2003)) of nasal cancer in the rat, Conolly et al. (2004) developed a corresponding model for humans, which they used for the purpose of extrapolating the observed risk in the rat to human exposures. This human extrapolation model is conceptually similar to the modeling in Conolly et al. (2003) but does not incorporate any data on human responses to formaldehyde exposure. A particular contribution of this model toward extrapolation is that it uses, as input, DPX concentrations and values of local formaldehyde flux to the tissue as obtained from PBPK and fluid dynamic dosimetry models respectively (Conolly et al., 2000; Subramaniam et al., 1998). The modeling in Conolly et al. (2004, 2003), while still a statistical model where some key parameters are determined by model fit to the tumor data, incorporates more detailed biological hypothesis and mechanistic data than is normally employed in modeling cancer risk. Toxicodynamic models developed on the basis of an agent's MOA, if robust, are generally preferred over default approaches for extrapolation, with the extent of extrapolation determined by model uncertainty (U.S. EPA, 2005a).

In this section, we present extrapolations of the rat nasal cancer risk to humans carried out in Conolly et al. (2004). Continuous human lifetime extra risk estimates from this model following inhalation exposure to 1.0 ppb–1.0 ppm (1.23 μg/m^3–1.23 mg/m^3) formaldehyde concentrations are provided in Table 2-23, and compared with human risk estimates derived from EPA's modeling of the NPC mortality in the NCI occupational epidemiology data (note: the comparison with mortality estimates appears appropriate since Conolly et al. (2004) had modeled the tumors as rapidly fatal). This comparison is provided only for perspective, noting in particular that NPCs are specific to tumors only in the human nasopharynx (see Section 1.2.5). Conolly et al. (2004) developed two clonal growth models based on using different representations of the low dose-response for the cell division rate as input data. The first, denoted as *optimal* in the table, was derived from using the best fit, a J-shaped curve, to the dose-response for the TWA of the cell

labeling data in rats such that values at 0.7 ppm and 2.0 ppm (0.9 mg/m^3 and 2.46 mg/m^3) were below the control value; the second, presented as their *conservative* (in the sense of being more health protective) approach, was derived from using a hockey-stick shape to replace the J-shape in the low-dose portion of the *optimal* case such that values at the two lowest concentrations were the same as the control. In either case, risk estimates reported in Conolly et al. (2004) were based on using maximum likelihood estimate (MLE) values for all model parameters except the parameter *kmu* associated with formaldehyde's mutagenic potential for which they used an upper-bound value; (*kmu* is the constant of proportionality that relates DPX concentrations to the probability of formaldehyde-induced mutation occurring per-cell generation).

The *optimal* model in Conolly et al. (2004) indicates lifetime human risk estimates to be substantially below baseline risk levels (i.e., negative values of extra risk) for formaldehyde exposures less than roughly 2 ppm (2.46 mg/m^3), while their *conservative* model predicts values that do not appreciably exceed baseline levels (i.e., extra risk less than 10^{-5}) for exposures less than 0.2 ppm (0.25 mg/m^3). At the EC_{0005} benchmark concentration of 0.19 ppm (0.23 mg/m^3) derived from the NCI occupational epidemiology data, the *conservative* model in Conolly et al. (2004) predicts roughly a 100-fold lower continuous lifetime risk than the central estimate indicated by EPA's analysis of the epidemiology data. The difference is roughly the same at lower exposure concentrations, while at 1.0 ppm (1.23 mg/m^3) the *conservative* model predicts a 1,000-fold lower value than EPA's central estimate based on the epidemiology data (see Appendix B.2.2).

The maximum likelihood value of the parameter *kmu* was estimated to be zero in the modeling, leading to the inference by the authors that formaldehyde's direct mutagenic action is not relevant to carcinogenicity in the rat or human, and that the observed tumor response in the rat can be explained on the basis of regenerative cellular proliferation in response to cell injury. These results have been interpreted by some to mean that exposures protective of the effects of cell proliferation are adequate to protect against formaldehyde-induced nasal cancers (Conolly et al., 2004; Slikker et al., 2004). The uncertainty in these estimates and conclusions are evaluated below.

Table 2-23. BBDR model estimated extra risk of SCC in human respiratory tract compared with EPA's modeling of extra risk of NPC from the human occupational epidemiology data

Formaldehyde concentrations	0.001 ppm	0.01 ppm	0.10 ppm[a]	1.0 ppm
Conolly et al. (2004) optimal estimate[b]	-1.0×10^{-5}	-1.0×10^{-4}	-9.1×10^{-4}	-5.0×10^{-3}
Conolly et al. (2004) conservative estimate[b]	$+3.1 \times 10^{-8}$	$+3.2 \times 10^{-7}$	$+3.5 \times 10^{-6}$	$+2.7 \times 10^{-4}$
EPA analysis-NCI NPC mortality MLE (UCL)[c]	$+1.2 \times 10^{-6}$ ($+2.1 \times 10^{-6}$)	$+1.3 \times 10^{-5}$ ($+2.3 \times 10^{-5}$)	$+1.8 \times 10^{-4}$ ($+4.1 \times 10^{-4}$)	$+2.7 \times 10^{-1}$ ($+8.7 \times 10^{-1}$)

[a]For reference, the mortality-based LEC_{0005} derived from the NCI occupational data is 0.11 ppm (EC_{0005} is 0.19 ppm).
[b]Conolly et al. (2004) risk estimates were based on using MLE values for all model parameters except the parameter associated with formaldehyde's mutagenic potential for which they used an upper bound.
[c]See section 2.2.1; MLE = maximum likelihood estimate; UCL = 95% upper confidence limit.

Uncertainty in the dose-response estimates

The ratio of the BMCL to the BMC is a convenient way to express the statistical uncertainty in the benchmark concentration derived by a given model. (This ratio is also dependent on the value of the benchmark response considered.) Table 2-22 indicates this ratio to be tight, ranging from 0.83 to 0.96 across the models at the BMR of 0.1. However, it is well-recognized (U.S. EPA, 2005a) that there is a large uncertainty inherent to using statistical models to extrapolate outside the range of observed data. For example, in the context of the multistage Weibull model fit to the formaldehyde time-to-tumor data in Table 2-22, the slope at the origin, q1, was zero, whereas the upper bound on this value, q1*, was 0.02 ppm^{-1}; as shown in Table 2-22, this value is comparable to that derived using EPA's straight line extrapolation.

The level of confidence in various components of the biologically based modeling approach and its use for extrapolation is next addressed; the relevant question is whether the BBDR modeling decreases uncertainty in extrapolating risk or, by explicitly identifying the sources of uncertainty, points to approaches and data needs that may help reduce the uncertainty.

Uncertainties and confidence in the BBDR modeling and extrapolation

EPA carefully evaluated the level of confidence and sources of uncertainties in different components of both the rat BBDR model and the corresponding human extrapolation model (Table 2-24). Seven issues that were evaluated are tabulated below, and elaborated in more detail in Appendix B.2.2 and supporting references. Of these, issue numbers 3, 6 and 7—related to replication rates of normal and initiated cells and the use of historical control animals—were found to have major impacts on qualitative and quantitative conclusions drawn from the modeling, and are briefly discussed below.

Table 2-24. Evaluation of BBDR modeling issues

	Issue	Supporting references for evaluation
1	Confidence in FA airflow and flux model, and assessment of interindividual variability in FA flux; airway reconfiguration due to long-term dosing	Kimbell et al. (2001a); Subramaniam et al. (1998); Kimbell et al. (1997a); Garcia et al. (2009); Subramaniam et al. (2008); Cohen Hubal et al. (1997); Morgan (1997); Monticello et al. (1996); Kimbell et al. (1997b)
2	Uncertainties in FA-DPX PBPK model	Subramaniam et al. (2008); Subramaniam et al. (2007)
3	Uncertainties and variability in the rat cell labeling data, the derivation of cell division rates from these data, and their applicability to human cell division rates	Subramaniam et al. (2008); Conolly et al. (2004)
4	Use of an approximate method by Hoogenveen et al. to solve the two-stage clonal expansion model equations	Subramaniam et al. (2007); Crump et al. (2005)
5	Assumption that all observed SCC in rats were rapidly fatal; Model assumption of a time delay from occurrence of malignant cell to death	Subramaniam et al. (2007); Crump et al. (2005); Crump et al. (2008)
6	Sensitivity of model results to the use of historical control animals drawn from all NTP cancer bioassays	Crump et al. (2008); Subramaniam et al. (2007)
7	Uncertainties in assumed division and death rates of initiated cells	Crump et al. (2009); Crump et al. (2008); Subramaniam et al. (2008)

Uncertainty-variability in cell replication dose-response of normal cells

Use of the raw cell labeling data from Monticello et al. (1996; 1991) to calculate replication rates of normal cells for input to the TSCE models in Conolly et al. (2004, 2003) involved several steps and assumptions. First, as shown in Table 2-21, the first phase for early exposure periods Monticello et al. (1991) employed injection labeling with a 2-hour pulse labeling, whereas the second phase for longer exposure periods Monticello et al. (1996) used osmotic mini-pumps for labeling with a 120-hour labeling time. These data were pooled by using a normalization procedure for the injection labeled data. Second, the average values from the labeling (averaged over the replicate animals and after the above normalization) were weighted by the exposure times in Monticello et al. (1996; 1991) and averaged over the nasal sites. Thus, the data were combined into one TWA for each exposure concentration. Third, Monticello et al. (1996; 1991) used unit length labeling index (ULLI) to quantify cell replication within the respiratory epithelium. ULLI is a ratio between a count of labeled cells and the corresponding length (in millimeters) of basal membrane examined. Therefore, ULLI had to be converted to the per-cell labeling index (LI), which is the ratio of labeled cells to all epithelial cells, in this case, along some length of basal membrane and its

associated layer of epithelial cells. This was accomplished by using data from a different experiment (Monticello et al., 1990a) where both quantities had been measured for two sites in the nose. Fourth, cell division rates were then calculated from the TWA using an approximation developed by Moolgavkar and Luebeck (1992).

Fifth, the empirical data could be used in Conolly et al. (2003) to directly calculate cell replication rates only for approximately the lower one-fourth of the full flux range (0−39,600 pmol/mm^2-h) needed to model the bioassay data. The unknown cell replication rates for the upper three-fourths of the flux range were determined by linear interpolation to a maximum cell replication rate that was estimated as a statistical parameter fit to model predictions of the tumor incidence data (see (Subramaniam et al., 2008) for further details and biological implications of this procedure).

Finally, because there are no equivalent labeling index data available for the human respiratory epithelium, the above dose-response for normal cell replication derived for the rat was also directly assumed to apply to the human except for different values for the fraction of rat and human nasal epithelial cells capable of dividing (Conolly et al., 2004).

The TSCE model is generally sensitive to normal cell division rates, and there are considerable uncertainties (quantitative and qualitative) and variability in the dose-response for the replication rates of normal cells (α_N) as characterized in the above steps. For example, Figure 2-6, below, shows α_N as a function of formaldehyde flux to the rat nasal epithelial tissue [using only values derived from the continuous ULLI data in (Monticello et al., 1996)]. Corresponding to any particular dose (in terms of formaldehyde flux to tissue) α_N varies by one to two orders of magnitude. As shown in Appendix B.2.2, a variety of cell replication dose-response curves can be drawn to fit these data, and the use of an exposure TWA of cell labeling data over sites was found to be problematic on multiple accounts. Furthermore, the formula relating LI to α_N was for continuous labeled data and its use for pulse labeled data, as evaluated in the appendix, was found to be extremely uncertain.

The results in Table 2-23 for the *optimal* and *conservative* models in Conolly et al. (2003) represent a sensitivity analysis of the impact on risk estimates of varying the dose-response for normal cell replication rates at the low-dose range, and the differences between the two model results point to large variations in predicted human risk estimates from incorporating some of the variability and uncertainty in normal cell division rates in inputs to the TSCE model. In the neighborhood of the POD from the observed occupational epidemiology data, these models compute extra risk estimates of -9.1×10^{-4} and $+3.5 \times 10^{-6}$ respectively compared to a value of $+4.1 \times 10^{-4}$ indicated by the epidemiology data.

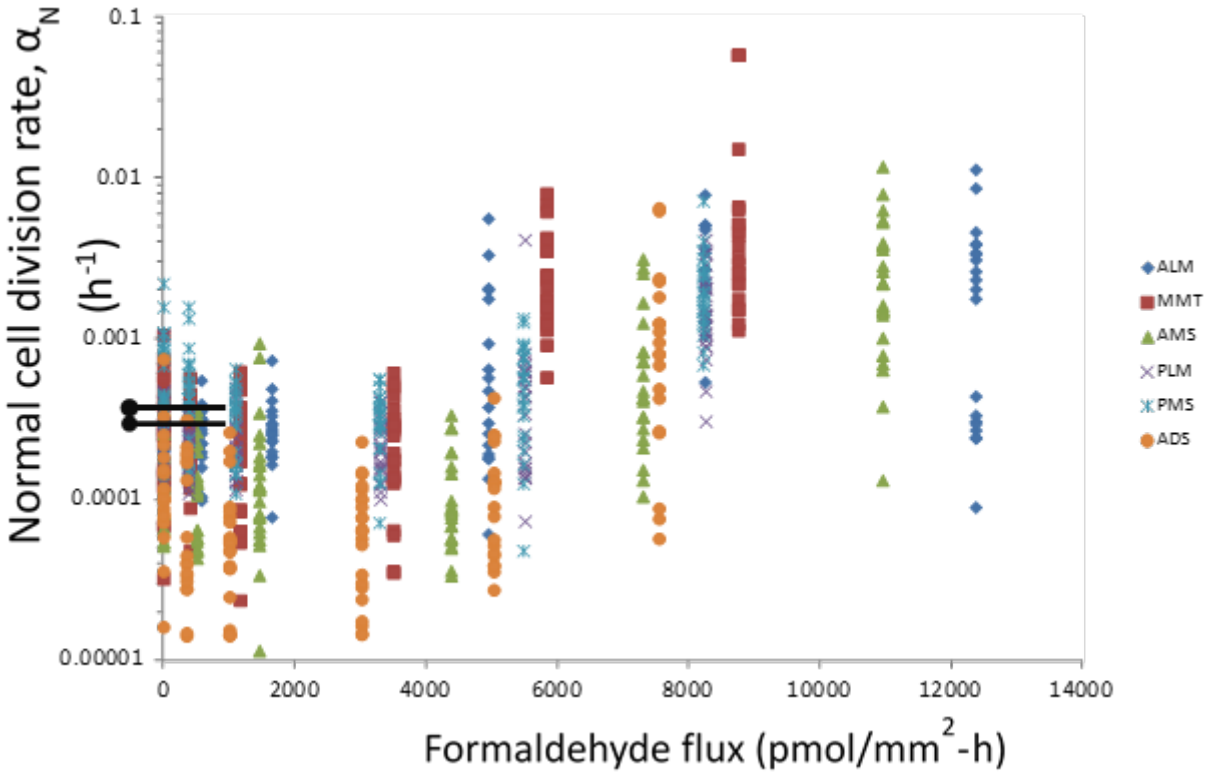


Figure 2-6. Dose-response for normal cell division rate, α_N, versus formaldehyde flux to tissue for the F344 rat nasal epithelium.

Values were derived from continuous unit length labeled data by Monticello et al. (1996). Each point represents a measurement for one rat, at one nasal site, and at a given exposure time. Data shown for six nasal sites (legend, nasal sites are as denoted in original paper) and four exposure durations (13, 26, 52, 78 weeks). For comparison purposes, the double black bars on the y-axis indicate the extent of difference between two curves, mod0 and mod5, for the dose-response for cell division rates of initiated cells.

The assumption in Conolly et al. (2004) that cell division rates exhibit a similar dose-response across rats and humans appears uncertain (Conolly et al. (2004) did consider different values for rats and humans for the fractions of cells with replicative potential) (see Appendix B.2.2). EPA was unable to find a rationale for this assumption in the literature. To the contrary, it seems possible that basal cell division rates may scale allometrically across species, considering that enzymatic metabolism is likely to play a role in mitosis. [For example, West and Brown (2005) argue that DNA nucleotide substitution rates and inverse of lifespan scale as mass to the inverse one-fourth power.]

Miller et al. (2017) found the modeling in Conolly et al. (2004) [that is, their human extrapolation model] to be sensitive to the fraction of cells considered to have replicative potential in the human respiratory tract, a parameter in the human model. For example, added risk over background increased (by 87%) from -1.0×10^{-3} to -1.3×10^{-4} at 0.4 ppm exposure concentration but decreased (by 127%) from $+7.7 \times 10^{-4}$ to -2.1×0^{-4} at 2.0 ppm, when this parameter was changed

from that experimentally observed by Mercer et al. (1994) for various cell types to a value of 1.0 (i.e., all cells to have replicative potential) for the nonsmoking population at resting breathing.

Miller et al. (2017) also reported new results obtained with the Conolly et al. (2004) model in regards the site distribution of extrapolated human risk estimates over the respiratory tract. At 0.2 ppm and 1.2 ppm (0.25 mg/m^3 and 1.48 mg/m^3) inhaled exposure concentrations of formaldehyde, the highest risk was predicted to occur in nasal tissue that received the lowest formaldehyde flux, but which comprised the largest surface areas. Based on the flux patterns displayed in Kimbell et al. (2001), this likely overlaps with the human nasopharyngeal region, and indicates an important role for dosimetry in regards the epidemiological observation of nasopharyngeal carcinomas. For the high exposure concentrations (3.6 ppm and 4.5 ppm; 4.43 mg/m^3 and 0.62 mg/m^3), the highest risk region was instead predicted to occur in regions of the nose that received intermediate levels of formaldehyde flux.

Kinetics of initiated cells

There are no data on initiated (I) cells (the available empirical cell labeling data are for normal [N] cells). Therefore, Conolly et al. (2004) assumed relationships that linked the division rate, α_I, and death rate, β_I, for initiated cells to the division rate for normal cells, α_N, as a function of local formaldehyde flux (since local flux was the most sensitive dose metric):

$$\alpha_I(flux) = \alpha_N(flux) \times \{c_1 - c_2 \cdot \max [\alpha_n(flux) - \alpha_{Nbasal}, 0]\}- \quad (2\text{-}2)$$

$$\beta_I(\text{flux}) = \alpha_N(\text{flux}), \text{ for all values of flux. } - \quad (2\text{-}3)$$

where c_1 and c_2 are constants estimated by fitting the clonal expansion model to the tumor incidence data. No biological rationale was provided for these assumptions; however, these assumptions allowed for a good fit to the rat tumor incidence data. The TSCE model is known to be very sensitive to the kinetics of initiated cells, and the authors did not examine whether other expressions would also fit the rat data but lead to different predictions of human risk. Therefore, to evaluate the sensitivity of model predictions to the assumed relation (eq 2-2) between α_I and α_N in the low flux region, EPA slightly modified this relation for α_I(flux) for flux <475 pmol/mm^2-h, while keeping it identical to the values in Conolly et al. (2004) for 475 <flux levels <39,300 pmol/mm^2-h, and retaining the biological constraints imposed on it in the original model (i.e. mod0 in Table 2-25). The sensitivity analysis evaluated the effect both upon the fit to the rat tumor incidence data and the predictions of human risk.

Six such modified implementations of α_I(flux) were considered (see mod-1, mod1-5 in Figure 2-7 and in Table 2-25), in each case constrained to be small enough that they did not degrade the fit to the rat tumor incidence data when applied in the rat model or the fit to background incidence rates in the U.S. population when applied in the human model. The

maximum extent of these modifications to the assumed replication rates of initiated cells is overlaid by the double black bars in Figure 2-6, above, on the rates for normal cells, α_N(flux), that are derived from empirical data. As seen in the Figure, the extent of the modifications is extremely small in relation to the empirical variability seen in normal cells. Thus, the modifications considered in the sensitivity analysis appear biologically reasonable.

EPA's sensitivity analyses retained the same values for β_I (equation 2-3) as considered in the original analysis. However, the ratio α_I:β_I over the flux range in the modeling was closely monitored. Because this ratio represents the growth advantage of initiated cells in the model, it was kept close to the value of 1.0, similar to the range of 0.96–1.07 for the values of α_I/β_I in (Conolly et al., 2004) [mod0]. In the sensitivity analysis, α_I/β_I varied from 0.96–1.07 in mod-1; 0.96–1.08 for mod1, mod2, mod3, mod4; and 0.96–1.10 for mod5. Table 2-25 provides MLEs of continuous lifetime human extra risk estimates at 0.15 ppm (0.18 mg/m^3) exposure concentration for the original Conolly model (mod0) and compares those derived from the above modifications. For perspective, the table also compares with human risk estimates derived from EPA's modeling of the NPC mortality[52] in the NCI occupational epidemiology data (see Section 2.2.1).

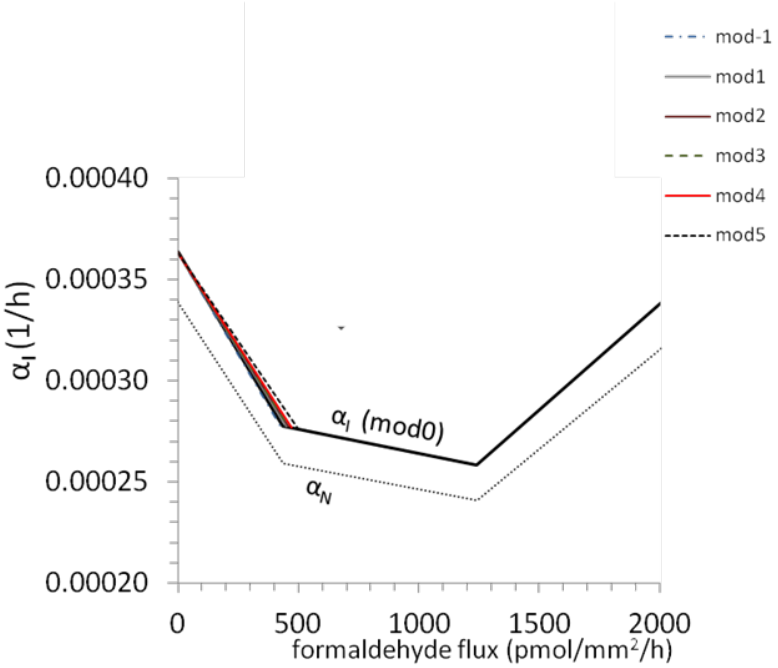


Figure 2-7. Small variations to α_I(flux) for flux <475 pmol/mm^2-h carried out for sensitivity analysis.

Mod0 is the original model in Conolly et al. (2004); mod-1 decreases α_I and mod1-5 increase α_I in mod0 for low flux.

[52]The comparison with mortality estimates appeared appropriate since the tumors were modeled as rapidly fatal in Conolly et al. (2004, 2003).

Table 2-25. Sensitivity of BBDR modeled human SCC risk at 0.15 ppm to small variations in normal (α_N) and initiated (α_I) cell replication rates

Model*	Extra risk
mod0: Conolly et al. (2004), J-shaped α_N, α_I	-1.0×10^{-3}
mod-1: Decrease α_I for low flux in mod0	-1.5×10^{-3}
mod1: Increase α_I for low flux in mod0	-3.0×10^{-4}
mod2: Increase α_I for low flux in mod0	$+9.0 \times 10^{-5}$
mod3: Increase α_I for low flux in mod0	$+3.0 \times 10^{-4}$
mod4 Increase α_I for low flux in mod0	$+9.0 \times 10^{-4}$
mod5: Increase α_I for low flux in mod0	$+3.0 \times 10^{-3}$
Conolly et al. (2004), hockey-stick shaped α_N, α_I	$+5.7 \times 10^{-6}$
EPA analysis of NCI NPC	$+5.5 \times 10^{-3}$

*See Figure 2-7 for depiction of mod0, mod-1, mod0-5.

The results in this table indicate that extremely small differences in assumptions for α_I appear to have extremely large effects on the human model predictions. This analysis is continued in Appendix B.2.2, where similar sensitivity of model predictions is demonstrated over a large range of exposure concentrations. Larger variations in α_I (see Crump et al., 2008), while still in agreement with the model constraint of reproducing the observed tumor incidence data and the background rate of lung tumors in humans, considerably broaden the range of predicted risk on either side (below and above) of the baseline risk. Such an extreme sensitivity indicates that the formaldehyde human TSCE model is unstable in response to the slight perturbations carried out to the assumed values of α_I, and is therefore not robust. It is well known that models are generally uncertain outside of the range of the data over which they were calibrated (Crump et al., 2010) and this is indeed the case with the rat BBDR model. As discussed by Crump et al. (2009; 2008), the human extrapolation BBDR model, on the other hand, is noteworthy for its extreme uncertainty at *all* exposure concentrations, above as well as below the HECs that were calculated in the benchmark modeling section.

There are currently no data of any kind, even in rats, to inform the effect of formaldehyde on the kinetics of initiated cells. However, assuming that initiated cells related to tumors in the respiratory tract can be identified and their division rates measured, it is reasonable to suppose that these rates would be at least as variable as division rates of normal cells. Based on the normal variation in such rates observed in normal cells in Figure 2-7, and the extreme sensitivity of the formaldehyde model to small differences in assumed division rates of initiated cells, EPA concluded that it would be impossible to measure these accurately enough to lead to any substantive reduction in the large uncertainty in risk estimated by this model.

Use of historical control animals

Because SCC in the nose is a rare tumor, Conolly et al. (2004, 2003) included in their model 7,684 control rats from all NTP cancer bioassays in addition to the 347 control animals in the Kerns et al. (1983) and Monticello et al. (1996) inhalation bioassays used in the dose-response modeling. In general, the inclusion of all NTP historical control animals regardless of exposure route, time of study, etc. is problematic because there are legitimate questions regarding comparability of results in rats from different stocks, studied at different times, in different laboratories, and by different routes of exposure and evaluated by using somewhat different pathological procedures (Haseman and Hailey, 1997; Rao et al., 1987). In particular, the incidence rate in the inhalation historical controls was found to be an order of magnitude lower than the rate in all historical controls combined (see Subramaniam et al., 2007). Therefore, EPA examined the sensitivity of the BBDR model predictions to the use of historical NTP control animals by restricting the historical controls to only inhalation studies or by using only the concurrent controls.

When the NTP control data were restricted to those animals from NTP inhalation studies, the upper-bound human risk estimate obtained by Conolly et al. (2004) (i.e., with everything else in their modeling retained unchanged) was increased by 50-fold (Crump et al., 2008). If only concurrent controls are used, as is normally the practice in dose-response analysis of animal bioassays, the Conolly et al. (2004) model for extrapolation of risk to humans becomes numerically unstable, i.e., the MLE and upper-bound estimates of risk become infinite (Subramaniam et al. (2007), Crump et al. (2008)).

Overall confidence in the formaldehyde BBDR models

The other issues listed in Table 2-24 are evaluated at length in Appendix B.2.2. Although CFD model predictions of formaldehyde flux to the respiratory lining have not been verified experimentally (due to formidable experimental challenges), predictions from other models that use the calculated formaldehyde flux as input have been shown to agree with various kinds of available data, and thus project a reasonable, albeit indirect, level of confidence in the formaldehyde dosimetry modeling in both the rat and human nasal passages (see Appendix B.2.2). The CFD models of formaldehyde flux are based on data collected from a single individual of each species. Therefore, interindividual differences in regional dosimetry, particularly in the human, are not accounted for (Garcia et al., 2009; Subramaniam et al., 2008).

Repair of DPX was assumed to be rapid and complete in 18 hours in the PBPK model for DPX (Conolly et al., 2000); this assumption was found to be highly uncertain (Subramaniam et al., 2008). While it has no impact on the rat BBDR model predictions (see Appendix B.2.2), the impact of this assumption on the human extrapolation model, on the other hand, was significant (Crump et al., 2008). Furthermore, more recent results by Lai et al. (2016) indicate that in vivo DPX repair may be slow and that DPX readily accumulates long-term in the nasal respiratory tissue in contrast to its rapid hydrolysis in vitro.

In summary, the human extrapolation modeling in Conolly et al. (2004) is extremely uncertain on two accounts, and does not provide robust measures of human nasal SCC risk at *any* exposure concentration. Therefore, the human extrapolation model is not used in this assessment to directly calculate risk at human exposure scenarios. On the other hand, the rat BBDR modeling improves the dose-response modeling of the observed nasal cancers in the F344 rat, and multiple BBDR model implementations provide similar estimates of risk and confidence bounds in the general range of the observed rat tumor incidence data. Therefore, the rat BBDR models are used to calculate benchmark concentrations for PODs, and the benchmark response was extended slightly below the observed. There is reasonable confidence in flux estimates derived from the rat and human CFD models, which were accordingly used in deriving HECs corresponding to these PODs. A candidate RfC and candidate unit risk estimates using these values are included in the following section.

RfC approach for precursor lesion data in the rat: cell proliferation and hyperplasia

The highly curvilinear and steeply increasing dose-responses for DPX formation and cell proliferation, concomitant with the highly nonlinear observed tumor incidence in the F344 rat, have led to mechanistic arguments that formaldehyde's nasal carcinogenicity arises only in response to significant cytotoxicity-induced regenerative cell proliferation (Swenberg et al., 2011; Conolly et al., 2002; Morgan, 1997). In particular, Conolly et al. (2003) and Slikker et al. (2004) inferred from BBDR modeling results that the direct mutagenicity of formaldehyde is less relevant compared to the importance of cytotoxicity-induced cell proliferation in explaining the rat tumor response. Thus, candidate RfCs (cRfCs) derived from available experimental data relevant to this mechanism are presented and discussed. These cRfCs are interpreted as formaldehyde concentrations below which it is unlikely that hyperplastic lesions develop or that cancers arising from cytotoxicity-induced regenerative cell proliferation occur. In this interpretation, cytotoxicity-induced regenerative cell proliferation, which increases the probability of errors in DNA replication, and the subsequent development of hyperplastic lesions, are considered to be precursor events that, if protected against, would prevent these mechanisms from contributing to the cancer response. Below these cRfCs, formaldehyde may still increase the risk of nasal or upper respiratory cancer through *direct* mutagenicity or other mechanisms, but the magnitude of cancer risk may be significantly lower due to the absence of increased cellular proliferation or hyperplasia.

The following benchmark PODs and corresponding HECs were developed based on increased cell proliferation as well as hyperplasia: (a) 0.44 ppm (0.54 mg/m^3) corresponding to the $BMCL_{01}$ in Schlosser et al. (2003), and roughly two- to three-fold lower estimates based on examining data from other cell labeling studies (as discussed above in the section on modeling precursor lesion data), resulting in an overall range from 0.18 to 0.54 mg/m^3; and (b) 0.16 ppm (0.20 mg/m^3) based on EPA's modeling of the incidence of basal hyperplasia reported by Kleinnijenhuis et al. (2013) in Wistar rats. To these values, it is necessary to apply a UF = 3 to reflect other uncertainties in extrapolating from animals to humans and a UF = 10 to account for human

variability (total UF = 30). This results in cRfCs that range from **0.006 mg/m³ to 0.018 mg/m³** when based on cell proliferation data and a cRfC of **0.007 mg/m³** from the hyperplasia data.

As noted earlier, it has been argued that the rat nasal tumors can be quantitatively explained based solely on formaldehyde's cytotoxic potential. In accordance with this point of view, a cRfC estimated from benchmark concentrations derived using the two rat BBDR models may be a reasonable approximation for the dose at which there is no regenerative cell proliferative contribution to the nasal or upper respiratory cancer response. A cRfC of **0.017 mg/m³** may be obtained in this manner corresponding to the average HEC estimated using the two models at a benchmark response of 0.005 extra risk reduced by a UF of 30. This value is encompassed by the overall range of **0.006–0.018 mg/m³** obtained as explained above for the cRfCs based on cell proliferation and hyperplasia.

However, Chapter 1 of this assessment also provides multiple lines of evidence that the direct mutagenicity of formaldehyde plays a key role in its carcinogenicity. Cytogenetic effects in occupational studies and the formation of DPXs in experimental animals have been reported at exposures well below those considered to be cytotoxic (e.g., approximately 0.7–2 ppm or 0.9–2.5 mg/m³ in rats), and as noted earlier, DPX formation was detected in rats at exposures ranging from 0.3 ppm (0.37 mg/m³) to 15 ppm (18.5 mg/m³). The DPX dose-response shows a trend consistent with an increase over baseline levels at 0.7 ppm (0.86 mg/m³), which becomes statistically significant at 2 ppm (2.46 mg/m³) and above.

Furthermore, the previously mentioned inference that formaldehyde's direct mutagenic action is relatively irrelevant to explaining the observed rat tumor response was found to be extremely uncertain in EPA's uncertainty analysis. A reanalysis presented in Subramaniam et al. (2007) indicated that, depending on the choice of control animals and alternate model assumptions, a large contribution from formaldehyde's mutagenic potential may be needed to explain formaldehyde carcinogenicity at low dose as well as in describing the observed tumor incidence. Finally, as discussed in Section 1.2.5, *Evidence on mode of action for URT cancers*, genotoxicity is itself thought to be one of the mechanisms by which formaldehyde exerts its cytotoxic action. Thus, it appears difficult to argue for a demarcation along the concentration axis of one MOA relative to the other. Therefore, because formaldehyde-induced tumors are not explained *only* by the cell proliferative MOA at *any* exposure, and since EPA does not develop an RfC specifically for one MOA when other MOAs also contribute to the tumor response, the use of an RfC approach is not preferred.

Low-dose risk without extrapolating models below the observed data

The various arguments presented in the last two paragraphs of the previous section on an RfC-like approach for cancer, particularly regarding formaldehyde's direct mutagenic potential, provide greater support for a low-dose linear approach in extrapolating low-dose formaldehyde cancer risk from the rat data. Following the procedures in EPA's cancer guidelines (U.S. EPA, 2005a) to be applied when knowledge of the MOA does not support an alternative approach or

when direct mutagenicity does not contribute to the cancer response, this extrapolation was carried out as a straight line drawn to the origin from the HEC corresponding to the BMDL. Unit risks so calculated are shown in Table 2-26 below. The unit risks corresponding to BMRs at the 0.005 or 0.01 extra risk levels, spanned a remarkably tight range, 0.01–0.03 per ppm**,** across the different methods and dose metrics (see Table 2-22). It is useful to contrast the unit risk value at the 0.005 extra risk with that obtained for the statistical upper bound on the coefficient associated with the first-order term in the multistage Weibull model described above in the statistical time-to-tumor modeling (denoted q1* in an earlier EPA approach to low-dose linear extrapolation). q1* was determined to be equal to 0.02 per ppm, and falls within this tight range.

Table 2-26. Unit risk estimates derived from benchmark estimates[a]

Models	Dose metric	Unit risk estimates from various PODs (1/ppm)			
		$BMCL_{005}$	$BMCL_{01}$	$BMCL_{05}$	$BMCL_{10}$
Weibull with threshold (Schlosser et al., 2003)	Flux		0.014	0.066	0.127
	DPX		0.014	0.066	0.127
Multistage Weibull time-to-tumor	Flux		0.033	0.109	0.189
Rat BBDR model	Flux	0.012	0.023		
Rat BBDR model	Flux	0.011	0.022		

[a]Unit risks derived using flux as dose metric increase by a factor of 1.4 if flux estimates based on Schroeter et al. (2014) are used instead of Kimbell et al. (2001a). Also, see other footnotes from Table 2-22.

In conclusion, use of biologically based modeling allowed the use of various data, including mechanistic information, in an integrated manner for modeling the incidence of nasal SCC in F344 rats and for deriving benchmark levels for extrapolation. A conventional multistage Weibull time-to-tumor modeling was also used to model these data. For a given benchmark response level, PODs and their corresponding HECs are remarkably similar across multiple models and dose metrics (formaldehyde inhaled exposure concentrations, formaldehyde inhaled flux to tissue, DPX concentrations). Biologically based clonal expansion models were carefully evaluated for directly extrapolating the rat nasal cancer risk to human exposure scenarios. Predictions using these models for humans were found to be not robust at any exposure concentration. Accordingly, the clonal expansion modeling of the rat data was employed to derive multiple PODs and corresponding HECs but not used for extrapolating to human exposure scenarios.

Selection of a Unit risk Estimate for Nasal Cancers

The unit risk estimates derived using the available human and animal data on nasal cancers are similar (see Table 2-27), with the human estimate being only slightly lower than those values estimated using rat bioassay and mechanistic data.

Table 2-27. Comparison and basis of unit risk estimates for nasopharyngeal cancer in humans and nasal squamous cell carcinomas in rats

	Human NPC estimate	Animal nasal cancer estimate
Study/endpoint	Beane Freeman et al. (2013) (NCI industrial cohort): NPC mortality	Monticello et al. (1996); Kerns et al. (1983): Incidence of nasal SCC in rats
Model features	Estimation of IUR using Poisson regression model and life-table analysis: • U.S. national incidence data • Regression coefficients from log-linear models of nasopharyngeal cancer (NPC) mortality (exposed and unexposed workers) • Linear low-dose extrapolation from LEC	Multiple mechanistic and statistical models, including BBDR modeling, used for modeling tumor incidence Mechanistic information included: • Dosimetric (CFD) modeling of formaldehyde flux to rat, monkey and human airway lining • PBPK model for rats incorporating dose-response data on DPXs • site-specific cell labeling measurements in nose A linear low-dose extrapolation from human equivalent dose at BMCL was employed
POD	95% lower bound on concentration at 0.05% incidence (approx. 0.05 ppm)	95% lower bound on concentration at 0.5% incidence (approx. 0.2 ppm)
Unit risk estimatea	7.4×10^{-3} per mg/m^3 (9.1×10^{-3} per ppm)	8.9×10^{-3} to 1.8×10^{-2} per mg/m^3 (1.1×10^{-2} to 2.2×10^{-2} per ppm)

[a]Note that these estimates are provided for comparison purposes and do not represent ADAF-adjusted values.
ADAF = age-dependent adjustment factor.

A comparison of the preferred unit risk estimates based on human and rodent data summarized above reveals that the different databases yield similar estimates. When data from epidemiological studies of sufficient quality are available, these data are generally preferred for estimating risks (U.S. EPA, 2005a). In the case of formaldehyde, the NCI epidemiological study (Beane Freeman et al., 2013) is a high-quality study for the purposes of deriving quantitative risk estimates, and the estimates based on this study are preferred to the estimates based on the rat data. Although there are uncertainties inherent in estimates from both the human and rodent databases, the estimates based on the human data are considered better estimates of the risk to humans.

Next, given that it was concluded in Section 1.2.5 that a mutagenic MOA was operative for URT cancers, the unit risk estimate for NPC is adjusted for potential increased early-life susceptibility, in accordance with EPA guidelines (U.S. EPA, 2005b) (see Section 2.2.4).

Uncertainties and Confidence in the Preferred Unit Risk Estimate for Nasal Cancers

The strengths and uncertainties in the unit risk estimate for NPC incidence are summarized in Table 2-28. One of the largest sources of uncertainty in the NPC estimate has to do with the

rarity of the cancer and, thus, the small number of exposed cases (n = 8) that informed the dose-response analysis.

Table 2-28. Strengths and uncertainties in the cancer type-specific unit risk estimate for nasopharyngeal cancer

Strengths	Uncertainties
• IUR estimated from data that is directly relevant to humans. • Based on the results of a large, *high* confidence epidemiology study involving multiple industries with detailed, individual cumulative exposure estimates and allowance for cancer latency. • Low-dose linear extrapolation is supported by a mutagenic mode of action (i.e., not a default). • Similar unit risk estimates derived using rat bioassay and mechanistic data on nasal cancers.	• NPC is a very rare cancer. This study followed more than 25,000 workers for over 40 years and observed a statistically significant increase in RR associated with the highest category of average exposure intensity, however, only 10 cases occurred. The small number of deaths creates uncertainties for the dose-response modeling (borderline model fit for cumulative exposure including exposed and unexposed person-years, $p = 0.07$). • Uncertainty about optimal exposure metric(s). Cumulative exposure is the standard metric used for unit risk estimates. Use of cumulative exposure assumes equal importance of concentration and duration on cancer incidence; yet, associations with peak exposure in epidemiological studies and the nonlinear shape of the dose-response from animal bioassays suggests greater influence of concentration. • Although statistically significant increases in risk for NPC were reported by multiple studies for several metrics of exposure (duration, cumulative, time since first exposure, peak), the relationship with cumulative exposure in the study used for IUR derivation was less precise (p-trend = 0.07 based on the regression coefficient for the continuous model). • Some uncertainty in the low-dose extrapolation is introduced based on the potential for endogenous formaldehyde to reduce the uptake of the inhaled gas at low doses, as demonstrated in modeling efforts by Schroeter et al. (2014) and Campbell Jr et al. (2020).

Based on the attendant strengths and uncertainties outlined above, there is **medium** confidence in the unit risk estimate for NPC incidence. The greatest uncertainty was related to the small number of cases that contributed to the statistical analysis and resulting imprecision in modeling the shape of the dose-response curve.

2.2.2. Derivation of a Myeloid Leukemia Unit Risk Estimate Based on Human Data

Choice of Epidemiology Study

Similar to the unit risk estimate for NPC, the estimate for myeloid leukemia is based on results from the latest follow-up of the NCI cohort of industrial workers exposed to formaldehyde (Beane Freeman et al., 2009), the largest (25,619 workers) of the three independent industrial worker cohort studies and the only one with sufficient individual exposure data for dose-response modeling. Beane Freeman et al. (2009) conducted dose-response analyses of 123 deaths attributed to leukemia and leukemia subtypes, as well as deaths from other LHP malignancies. As previously

described, this well-conducted study is the only one that used internal comparisons rather than standardized mortality ratios (reducing the impact of potential unmeasured confounding), and it included a detailed exposure assessment conducted for each worker based on exposure estimates for different jobs held and tasks performed (Stewart et al., 1986), and exposure estimates were made using several different metrics—peak exposure, average intensity, cumulative exposure, and duration of exposure.

For the LHP cancers, the strongest trends for the subtypes of interest were generally observed with the peak exposure metric (Beane Freeman et al., 2009). For myeloid leukemia, Beane Freeman et al. (2009) reported an increasing trend in mortality risk (p = 0.07 for all person-years) for peak exposure, but no trend was observed for cumulative exposure. For myeloid leukemia and other/unspecified leukemias combined, recognizing that a substantial proportion of the unspecified leukemias are probably myeloid leukemias, there was a nearly significant (log-linear) trend with cumulative exposure (p = 0.10 for all person-years) (personal communication from Laura Beane Freeman, NCI, to Jennifer Jinot, U.S. EPA, 21 February 2014). No exposure-response relationships were indicated for multiple myeloma for any of the exposure metrics.

Another study, Hauptmann et al. (2009), was a case-control study of LHP cancers, with exposure-response analyses, nested in the cohorts of "professional" workers (funeral industry workers, in this case) studied by Hayes et al. (1990) and Walrath and Fraumeni (1984, 1983). Hauptmann et al. (2009) estimated exposures for each case and control using multiple exposure metrics. Because of limitations in the exposure assessment, this study, while useful for hazard assessment, was not used by EPA to derive quantitative risk estimates. Of primary concern, the worker histories were obtained from surrogate responders (next of kin who had worked in the funeral home with the study subject and coworkers). This is a valid approach for general metrics such as 'ever embalming' or 'years of embalming', and statistically significant associations (for ever embalming) and trends (for years of embalming) were observed for myeloid leukemia. However, there is less confidence for more specific variables such as number and duration of embalmings per calendar period and frequency of spills per calendar period, variables that are needed in the study's exposure model to estimate cumulative exposure. For example, where information on a particular variable was obtained from multiple respondents, Hauptmann et al. (2009) reported a substantial amount of discordance for variables such as number of any embalmings and number of autopsied embalmings. Furthermore, considerable amounts of data were missing. For example, Hauptmann et al. (2009) reported that all but 16 of 44 cases of LHP cancer of nonlymphoid origin had 30% or more of their detailed work history missing. Thus, although the results of the Hauptmann et al. (2009) study were supportive of the hazard assessment, the uncertainty in the quantitative estimates of cumulative exposure was considered dissuasive for the development of quantitative cancer risk estimates.

Exposure-response Modeling of the National Cancer Institute Cohort

The NCI cohort study (Beane Freeman et al., 2009), was the only study with adequate data for exposure-response modeling; however, the derivation of a unit risk estimate for myeloid leukemia from these data is not straightforward, and several quantitative risk assessment approaches were considered. Beane Freeman et al. (2009) used log-linear Poisson regression models stratified by calendar year, age, sex, and race and adjusted for pay category (salary/wage/unknown) to estimate RRs for various categorical exposure groups (see Table 2-29). The NCI investigators used the low-exposure category as the reference category to "minimize the impact of any unmeasured confounding variables since nonexposed workers may differ from exposed workers with respect to socioeconomic characteristics" (Hauptmann et al., 2004). A 2-year lag interval was used to determine exposures to account for a latency period for LHP cancers.

The log-linear trend tests conducted by Beane Freeman et al. (2009) used exposure as a continuous variable (except for peak exposure, for which categorical ranks were used) (general model form: $RR = e^{\beta X}$, where β represents the regression coefficient and X is exposure). As shown by Callas et al. (1998), the Poisson regression model converges to the Cox proportional hazards model as the age strata are made infinitely small, and when age is well characterized and adjusted for, as it was in the Beane Freeman et al. (2009) Poisson regression model, these two models yield essentially the same RR point estimates and CIs.

Dr. Beane Freeman provided EPA with the regression coefficient estimates from the log-linear trend test models for cumulative exposure for several LHP cancer subtype groupings. These estimates are presented in Table 2-30. As with the NPC calculations, the nonexposed person-years were included in the primary unit risk estimate derivations and other quantitative approaches to be more inclusive of all the exposure-response data. Results for the exposed person-years only are presented for some of the unit risk estimates for comparison.

Table 2-29. Relative risk estimates for mortality from multiple myeloma (ICD-8 code 203), leukemia (ICD-8 codes 204–207), myeloid leukemia (ICD-8 code 205), and other/unspecified leukemia (ICD-8 code 207) by level of formaldehyde exposure for different exposure metrics

Cancer type	Relative risk (number of deaths)				*p*-Trend	
					All person-years[a]	Exposed only[b]
Peak exposure (ppm)						
	0	>0 to <2.0[c]	2.0 to <4.0	≥4.0		
Multiple myeloma	2.74 (11)	1.0 (14)	1.65 (13)	2.04 (21)	>0.50	0.08
Leukemia	0.59 (7)	1.0 (41)	0.98 (27)	1.42 (48)	0.02	0.12
Myeloid leukemia	0.82 (4)	1.0 (14)	1.30 (11)	1.78 (19)	0.07	0.13

Cancer type	Relative risk (number of deaths)				*p*-Trend	
					All person-years[a]	Exposed only[b]
Other/unspecified leukemia	0.61 (2)	1.0 (13)	0.86 (8)	1.15 (13)	0.50	>0.50
Average Intensity (ppm)						
	0	**>0 to <0.5[c]**	**0.5 to <1.0**	**≥1.0**		
Multiple myeloma	2.18 (11)	1.0 (25)	1.40 (11)	1.49 (12)	>0.50	>0.50
Leukemia	0.54 (7)	1.0 (67)	1.13 (25)	1.10 (24)	0.50	>0.50
Myeloid leukemia	0.70 (4)	1.0 (24)	1.21 (9)	1.61 (11)	0.40	0.43
Other/unspecified leukemia	0.58 (2)	1.0 (21)	0.98 (7)	0.84 (6)	>0.50	>0.50
Cumulative Exposure (ppm × years)						
	0	**>0 to <1.5[c]**	**1.5 to <5.5**	**≥5.5**		
Multiple myeloma	1.79 (11)	1.0 (28)	0.46 (5)	1.28 (15)	>0.50	>0.50
Leukemia	0.53 (7)	1.0 (63)	0.96 (24)	1.11 (29)	0.08	0.12
Myeloid leukemia	0.61 (4)	1.0 (26)	0.82 (8)	1.02 (10)	0.44	>0.50
Other/unspecified leukemia	0.77 (2)	1.0 (15)	1.65 (10)	1.44 (9)	0.13	0.15

[a]Likelihood ratio test (1 degree of freedom) of zero slope for formaldehyde exposure (continuous variable, except for peak exposure metric) among all (nonexposed and exposed) person-years.
[b]Likelihood ratio test (1 degree of freedom) of zero slope for formaldehyde exposure (continuous variable, except for peak exposure metric) among exposed person-years only.
[c]Reference category for all categories with the same exposure metric.
Source: Beane Freeman et al. (2009)

Table 2-30. Regression coefficients for leukemia, myeloid leukemia, and myeloid plus other/unspecified leukemias mortality from NCI trend test models of cumulative exposure[a]

Cancer type	Person-years	β (per ppm × years)	Standard error (per ppm × years)
Leukemia	All	0.01246	0.006421
	Exposed only	0.01131	0.00661
Myeloid leukemia	All	0.009908	0.01191
	Exposed only	0.008182	0.01249
Myeloid leukemia plus other/unspecified leukemia[b]	All	0.01408	0.007706
	Exposed only	0.01315	0.007914

[a]Models were stratified by calendar year, age, sex, and race and adjusted for pay category; exposures included a 2-year lag interval.
[b]*p*-trend values for the myeloid and other/unspecified leukemia categories combined are 0.10 for all person-years and 0.13 for exposed person-years only.
Source: Personal communications from Laura Beane Freeman to John Whalan (August 26, 2009) and to Jennifer Jinot (February 21, 2014).

Approaches Used for Quantitative Risk Assessment of Myeloid Leukemia

As discussed above, cumulative exposure, which incorporates both exposure intensity and duration, is the preferred exposure metric for the evaluation of long-term exposure to chemicals and effects on cancer, and it is the exposure metric of choice for the estimation of cancer risks in this assessment. EPA explored several approaches for deriving a unit risk estimate for myeloid leukemia based on cumulative exposure.

EPA considered a standard approach for deriving the unit risk estimate using the regression coefficient for myeloid leukemia and cumulative exposure; however, the *p*-value (0.44) for that regression coefficient was far from 0.05, indicating a poor model fit. The poor model fit could be due, at least in part, to inadequate statistical power, likely exacerbated by the underreporting of myeloid leukemia deaths suggested by the analyses by Percy et al. (1990; 1981). Table 2-30 shows that the regression coefficient for all person-years for myeloid leukemia is only slightly lower than that for all leukemia, which had a lower *p*-value of 0.08 and which should include all the myeloid leukemia deaths, both specified and unspecified. The "other/unspecified" leukemias comprise a sizable portion of all leukemia deaths (almost 30%) in the cohort and presumably include a good proportion of unclassified myeloid leukemias. The results of two NCI studies done at different times to evaluate the accuracy of death certificates by comparing the underlying cause of death on death certificates to original hospital diagnoses suggest that a third to a half of leukemias not otherwise specified on death certificates were diagnosed as myeloid leukemias in the hospital (Percy et al., 1990; Percy et al., 1981).[53] Thus, two additional approaches for deriving a unit risk estimate for myeloid leukemia, which attempted to address the underreporting of myeloid leukemias, were considered.

One approach involved using the all leukemia grouping.[54] Use of the all leukemia background rates in the life-table calculations (described in more detail below) might inflate the

[53]In the Percy et al. (1990; 1981) studies, only about 10% of leukemia deaths were classified as "other or unspecified" based on hospital diagnoses [versus 29% from death certificates in the Beane Freeman et al. (2009) study], and 51% (Percy et al., 1981) and 53% (Percy et al., 1990) of leukemia deaths were myeloid leukemias based on hospital diagnoses [versus 39% from death certificates in the Beane Freeman et al. (2009) study], suggesting that about a third or more of the "other or unspecified" leukemia deaths in the Beane Freeman et al. (2009) study were probably myeloid leukemias. Percy et al. (1990) reported in their study that "Of the nearly 600 deaths from leukemia NOS [other or unspecified] nearly 50% were originally diagnosed as myeloid... Obviously myeloid leukemia is grossly underreported on death certificates."
[54]The all leukemia category includes all 123 leukemias observed in the cohort. Of these, 48 (39.0%) were myeloid, 37 (30.1%) were lymphoid, and 36 (29.3%) were other/unspecified; the remaining 2 (1.6%) were monocytic leukemias (ICD-8 code 206).

unit risk estimate by increasing the background risk relative to which the formaldehyde-related risks are calculated. However, the inclusion of any leukemia subtypes not related to formaldehyde exposure should theoretically dampen the exposure-response relationship (lowering the regression coefficient) relative to that for all the myeloid leukemias alone; thus, this should mitigate at least some of the effect of using the all leukemia background rates.

The preferred approach involved using a combined grouping of the myeloid leukemia and other/unspecified leukemias subcategories. The myeloid and other/unspecified leukemias grouping had a stronger association with cumulative exposure (p-trend = 0.10 for all person-years) in the Beane Freeman et al. (2009) study than did myeloid leukemia alone and it captures the unclassified myeloid leukemias with the least inclusion of nonmyeloid leukemias. There is likely more uncertainty associated with the background rates for the other/unspecified leukemias than for the specified myeloid and lymphocytic leukemia subtypes (discussed further below); however, the benefits of focusing on the myeloid plus other/unspecified leukemias rather than the broader "all leukemias" grouping in attempting to be more inclusive of all the myeloid leukemias were deemed to outweigh any additional uncertainty associated with the background rates.

Although the unit risk estimate based on the preferred approach of using myeloid plus other/unspecified leukemias inevitably includes some nonmyeloid leukemias, it is considered the best approach for deriving a unit risk estimate for myeloid leukemia specifically.[55] Results for all the approaches will be presented for comparison, and it will be apparent that the different approaches yield similar unit risk estimates. Because the purpose in presenting the results from the various approaches is to compare relative quantitative differences across the different approaches, not all the sensitivity analyses that would be presented in a final assessment were performed for each approach (e.g., performing comparison analyses based on exposed person-years only).

Prediction of Lifetime Extra Risk of Myeloid Leukemia Mortality and Incidence

Lifetime extra risk estimates for myeloid leukemia mortality were calculated from the regression results using the different approaches discussed above and the same general methodology described for the NPC mortality estimates. U.S. age-specific 2006 all-cause mortality rates (NCHS, 2009) were used in the life-table programs. For the cause-specific background mortality rates, NCHS age-specific 2006–2010 mortality rates for all race and sex groups combined were used for all leukemia

[55]Although the inclusion of cancer subtypes not necessarily causally associated with the chemical exposure in the grouping of cancers represented in the regression coefficient and the corresponding background rates for the life-table analysis is overt here, it is not uncommon that, due to data limitations, unit risk estimates based on human data reflect cancer groupings broader than what might be strictly causally associated with the chemical exposure (e.g., all leukemias, or all lung cancers). As noted in the text, any inclusion of unassociated cancer subtypes in the derivation of the regression coefficient should theoretically attenuate the coefficient in a manner that would offset the use of the unassociated subtypes in the background rates in the life-table analysis.

(http://seer.cancer.gov/csr/1975_2010/results_merged/sect_13_leukemia.pdf) and NCHS (2006) age-specific mortality rates were used for myeloid leukemia (ICD-10 C92) and for other/unspecified leukemias (C94-C95) (NCHS, 2006). In addition, a 2-year lag period was used, as selected by Beane Freeman et al. (2009).

The resulting point estimates and one-sided 95% UCLs for the extra risk of myeloid plus other/unspecified leukemias are shown in Table 2-31. The model predicts extra risk estimates that are fairly linear for exposures below about 0.01–0.1 ppm (0.012-0.123 mg/m^3) but not for exposures above 0.1 ppm (0.123 mg/m^3).

Table 2-31. Extra risk estimates for myeloid plus other/unspecified leukemia mortality from various levels of continuous lifetime exposure to formaldehyde

Exposure concentration (ppm[a])	Extra risk	95% UCL on extra risk
0.0001	1.32×10^{-6}	2.51×10^{-6}
0.001	1.32×10^{-5}	2.51×10^{-5}
0.01	1.34×10^{-4}	2.58×10^{-4}
0.1	1.59×10^{-3}	3.38×10^{-3}
1	8.40×10^{-2}	6.26×10^{-1}
10	9.81×10^{-1}	9.90×10^{-1}

[a]Values used in the derivation of the unit risk estimate are presented in ppm throughout this section. To convert from ppm to mg/m^3, 1ppm = 1.23 mg/m^3.

Although the background mortality rates of leukemia are higher (lifetime risk of 0.0062 according to the life-table analysis) than those of NPC, the 1% extra risk level typically used as the basis for the POD for epidemiological data still corresponds to an RR estimate (2.5) that would be above the highest categorical result reported, even after adjusting the RR estimates upward relative to the 0-exposure group (because our primary analyses include the nonexposed workers). A 0.5% extra risk level yields an RR estimate of 1.8, which better corresponds to the RRs in the range of the data. Thus, the LEC value corresponding to 0.5% extra risk (LEC_{005}) was selected for the POD for all leukemia and for myeloid leukemia and myeloid plus other/unspecified leukemias, which have lower background rates than all leukemia (lifetime risks of 0.0031 and 0.0046, respectively).

There are insufficient data to establish the MOA(s) for formaldehyde-induced myeloid leukemia; thus, linear low-dose extrapolation was performed as the default approach, in accordance with EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a). The EC_{005}, LEC_{005}, and IUR estimates for myeloid plus other/unspecified leukemia mortality are presented in Table 2-32.

Table 2-32. EC_{005}, LEC_{005}, and inhalation unit risk estimates for myeloid plus other/unspecified leukemia mortality from formaldehyde exposure based on log-linear trend analyses of cumulative exposure data from the Beane Freeman et al. (2009) study

Person-years	EC_{005} (ppm)	LEC_{005} (ppm)	Unit risk[a] (per ppm)	Unit risk (per mg/m^3)
All	0.253	0.133	3.8×10^{-2}	3.1×10^{-2}
Exposed only	0.269	0.135	3.7×10^{-2}	3.0×10^{-2}

[a]Unit risk = $0.005/LEC_{005}$.

All leukemia and myeloid leukemia have substantial survival rates[56]; thus, it is preferable to derive incidence estimates. Unit risk estimates for leukemia incidences were calculated as described above for the NPC incidence estimates. Age-specific background incidence rates for 2006–2010 for leukemia and its major subtypes (myeloid and lymphocytic leukemia) from Surveillance, Epidemiology, and End Results (SEER) 18, a registry covering about 28% of the U.S. population, were obtained from the SEER website (http://seer.cancer.gov/csr/1975_2010/results_merged/sect_13_leukemia.pdf). Age-specific background incidence rates for other/unspecified leukemias were estimated by subtracting the myeloid and lymphocytic leukemia rates from the rates for all leukemia; these estimated rates would also include monocytic leukemia, but the contribution of monocytic leukemia is negligible.

The incidence-based calculation relies on the assumptions that incidence and mortality for these leukemia subtype groupings have the same exposure-response relationship for formaldehyde exposure and that the incidence data are for first occurrences of the cancers or that relapses provide a negligible contribution. The first assumption is more uncertain for all leukemia, myeloid leukemia, and myeloid plus other/unspecified leukemias than it was for NPC because these are groupings of subtypes with quite different survival rates (e.g., see footnote 53). The incidence-based calculation also takes advantage of the fact that incidence rates for these cancer types are negligible compared with the all-cause mortality rates and thus no special adjustment to the population at risk to account for live individuals who have been diagnosed with these cancers is necessary.

The EC_{005}, LEC_{005}, and IUR estimates for myeloid plus other/unspecified leukemia incidence are presented in Table 2-33. The incidence unit risk estimate is about 10% higher than the mortality estimate. This difference is lower than the ~24% increase that would have been seen for specified myeloid leukemias alone (i.e., ICD-8 205). This is because the difference between age-specific mortality and incidence rates for the other/unspecified leukemias is not very large, and for

[56]Survival rates were 55.0% at 5 years for all leukemia [http://seer.cancer.gov/statfacts/html/leuks.html], 23.4% at 5 years for acute myeloid leukemia [http://seer.cancer.gov/statfacts/html/amyl.html], and 59.1% at 5 years for chronic myeloid leukemia [http://seer.cancer.gov/statfacts/html/cmyl.html] based on 2002–2009 SEER data.

some age groups the mortality rates are actually larger than the incidence rates. This irregularity is to be expected for "other/unspecified" classifications because greater attention is given to diagnosing incident leukemia cases than to accounting for causes of death, so one would anticipate less underreporting of myeloid leukemias as incident cases than as causes of death on death certificates.

Table 2-33. EC_{005}, LEC_{005}, and inhalation unit risk estimates for myeloid plus other/unspecified leukemia incidence from formaldehyde exposure based on Beane Freeman et al. (2009) log-linear trend analyses for cumulative exposure

Person-years	EC_{005} (ppm)	LEC_{005} (ppm)	Unit risk[a] (per ppm)	Unit risk (per mg/m^3)
All	0.224	0.118	4.2×10^{-2}	3.4×10^{-2}
Exposed only	0.239	0.120	4.2×10^{-2}	3.4×10^{-2}

[a]Unit risk = $0.005/LEC_{005}$.

The EC_{005} and LEC_{005} estimates for mortality and incidence and incidence unit risk estimates for all leukemia and for myeloid leukemia using the alternate approaches discussed above are presented in Table 2-34. The same underlying life-table methodology was used for each of these approaches—only the regression coefficients and background cancer rates differed. As discussed above, and consistent with the results just presented, the preferred approach (shaded in Table 2-33 to 2-35) is the life-table analysis using the regression coefficient and background rates for myeloid plus other/unspecified leukemias because this grouping captures the unclassified myeloid leukemias with the least inclusion of nonmyeloid leukemias.

Table 2-34. EC_{005} and LEC_{005} estimates for mortality and incidence and incidence unit risk estimates for all leukemia and for myeloid leukemia using alternate approaches (all person-years)

Approach (by cancer type used as basis for regression coefficient and cause-specific background rates)	EC_{005} (ppm) LEC_{005} (ppm)		Unit risk estimate (per ppm)[a]	Unit risk estimate (per mg/m^3)
	Incidence	Mortality	(Incidence)	(Incidence)
Myeloid leukemia	0.378 0.127	0.468 0.157	3.9×10^{-2}	3.2×10^{-2}
All leukemia	0.156 0.0846	0.229 0.124	5.9×10^{-2}	4.8×10^{-2}
Myeloid + Other/Unspecified[b]	**0.224 0.118**	**0.253 0.133**	**4.2×10^{-2}**	**3.4×10^{-2}**

Note: Shaded estimate is preferred.
[a]Unit risk estimate = $0.005/(LEC_{005}$ for incidence).
[b]Incidence background rates also include monocytic leukemia, but that contribution is negligible.

The preferred unit risk estimate for myeloid leukemia is the estimate of **4.2×10^{-2} per ppm (3.4×10^{-2} per mg/m^3)** derived using incidence rates (and regression coefficient) for myeloid plus other/unspecified leukemias, for all (exposed and nonexposed) person-years.[57] The results from the exposed person-years only are essentially indistinguishable (see Table 2-33). The unit risk estimates from the other approaches considered are fairly close, with the unit risk estimate based on the myeloid leukemia category being virtually identical to the preferred estimate based on myeloid plus other/unspecified leukemias and the estimate based on all leukemia being somewhat greater (see Table 2-34).

Table 2-35 summarizes some of the key information comparing the different approaches considered for the derivation of the unit risk estimate for myeloid leukemia.

Table 2-35. Exposure-response modeling (all person-years) and (incidence) unit risk estimate derivation results for different leukemia groupings

Cancer grouping	Number of deaths in NCI cohort	Regression coefficient (per ppm × year)	SE (per ppm × year)	*p*-Value	Unit risk estimate (per ppm)	Unit risk estimate (per mg/m^3)
Myeloid leukemia	48	0.009908	0.01191	0.44	3.9×10^{-2}	3.2×10^{-2}
All leukemia	123	0.01246	0.006421	0.08	5.9×10^{-2}	4.8×10^{-2}
Myeloid + Other/Unspecified leukemias	**84[a]**	**0.01408**	**0.007706**	**0.10**	**4.2×10^{-2}**	**3.4×10^{-2}**

Note: Shaded estimate is preferred.

[a]This is the sum of the leukemias classified as myeloid and those classified as "other/unspecified". At least 70–80% of this number is expected to be myeloid leukemias, assuming that a third to a half of leukemias not otherwise specified on death certificates are myeloid leukemias, as discussed above.

In summary, as discussed above, EPA explored several approaches for deriving a unit risk estimate for myeloid leukemia based on cumulative exposure. The first approach involved using the grouping of leukemias classified as myeloid leukemia on the death certificate. The regression coefficient for this grouping had a *p*-value (0.44) indicative of a poor model fit. It was reasoned that

[57]Comparable to calculations done for NPC above, a rough calculation was done to ensure that the unit risk estimate derived for myeloid leukemia incidence is not implausible in comparison to actual case numbers. For example, assuming an average constant lifetime formaldehyde exposure level of 20 ppb for the U.S. population, the inhalation unit risk estimate for myeloid (and other/unspecified) leukemia equates to a lifetime extra risk estimate of 8.4×10^{-4}. Assuming an average lifetime of 75 years (this is not EPA's default average lifetime of 70 years, but rather a value more representative of actual demographic data) and a U.S. population of 300,000,000, this lifetime extra risk estimate suggests a crude upper-bound estimate of 3,400 incident cases of myeloid leukemia attributable to formaldehyde exposure per year. This upper-bound estimate is well below the estimated 17,100 total incident myeloid leukemia (not including other/unspecified leukemias) cases per year calculated from the SEER myeloid leukemia incidence rate of 5.7/100,000 (age-adjusted incidence rate for AML and CML combined from 2008-2012 SEER-18 data; www.seer.cancer.gov).

the poor model fit could be due, at least in part, to the underreporting of myeloid leukemia deaths discussed above. It can be seen in Table 2-35 that the regression coefficient for myeloid leukemia is only slightly lower than that for all leukemia, which had a lower *p*-value of 0.08 and should include all the myeloid leukemia deaths, both specified and unspecified. Thus, a second approach involved using the all leukemia grouping, which includes other subtypes likely not associated with formaldehyde exposure. The preferred approach involved using the combined grouping of the myeloid leukemia and other/unspecified leukemias subcategories. The myeloid and other/unspecified leukemias grouping had a stronger association with cumulative exposure ($p = 0.10$) in the Beane Freeman et al. (2009) study than did myeloid leukemia alone and it captures the unclassified myeloid leukemias with the least inclusion of nonmyeloid leukemias. The benefits of focusing on the myeloid plus other/unspecified leukemias rather than the broader "all leukemia" grouping in attempting to be more inclusive of all the myeloid leukemias were deemed to outweigh any additional uncertainty associated with the background rates for the other/unspecified leukemias (discussed further below). It is reassuring that the unit risk estimates from the three different approaches are quite similar, with the preferred estimate based on myeloid plus other/unspecified leukemias being essentially identical to the estimate based on the myeloid leukemia category and both those estimates being about two-thirds of the estimate for all leukemia.

Uncertainties and Confidence in the Preferred Unit Risk Estimate for Myeloid Leukemia

The strengths and uncertainties in the unit risk estimate for myeloid leukemia incidence are summarized in Table 2-36. The primary uncertainty in this estimate relates to the complexities in the study-specific data for cumulative formaldehyde exposure and mortality from myeloid leukemia.

Table 2-36. Strengths and uncertainties in the cancer type-specific unit risk estimate for myeloid leukemia

Strengths	Uncertainties
• IUR estimated from data that is directly relevant to humans. • Based on the results of a large, *high* confidence epidemiological study involving multiple industries with detailed, individual cumulative exposure estimates and allowance for cancer latency.	• Uncertainties with a potentially greater impact: o Although the dose-response relationship with peak exposure was marginally significant (p = 0.07), and statistically significant associations were reported for several metrics of exposure in other studies, the reported relationship with cumulative exposure showed a nonsignificant, small increase in risk for myeloid leukemia (based on the regression coefficient for the continuous model), potentially due in part to misclassification of myeloid leukemia cases. o The association with cumulative exposure was stronger for the other/unspecified grouping of leukemia diagnoses (*N* = 36) than for myeloid leukemia alone (*N* = 48). Although a sizable proportion of this category is assumed to include myeloid leukemia cases, the stronger association is surprising given the more heterogeneous set of leukemia cases in this category, some presumably not associated with formaldehyde exposure. Hence, the association would be expected to be attenuated.

Strengths	Uncertainties
• Moderate number of deaths to model (*N* = 84).	o Uncertainty about optimal exposure metric(s). Use of cumulative exposure assumes equal importance of concentration and duration on cancer incidence. The specific metrics analyzed differed across studies, and the results of the NCI study were not completely consistent with those of other studies (associated only with peak exposure). o Uncertainties likely to have a minor impact: o Grouping of myeloid leukemias used for exposure-response modeling includes nonmyeloid leukemias. o Borderline model fit for myeloid plus other/unspecified leukemias (p = 0.1) and uncertain shape of exposure-response function.

Based on the attendant strengths and uncertainties outlined above, there is **low** confidence in the unit risk estimate for myeloid leukemia incidence. However, given the strength of the evidence integration judgment (i.e., **evidence demonstrates** formaldehyde inhalation causes myeloid leukemia in humans), and the associated public health burden that it poses (e.g., myeloid leukemia is far more prevalent than NPC), EPA thoroughly considered the complexity in the data and used an innovative approach to derive and present a potential unit risk estimate for myeloid leukemia. A charge question will be provided for the peer-review panel regarding the development of a unit risk estimate for myeloid leukemia and asking for advice about how, if at all, the unit risk estimate might inform the quantification of risk for cancer. This uncertainty is discussed further in the summary section below.

2.2.3. Summary of Unit Risk Estimates and the Preferred Estimate for Inhalation Unit Risk

Table 2-37. Inhalation unit risk estimates by cancer type based on human data[a]

Cancer subtype	Unit risk estimate (per ppm)		Unit risk estimate (per mg/m^3)	
	Mortality	Incidence	Mortality	Incidence
Nasopharyngeal	4.5×10^{-3}	9.1×10^{-3}	3.7×10^{-3}	7.4×10^{-3}
Myeloid leukemia[b]	3.8×10^{-2}	4.2×10^{-2}	3.1×10^{-2}	3.4×10^{-2}

[a]Based on entire cohort (exposed and unexposed).
[b]Based on myeloid plus other/unspecified leukemias.

The unit risk estimates for NPC and myeloid leukemia derived using data from the NCI occupational cohort are summarized in Table 2-37. As discussed previously, the NPC unit risk estimate based on data from the human occupational epidemiology study of the NCI updated by Beane Freeman et al. (2013) was preferred over estimates based on rodent cancer bioassay data, although these estimates were very similar (Table 2-27). The best estimate that could be

developed for myeloid leukemia was also derived from the human occupational epidemiology study of the NCI updated by Beane Freeman et al. (2009). However, the data reported for myeloid leukemia (Beane Freeman et al., 2009) are complex and there are reasons for and against the use of these data in the derivation of the IUR. Given the the strength of the evidence integration judgment (i.e., **evidence demonstrates** formaldehyde inhalation causes myeloid leukemia in humans), and the associated public health burden that it poses (e.g., myeloid leukemia is far more prevalent than NPC), EPA thoroughly considered the complexity in the data and used an innovative approach to derive and present a potential unit risk estimate for myeloid leukemia. Some important uncertainties are discussed in greater detail below.

- Despite the quality of the literature base for the formaldehyde assessment and the confidence in the qualitative hazard information for myeloid leukemia, the only study suitable for dose-response quantification for myeloid leukemia may be viewed as insufficient for developing a quantitative estimate of risk with an acceptable level of confidence.

    - The Beane Freeman study (2009) failed to observe an association between cumulative formaldehyde exposure and myeloid leukemia (p = 0.44), despite a reasonable number of cases (n = 48) and adequate follow-up. The peak exposure metric was marginally associated (p = 0.07). This result raises questions about the relative importance of the intensity of exposure and duration in the association of myeloid leukemia mortality. On the other hand, myeloid leukemia mortality increased with TSFE, cumulative exposure, and exposure duration in two other occupational cohorts (garment workers and embalmers).

    - The available animal studies do not provide evidence supporting an association between formaldehyde inhalation and myeloid leukemia. Thus, there are no animal data that can be used to support the POD estimate that can be derived from the only suitable human study.

- Analyses from NCI comparing causes of death recorded on death certificates with original diagnoses in hospital records suggest a misclassification of myeloid leukemia cases (N = 48), with a significant proportion reported as "other/unspecified" (N = 36).

    - In the Percy et al. (1990; 1981) studies, only about 10% of leukemia deaths were classified as "other or unspecified" based on hospital diagnoses [versus 29% from death certificates in the Beane Freeman et al. (2009) study], and 51% (Percy et al., 1981) and 53% (Percy et al., 1990) of leukemia deaths were myeloid leukemias based on hospital diagnoses [versus 39% from death certificates in the Beane Freeman et al. (2009) study], suggesting that about a third or more of the "other or unspecified" leukemia deaths in the Beane Freeman et al. (2009) study were probably myeloid leukemias. Percy et al. (1990) reported in their study that "Of the nearly 600 deaths from leukemia NOS (other or unspecified) nearly 50% were originally diagnosed as myeloid... Obviously myeloid leukemia is grossly underreported on death certificates."

- Because it is likely that a proportion of myeloid leukemia cases were reported as "other/unspecified," a more complete estimate of the association of cumulative formaldehyde exposure with myeloid leukemia might be obtained using the regression results for a combination of myeloid leukemia and other/unspecified leukemia.

- Although a unit risk estimate that combines myeloid leukemia and other/unspecified leukemia overtly includes cancer subtypes not necessarily causally related with the chemical exposure, it is sometimes the case that, due to data limitations, unit risk estimates are based on less directly causal groupings (e.g., all leukemias, or all lung cancers). The inclusion of unassociated cancer subtypes in the derivation of the regression coefficient should theoretically attenuate the association.

- A comparison of the unit risk estimates for all leukemia, myeloid leukemia plus other unspecified leukemia, and myeloid leukemia (ICD-8/9: 205) indicates that all of the estimates are within a factor of 1.5. Unit risk estimates were 3.9×10^{-2}, 4.2×10^{-2}, and 5.9×10^{-2} for all leukemia, myeloid leukemia plus other unspecified leukemia, and myeloid leukemia (ICD-8/9: 205), respectively.

- The approach for combining myeloid leukemia and other/unspecified leukemia to estimate risk, while arguably consistent with the identified misclassification of myeloid leukemia on death certificates (Percy et al., 1990; Percy et al., 1981), is uncommon but retains significant quantitative uncertainties, including some inconsistencies in statistical results.

  - The combination of myeloid leukemia and other/unspecified leukemia in the regression model yields a *p*-value of 0.1. While the number of cases is increased by $n = 36$, cancers in this category, with the exception of the myeloid leukemia cases, were not identified to be causally related with formaldehyde exposure during the hazard evaluation. The inclusion of cancers not causally related with formaldehyde exposure would be expected to attenuate the association, but in contrast to this expectation, there was a stronger association for the regression model of other/unspecified leukemia alone ($p = 0.13$) compared to the model of myeloid leukemia alone ($p = 0.44$). There is not a clear explanation for why the association would be stronger for the more heterogeneous leukemia category.

  - There is likely more uncertainty associated with the background cancer rates in the U.S. population for the other/unspecified leukemias than for the specified myeloid and lymphocytic leukemia subtypes. The survival rates of the other/unspecified cancers had to be estimated by subtracting myeloid and lymphocytic leukemia rates from the rates for all leukemia.

- Given the completely unknown MOA for myeloid leukemia, it is possible, and perhaps likely, that there are dose and duration effects for the development of myeloid leukemia following formaldehyde inhalation that are not fully understood.

  - Acknowledging the complexity of the different dose metrics available in the observational studies, as well as the lack of an association between cumulative exposure and myeloid leukemia in the Beane Freeman study (2009), it is possible that the specific, individual exposure metrics in this study failed to fully capture the

patterns of exposure with which the development of myeloid leukemia is causally related. Importantly, this concern is independent of the identified hazard for myeloid leukemia, as myeloid leukemia mortality was increased in association with the peak exposure metric in this study (industrial workers) and others, as well as with duration-dependent metrics including TSFE, cumulative exposure, and exposure duration in two other occupational cohorts (garment workers and embalmers).

- As information supporting a nonlinear extrapolation from the identified POD is not available for myeloid leukemia, the current approach uses a default linear extrapolation. It is possible that additional study on the development of this cancer after formaldehyde exposure could provide support for the linear extrapolation or, alternatively, support a nonlinear approach.

2.2.4. Adjustment of Human-based Unit Risk Estimates for Potential Increased Early-life Susceptibility

When there is sufficient weight of evidence to conclude that a mutagenic MOA is operative in a chemical's carcinogenicity and there are inadequate chemical-specific data to assess age-specific susceptibility, as is the case for formaldehyde inhalation exposure-induced NPCs (see Section 1.2.5), EPA guidelines (U.S. EPA, 2005b) recommend the application of default age-dependent adjustment factors (ADAFs) to adjust for potential increased susceptibility from early-life exposure. In brief, the supplemental guidelines establishe ADAFs for three specific age groups. The current ADAFs and their age groupings are 10 for <2 years, 3 for 2 to <16 years, and 1 for 16 years and above (U.S. EPA, 2005b). For risk assessments based on specific exposure assessments, the 10-fold and three-fold adjustments to the unit risk estimates are to be combined with age-specific exposure estimates when estimating cancer risks from early-life (<16 years of age) exposure.

These ADAFs were formulated based on comparisons of the ratios of cancer potency estimates from juvenile-only exposures to cancer potency estimates from adult-only exposures from rodent bioassay data sets with appropriate exposure scenarios, and they are designed to be applied to cancer potency estimates derived from adult-only exposures. Thus, alternate life-table analyses were conducted for NPC to derive comparable adult-based unit risk estimates to which ADAFs would be applied to account for early-life exposure. In the NCI Poisson regression model, the RR estimates are adjusted for age, for the ages represented in the cohort. In deriving lifetime unit risk estimates, EPA generally extrapolates that relationship and assumes that RR is independent of age for all ages, for application of the RR exposure-response model across the full age range (0–85 years) considered in the life-table analysis. For the alternate life-table analyses, it was assumed that RR is independent of age for adults, which represent the lifestage for which the exposure-response data and the Poisson regression modeling results from the NCI cohort study specifically pertain, but that there is increased early-life susceptibility, based on the weight of evidence-based conclusion that formaldehyde carcinogenicity for NPC has a mutagenic MOA (see

Section 1.2.5), which supersedes the more general assumption that RR is independent of age for all ages including children.

In the alternate analyses, exposure in the lifetable was taken to start at age 16 years, the age cut-point that was established in EPA's supplemental guidelines (U.S. EPA, 2005b), to derive an adult-exposure-only unit risk estimate. The adult-exposure-only unit risk estimate, when rescaled as described below, yields an adult-based unit risk estimate that is comparable to the unit risk estimate calculated from a typical (i.e., with adult exposures only) rodent bioassay and to which ADAFs can be applied in the standard way to account for early-life exposure.[58] Other than the age at which exposure was initiated, the life-table analysis is identical to that conducted for the results presented in Section 2.2.1. Using this approach yields adult-exposure-only unit risk estimates of 3.15×10^{-3} per ppm (2.56×10^{-6} per μg/m^3) for NPC mortality and 6.09×10^{-3} per ppm (4.95×10^{-6} per μg/m^3) for NPC incidence; these results are about 70 and 67%, respectively, of the unit risk estimates derived for lifetime exposure under the assumption of age independence across all ages.

When EPA derives unit risk estimates from standard rodent bioassay data, there is a blurring of the distinction between lifetime and adult-only exposures because the relative amount of time that a rodent spends as a juvenile is negligible (e.g., 9 of 104 weeks <9%) compared to its lifespan. [According to the supplemental guidelines, puberty begins around 5–7 weeks of age in rats and around 4–6 weeks in mice (U.S. EPA, 2005b), and Sengupta (2013) suggests that adulthood in rats typically begins around postnatal day 63.] Thus, when exposure in a rodent is initiated at 5–8 weeks (most of the way through the juvenile period), as in the standard rodent bioassay, and the bioassay is terminated after 104 weeks of exposure, the unit risk estimate derived from the resulting cancer incidence data is considered a unit risk estimate from lifetime exposure, except when the ADAFs were formulated and are applied, in which case the same estimate is considered to reflect adult-only exposure. Yet, when adult exposures are considered in the application of ADAFs, the adult-exposure-only unit risk estimate is pro-rated over the full default human lifespan of 70 years, presumably because that is how adult exposures are treated when a unit risk estimate calculated in the same manner from the same bioassay exposure paradigm is taken as a lifetime unit risk estimate.

However, in humans, a greater proportion of time is spent in childhood (e.g., 16 of 70 years = 23%) (and for the purposes of unit risk estimates, exposure is considered to commence

[58]In this assessment, ***adult-exposure-only unit risk estimates*** refer to estimates derived from the life-table analysis assuming exposure only for ages ≥16 years. The adult-exposure-only unit risk estimates are merely intermediate values in the calculation of adult-based unit risk estimates and should not be used in any risk calculations. ***Adult-based unit risk estimates*** refer to estimates derived after rescaling the adult-exposure-only unit risk estimates to a (70-year) lifetime, as described later. The adult-based unit risk estimates are intended to be used in ADAF calculations (U.S. EPA, 2005b) for the computation of extra risk estimates for specific exposure scenarios. Note that the unit risk estimates in this section, which are derived under an assumption of increased early-life susceptibility, supersede those that were derived in Section 2.2.1 under the assumption that RR is independent of age.

at birth), and the distinction between lifetime exposure and adult-only exposure cannot be ignored when human data are used as the basis for the unit risk estimates. Thus, adult-exposure-only unit risk estimates were calculated distinct from the lifetime estimates that were derived in Section 2.2.1 under the assumption of age independence for all ages. In calculating the adult-exposure-only unit risk estimates, RR is assumed to be independent of age for adulthood. Next, the adult-exposure-only unit risk estimates need to be rescaled to a 70-year lifespan to be used in the ADAF calculations and risk estimate calculations involving less-than-lifetime exposure scenarios in the standard manner, which includes pro-rating even adult-based unit risk estimates over 70 years. Thus, the adult-exposure-only unit risk estimates are multiplied by 70/54 to rescale the 54-year adult period of the 70-year default lifespan to 70 years. Then, for example, if a risk estimate were calculated for a less-than-lifetime exposure scenario involving exposure only for the full adult period of 54 years, the rescaled unit risk estimate would be multiplied by 54/70 in the standard calculation and the adult-exposure-only unit risk estimate would be appropriately reproduced. Without rescaling the adult-exposure-only unit risk estimates, the example calculation just described for exposure only for the full adult period of 54 years would result in a risk estimate 77% (i.e., 54/70) of that obtained directly from the adult-exposure-only unit risk estimates, which would be illogical. The rescaled adult-based unit risk estimates for NPC mortality and incidence for use in ADAF calculations and risk estimate calculations involving less-than-lifetime exposure scenarios are presented in Table 2-38.

Table 2-38. Adult-based unit risk estimates for nasopharyngeal cancer for use in ADAF calculations and risk estimate calculations involving less-than-lifetime exposure scenarios

NPC response	Adult-based unit risk estimate	
	(per ppm)	(per μg/m^3)
Mortality	4.08×10^{-3}	3.31×10^{-6}
Incidence	7.90×10^{-3}	6.42×10^{-6}

An example calculation illustrating the application of the ADAFs to the human-data-derived adult-based (rescaled as discussed above) NPC (incidence) unit risk estimate for formaldehyde for a lifetime exposure scenario is presented below. For inhalation exposures, assuming ppm equivalence across age groups, i.e., equivalent risk from equivalent exposure levels, independent of body size, the ADAF calculation is fairly straightforward. Thus, the ADAF-adjusted lifetime NPC unit risk estimate is calculated as illustrated in Table 2-39.

Table 2-39. NPC incidence risk from exposure to constant formaldehyde exposure level of 1 μg/m³ from ages 0 to 70 years

Age group	ADAF	Unit risk (per μg/m³)	Concentration (μg/m³)	Duration adjustment	Partial risk[a]
0 to <2 years	10	6.42×10^{-6}	1	2 yr/70 yr	1.83×10^{-6}
2 to <16 years	3	6.42×10^{-6}	1	14 yr/70 yr	3.85×10^{-6}
≥16 years	1	6.42×10^{-6}	1	54 yr/70 yr	4.95×10^{-6}
				Total Lifetime (70 yr) Risk:	**1.06×10^{-5}**

[a]The partial risk for each age group is the product of the values in columns 2–5 [e.g., $10 \times (6.42 \times 10^{-6}) \times 1 \times 2/70 = 1.83 \times 10^{-6}$], and the total risk is the sum of the partial risks.

This 70-year risk estimate for a constant exposure of 1 μg/m³ is equivalent to a **lifetime unit risk estimate of 1.1×10^{-5} per μg/m³ (1.3×10^{-2} per ppm) for NPC incidence**, adjusted for potential increased early-life susceptibility, assuming a 70-year lifetime and constant exposure across age groups. Note that because of the use of the rescaled adult-based unit risk estimate, the partial risk for the ≥16 years' age group is the same as would be obtained for a 1 μg/m³ constant exposure directly from the adult-exposure-only unit risk estimate of 4.95×10^{-6} per μg/m³ that was presented above, as it should be. Recall that the adult-based unit risk estimate for NPC incidence for use in ADAF calculations and risk estimate calculations involving less-than-lifetime exposure scenarios is 6.42×10^{-6} per μg/m³ (7.90×10^{-3} per ppm).

In addition to the uncertainties discussed in Section 2.2.1 for the IUR estimates based on human data, there are uncertainties in the application of ADAFs to adjust for potential increased early-life susceptibility. The ADAFs reflect an expectation of increased risk from early-life exposure to carcinogens with a mutagenic MOA (U.S. EPA, 2005b), but they are general adjustment factors and are not specific to formaldehyde. Overall, the application of ADAFs to the NPC unit risk estimate could be overestimating or underestimating the true extent of any increased early-life susceptibility in the total cancer unit risk estimate, although the quantitative impact of this source of uncertainty is likely to be small.

2.2.5. Cancer Risk Based on Background Cancer Incidence and Internal Dose of Endogenous and Exogenous Formaldehyde

EPA has considered estimates derived by Swenberg et al. (2011) and Starr and Swenberg (2016) that are referred to by the authors as a "bottom-up" approach, to bound low-dose human cancer risks from formaldehyde exposure in a manner that only uses information regarding background incidence in the U.S. population of nasopharyngeal cancers (NPC), leukemia, and Hodgkin lymphoma; background (endogenous) metrics of internal formaldehyde dose in laboratory animals; and exogenous exposure to formaldehyde expressed in terms of an internal dose. The results in Starr and Swenberg (2016) are updates, based on newer data, to those presented earlier

in (Starr and Swenberg, 2013); however, the approach remains unchanged. Estimates using this approach are presented by the authors as providing a bounding "check" on risk estimates derived from high-dose data (Starr and Swenberg, 2013).

The data for the internal dose in these calculations were obtained from measurements in rats and monkeys of formaldehyde-induced DNA adducts experiments based on a highly sensitive mass spectrometry (MS) method using [$^{13}CD_2$]-formaldehyde (Yu et al., 2015a; Lu et al., 2011; Moeller et al., 2011; Lu et al., 2010a). The authors of these experiments conclude that their method can be used to distinguish whether formaldehyde-induced hydroxymethyl-DNA monoadducts, in particular the N^2-hydroxymethyl-dG (N2-hmdG) adduct, originate from endogenous or exogenous sources of formaldehyde. The experiments quantified these mono adducts formed from both sources in various tissues of rats and monkeys: nasal cavity, bone marrow, mononuclear WBCs, spleen, and thymus (rats); nasal cavity and bone marrow (monkeys). These adduct measurements and data on the background incidences of NPC, Hodgkin lymphoma, and leukemia in the U.S. population were then used (Starr and Swenberg, 2016) to develop cancer risk estimates by attributing all the background incidences to endogenous formaldehyde, using the measured endogenous N2-hmdG adducts formed by formaldehyde in specific tissues as a biomarker of exposure. Their risk model assumes a linear relation between cancer incidence and N2-hmdG adduct levels over the concentration range of endogenous adducts as well as in the low-exposure range for exogenous adducts.

Risk estimates from this approach are claimed by the authors to produce conservative upper bounds primarily on the grounds that: (a) the method attributes all of the background risks of specific cancers to endogenous formaldehyde (based on N2-hmdG adducts); (b) lower confidence bounds on measured adduct levels are used; and (c) a linear relation is assumed between cancer incidence and N2-hmdG adduct levels over the endogenous range as well as in the low-exposure range of interest for exogenous exposure.

Swenberg et al. (2011) and Starr and Swenberg (2016) then compared these values with the risk estimates in EPA's 2010 draft Toxicological Review, which were obtained by linearly extrapolating to lower doses from a POD (a lower bound on the concentration associated with the benchmark response) derived by dose-response modeling of the epidemiological data. When adduct data from rats were used, the estimates Swenberg and Starr estimated at 1 ppm (1.23 mg/m^3) exposure concentration were 2.67×10^{-4} for nasal cancer (based on Yu et al., 2015a) and were at most 12.6×10^{-4} for leukemia (based on the limit of detection, LOD, from Lu et al., 2010a), since no exogenous adducts were detected in bone marrow. In monkeys (Yu et al., 2015a), the Swenberg and Starr bottom-up estimates were 2.69×10^{-4} for NPC and were less than 1.24×10^{-6} for leukemia. In comparison, the EPA upper-bound risk estimates were higher than the adduct-based upper-bound estimates by 40-fold for NPC and at least 45-fold (rat adduct data) or over 45,000-fold (monkey adduct data) for leukemia.

There is considerable uncertainty in extrapolating downward from high-dose animal or occupational data, particularly in the case of a dose-response that is highly curvilinear; thus, an

approach that allows an upward linear extrapolation in lieu of the traditional downward extrapolation is appealing. The bottom-up approach uses cancer incidence in the general population and is independent of the tumor dose-response data (other than to identify the type of tumors of concern for analysis); therefore, it can potentially provide a perspective on the likely contribution of a specific MOA and on the uncertainty in risk estimates derived from higher dose data where other phenomena such as significant cytotoxicity and impact on DNA repair prior to mutations may be occurring.

An evaluation of this bottom-up approach identifies scenarios under which this approach will yield an underestimate of the total (endogenous plus exogenous) risk for a specific cancer type (Crump et al., 2014) (and elaborated further in Appendix B.2.3), leading EPA to conclude that the method does not necessarily provide an upper bound on the slope of the dose-response at low exogenous exposures. (Starr and Swenberg, 2013) note that the bottom-up approach is based on applying the concept of additivity to background disease processes (Crump et al., 1976). However, this concept of additivity to background only assumes local linearity in the proximity of zero exogenous dose to be reasonable, while the bottom-up approach assumes linearity over a large dose range; in particular, the bottom-up approach assumes a linear dose-response below zero exogenous dose, which is not required in the concept of additivity to background. As a result, it is unclear if, overall, the bottom-up approach results in a conservative bound on risk, given that extrapolation upwards in a sublinear dose-response would underestimate risk and underestimate the slope of the dose-response curve at higher doses. This is further discussed and illustrated in Crump et al. (2014). Furthermore, the bottom-up approach assumes direct interaction of inhaled formaldehyde with a particular target tissue; if other sites of interaction and mechanisms are involved, the measures of DNA adducts in a specific tissue could lead to underestimates of the cancer potency when utilizing the "bottom-up" approach. In view of these problems, the bottom-up approach is not carried forward in the candidate unit risks presented in this assessment.

2.2.6. Preferred Inhalation Unit Risk Estimate

The preferred IUR, summarized in Table 2-40, reflects the estimate for NPC incidence alone. The NPC unit risk estimates are based on the modeling results of the association of cumulative formaldehyde exposure with NPC mortality in an occupational cohort followed by the NCI (Beane Freeman et al., 2013). The regression coefficient from the exposure-response model (log-linear Poisson regression model) was applied to age-specific cancer incidence rates from the SEER database using life-table methods to estimate the POD from which to derive the (upper-bound) unit risk estimate. The IUR estimate is typically expressed as the (upper-bound) increase in cancer risk expected as a function of a change of 1 $\mu g/m^3$.

EPA has concluded that early-life exposure to chemicals that are carcinogenic through a mutagenic MOA might present a higher risk of cancer than exposure during adulthood (U.S. EPA, 2005b). In this document, it was determined that formaldehyde-induced carcinogenicity of the URT is attributable, at least in part, to a mutagenic MOA (see Section 1.2.5). Therefore, the cancer

unit risk estimate was adjusted by applying age-dependent adjustment factors (ADAFs). Table 2-40 can be used as a template for incorporating the ADAFs when addressing less-than-lifetime exposure scenarios. For exposure scenarios comprising primarily adult exposures, it may not be worth the additional complexity of calculating the ADAF-adjusted risk estimates, and one may choose to use the unadjusted cancer unit risk estimate presented in Table 2-40 with a "c" superscript, to calculate risk estimates in the standard way (i.e., without application of ADAFs).

Table 2-40. Inhalation unit risk[a, b]

Cancer type	Preferred unit risk estimate (ppm^{-1})	ADAF-adjusted unit risk estimate (ppm^{-1})	Preferred unit risk estimate $((\mu g/m^3)^{-1})$	ADAF-adjusted unit risk estimate $((\mu g/m^3)^{-1})$
Nasopharyngeal	0.0079[c]	0.013	6.4×10^{-6} [c]	1.1×10^{-5}

[a]The inhalation unit risk estimate is typically expressed as the (upper-bound) increase in cancer risk estimated for an exposure increase of 1 $\mu g/m^3$.
[b]The unit risk estimate is for cancer incidence.
[c]Adult-based (rescaled) unit risk estimate for NPC intended for the application of ADAFs.

Benchmark Response /Effective Concentration Estimates

For benefits analyses and certain other situations, "central" estimates of risk-per-unit dose may be preferred over (upper-bound) unit risk estimates. For nonlinear models, the POD-approach used by EPA for low-dose extrapolation, which is designed to distinguish between dose-response modeling in the observable range and inferences made about lower doses (U.S. EPA, 2005a) is not amenable to providing central estimates of risk at lower doses. Instead, the standard practice for IRIS assessments is to provide linear extrapolations of risk from the central estimate (here, the effective concentration [EC] estimate, which is the MLE of the exposure concentration associated with the benchmark response level of risk) corresponding to the POD, which is the lower bound on the EC (i.e., the LEC estimate). Table 2-41 presents estimates of risk-per-unit dose linearly extrapolated from the EC (i.e., BMR/EC estimates).

Table 2-41. Summary of BMR/EC estimates[a]

Cancer type	BMR/EC estimate (ppm^{-1})	ADAF-adjusted BMR/EC estimate[b] (ppm^{-1})	BMR/EC estimate $((\mu g/m^3)^{-1})$	ADAF-adjusted BMR/EC estimate[b] $((\mu g/m^3)^{-1})$
Nasopharyngeal	0.0046[c]	0.0076	3.7×10^{-6c}	6.2×10^{-6}

[a]The BMR/EC estimates based on a longitudinal occupational mortality study (Beane Freeman et al., 2013) are all for cancer incidence. The BMR is 0.0005 extra risk for NPC. The EC value is the exposure concentration associated with the BMR based on the Poisson regression model and life-table analysis (see Section 2.2.1). The

EC_{0005} for NPC was calculated from a life-table analysis of adult-exposure-only and then rescaled as discussed for the adult-based unit risk estimates in Section 2.2.4.

[b]See Section 2.2.4 for a discussion of the ADAF adjustments and how to apply the ADAFs for less-than-lifetime exposure scenarios.

[c]Adult-based (rescaled) BMR/EC estimate for NPC intended for the application of ADAFs (see Section 2.2.4).

Sources of Uncertainty Associated with the Preferred Unit Risk Estimate

In general, the major areas of uncertainty in unit risk estimates arise from limitations in the database, e.g., limitations resulting in the need for interspecies and high- to low-dose extrapolation and limitations in information on human variability, including especially sensitive populations. The ideal database would provide sufficient data for the direct calculation of robust cancer (incidence) estimates for the general population at environmental levels of exposure.

The availability of suitable human data from which to derive unit risk estimates eliminates one of the major sources of uncertainty inherent in most unit risk estimates—the uncertainty associated with interspecies extrapolation. The NCI study used as the basis for the preferred unit risk estimate is considered a well-conducted study for the purposes of deriving unit risk estimates. The NCI study is a large longitudinal cohort study that developed individual worker exposure estimates using detailed employment histories and formaldehyde concentration measurements. In addition to the detailed exposure assessment, the study used internal analyses and carefully considered potential confounding or modifying variables. Moreover, the NCI study comprises a large cohort that has been followed for a long time. Nonetheless, uncertainties in derived unit risk estimates are inevitable. The sources of uncertainty related to these limitations include use of a single study to derive the unit risk estimate, the inability to derive unit risk estimates for all potential cancer sites, and the derivation of (incidence) unit risk estimates for the general population from an occupational mortality study.

Overall confidence in the preferred unit risk estimate is **medium**. Although substantial uncertainty exists with respect to the low-exposure extrapolation, the estimate is based on human data from a large, high-quality epidemiological study. Furthermore, the estimate is similar to the estimate derived from rodent data.

Use of a single study to derive unit risk

Although several studies contributed to the hazard evaluation and causal conclusion for myeloid leukemia, a major limitation in the human database for formaldehyde is that there was only one independent[59] epidemiology study, the NCI study (Beane Freeman et al., 2013; Beane Freeman et al., 2009), with adequate exposure estimates for the derivation of unit risk estimates, as discussed above. Although the unit risk estimation from human data used data from one epidemiological study, it is a large longitudinal cohort study that included workers from 10

[59]Another study, by Marsh et al. (2007b; 2002; 1996), also derived exposure estimates for the individual workers; however, it examined one of the 10 plants included in the NCI study, and thus, is not an independent study.

different industrial plants, in different states, that produced or used formaldehyde in different products. These factors decrease the likelihood that the results are overly influenced by uncontrolled confounding related to either location or production process. The NCI study developed individual worker exposure estimates using detailed employment histories and formaldehyde concentration measurements. In addition to the detailed exposure assessment, the study used internal comparisons of risk from exposure and gave careful consideration to potential confounding or modifying variables. Thus, although the unit risk estimates are based on a single study, there is relatively high confidence in that study.

Inability to derive unit risk estimates for all potential cancer sites

The IUR is based on results for NPC from the NCI study; however, the NCI study did not support the computation of unit risk estimates for all the cancer sites with an evidence integration judgment of **evidence demonstrates** based on the totality of the evidence.
With the exception of myeloid leukemia, the contribution by these cancers to the total cancer risk associated with formaldehyde inhalation is unknown. The impact by myeloid leukemia suggested by the estimated unit risk estimate (myeloid leukemia plus other/unspecified leukemia) might increase the ADAF-adjusted IUR by almost four-fold.

Derivation of incidence estimates from mortality data

The NCI study is a retrospective mortality study, and cancer incidence data are unavailable for the cohort. Using mortality risk would markedly underestimate incidence for NPC because survival for this cancer type is relatively high. This limitation was addressed quantitatively in the calculation of cancer incidence risk estimates using the dose-response relationships from the mortality study, although as discussed above, it was necessary to make certain assumptions. It was assumed that cancer incidence and mortality have the same exposure-response relationship for formaldehyde exposure, which is reasonable for NPC at the low induction rates observed. Despite the uncertainties introduced, the incidence-based estimates are believed to be better estimates of cancer incidence risk than the mortality-based estimates, given the high survival rates for these cancers. The estimates may under- or overpredict the true risk, although the quantitative impact would be relatively low because the incidence estimates are constrained by the relative incidence:mortality rates and necessarily bounded by the mortality estimates, which are about 50% of the incidence estimates (see Tables 2-18 and 2-19).

Generalizability of estimates from a worker population

The NCI data represent an industrial worker cohort that is generally healthier than the U.S. population at large. Therefore, the unit risk estimates derived from the NCI worker cohort data could underestimate the cancer risk for the general population to an unknown extent, although the impact is expected to be relatively low for the majority of the population.

Industrial workers can also differ from the general population in factors other than health status. In terms of representing the general population in other ways, the NCI cohort was somewhat diverse, but the workers were predominantly white males (81%), then white females (12%), black males (7%), and black females (<1%), and they were all adults. Thus, for example, cancer risk in the general population could be underestimated if females are more susceptible than males, or overestimated if males are more susceptible than females. The potential for increased early-life susceptibility is addressed explicitly in Section 2.2.4.

High- to low-dose extrapolation

The availability of human data from this occupational epidemiology study for the derivation of quantitative cancer risk estimates removes the need to extrapolate from the findings of rodent bioassays, a major source of uncertainty in most risk assessments. However, another major source of uncertainty inherent in most unit risk estimates remains—the uncertainty associated with extrapolation from high (in this case occupational) exposures to lower (environmental or typical nonoccupational indoor) exposures. One factor contributing to uncertainty in the low dose-response comes from the potential for endogenous formaldehyde levels in respiratory tissue to reduce the uptake of the inhaled gas at low doses, as demonstrated in modeling efforts by Schroeter et al. (2014) and Campbell Jr et al. (2020). This would be expected to result in an overprediction of the true risk.

Although the actual exposure-response relationship at low-exposure levels is unknown, the use of linear low-dose extrapolation is supported by evidence that formaldehyde has a mutagenic MOA for NPC. The linear low-dose extrapolation from the 95% lower bound on the exposure level associated with the extra risk level serving as the benchmark response is considered to be a plausible upper bound on the risk at lower exposure levels. Actual low-dose risks may be lower to an unknown, but possibly substantial (e.g., over an order of magnitude) extent.

Additional Sources of Uncertainty Stemming from the NCI Study and Its Analysis

Other sources of uncertainty arise from the key epidemiological study and its analysis (Beane Freeman et al., 2013), including the retrospective estimation of formaldehyde exposures in the cohort, the modeling of the epidemiological exposure-response data, the exposure metric for exposure-response analysis, and potential confounding or modifying factors.

Exposure estimates

With respect to exposure estimation, the NCI investigators (Stewart et al., 1986) conducted a detailed retrospective exposure assessment to estimate the individual worker exposures. Formaldehyde exposures were estimated for specific jobs/tasks based on monitoring data, discussions with workers and plant managers, and assessment by industrial hygienists. Individual worker estimates were derived for a variety of exposure metrics based on work histories. This

exposure assessment was a major undertaking, involving over 100 person-months. Hauptmann et al. (2004) suggested that employment of such a detailed exposure assessment would tend to minimize exposure misclassification for average and cumulative exposure and duration of exposure but that peak exposure estimates could be more susceptible to misclassification because they were defined more qualitatively. In addition, the follow-up study did not account for exposures after 1980. Beane Freeman et al. (2013) suggest that any underestimation of total exposure resulting from the 1980 cutoff would be small because only 3.5% of all person-years were contributed by workers who were 65 years or younger and in exposed jobs in 1980 and because exposure levels were believed to have been much lower after 1980 than in earlier years.

Marsh et al. (1996) also estimated individual worker exposures at one of the 10 plants (Wallingford, Connecticut) studied by the NCI team. The Marsh et al. (1996) exposure estimates were about 10-fold lower than those derived by the NCI for the workers at the Wallingford plant. Marsh et al. (2002) hypothesized that "the NCI used data from several facilities to estimate exposures in a single facility." However, the NCI investigators maintain that they estimated exposures for each plant separately. While the exact reasons for such a large discrepancy are unclear, some differences in the assessment procedures which could have resulted in substantial differences in the estimates are apparent. First, according to Marsh et al. (1996), 91.7% of the white male Wallingford plant workers were specified as being exposed to formaldehyde in the NCI study, while only 83.3% were considered to have been exposed in the Marsh et al. (1996) analysis (it should be noted that these two cohorts of the Wallingford plant are not identical). Second, the NCI investigators (Stewart et al., 1987; Stewart et al., 1986) did their own exposure monitoring at all the plants, including the Wallingford facility, to standardize the data provided by the plants as well as to fill data gaps for certain jobs. There is no indication that Marsh et al. (1996) made any additional measurements themselves. Third, although the Marsh et al. (2002; 1996) papers are not entirely consistent on this point, those investigators apparently assumed that the job-specific exposures at the plant were essentially constant over the history of the plant, whereas the NCI team, based on interviews with plant personnel knowledgeable about equipment and process changes, assumed that past exposures were higher.

In any event, despite the discrepancies in the absolute exposure values, the relative exposures for both the Marsh et al. (2002; 1996) and NCI studies, as reflected in the exposure-response relationships, are less subject to misclassification and are considered to be reliable. The Wallingford plant is just one of the 10 plants in the NCI study (representing 4,389 of the 25,619 workers in the NCI cohort), but if the Marsh et al. (1996) exposure estimates, which are roughly 10-fold lower than the NCI estimates, are closer to the actual exposures for those workers, then the true potency of formaldehyde could be greater than that suggested by the unit risk estimates calculated above based on the NCI data. Furthermore, if the NCI exposure values were significantly overestimated across all 10 plants, then the actual potency could be higher still.

In summary, EPA has relatively high confidence in the NCI exposure assessment because of the large effort and high degree of expertise that NCI devoted to developing their detailed exposure estimates. Nonetheless, errors in retrospective exposure assignments are inevitable, and as a result, the unit risk estimates based on the NCI study could overpredict or underpredict the true risks to an unknown extent, although the discrepancy with the independently derived Marsh et al. (1996) exposure estimates suggests that the risks might be underestimated.

Exposure-response modeling

With respect to the exposure-response model, the log-linear Poisson regression model used by the investigators (Beane Freeman et al., 2013; Beane Freeman et al., 2009) for their trend tests (i.e., RR = $e^{\beta X}$) is generally an appropriate model for the analyses of epidemiological cancer data.[60] As discussed above, when age is well characterized and adjusted for, as it was in the NCI study, the results of the Poisson regression model should be essentially the same as results from the Cox proportional hazards model (Callas et al., 1998). The investigators reported efforts to check for deviations from log-linearity by adding a quadratic term to their models; none of these additional terms was statistically significant. However, the "true" underlying exposure-response relationships are unknown.

Even if the correct exposure-response model for NPC was known, there would be substantial uncertainty in estimating the model parameters because there are only 10 NPC deaths to model. Additionally, a 15-year lag was used for all the NCI solid cancer models. The actual best lag interval is unknown; the NCI investigators reported that lag intervals between 2 and 20 years yielded similar results.

Exposure metrics

Another potentially significant source of uncertainty is associated with the exposure metrics. With the log-linear model used for modeling the occupational data, the peak exposure metric gave the strongest exposure-response relationship between formaldehyde exposure and increased risk of NPCs. However, as discussed above, there are limitations in the peak exposure metric, and it is unclear how to extrapolate RR estimates based on peak exposure estimates to meaningful estimates of lifetime extra risk of cancer from environmental exposure (i.e., extra risk from lifetime continuous low-level environmental exposures). The cumulative exposure metric also yielded nearly statistically significant exposure-response relationships (p = 0.07) and was used for the cancer risk calculations in this assessment. The "true" exposure metric best describing the toxicologically relevant dose of formaldehyde for carcinogenesis is unknown. If a peak-exposure type of metric is the best representative of the toxicologically relevant dose, this suggests that there are dose-rate effects in the exposure-response relationship for formaldehyde and cancer. If this is

[60]EPA relied on the results of the NCI exposure-response analyses and did not investigate other possible exposure-response models beyond those conducted by NCI.

the case, the unit risk estimates presented here, which are based on a linear low-dose extrapolation, may overpredict the true risks to an unknown, but possibly substantial, extent.

Influence of confounding or effect modification

Beane Freeman et al. (2013) provided a detailed description of their evaluation of potential confounding and modifying factors in their analyses. The important factors of age, race, sex, calendar year, and pay category were taken into account in the Poisson regression and trend analyses. Furthermore, they used the low-exposure person-years, rather than the unexposed person-years, as their referent group to minimize any potential confounding effects resulting from differences in socioeconomic or other characteristics between exposed and unexposed workers. When the slope estimate (i.e., regression coefficient) for the exposed person-years only was used in the analyses presented here, the unit risk estimate was essentially identical to that calculated from the slope estimate for all person-years (see Tables 2-18, 2-19, 2-23, and 2-24).

In addition, these investigators evaluated routine respirator use, exposure to formaldehyde-containing particulates, durations of exposure to 11 other chemicals/substances in the plants (antioxidants, asbestos, carbon black, dyes and pigments, hexamethylenetetramine, melamine, phenol, plasticizers, urea, wood dust, and benzene), and duration of employment as a chemist or laboratory technician. Only 133 workers ever routinely used a respirator (Hauptmann et al., 2003). RR estimates reportedly did not change substantially when adjusted for exposure to any of the other 10 chemicals/substances in the NPC (with cumulative exposure) or leukemia analyses (Beane Freeman et al., 2013). Only one of the workers who died of NPC was identified as being exposed to wood dust, a recognized nasopharynx carcinogen. Adjusting for duration of time spent working as a chemist or laboratory technician did not substantially alter the results for NPC (Beane Freeman et al., 2013).

Beane Freeman et al. (2013) reported that their analyses showed no evidence of plant heterogeneity for the solid tumor results. In addition, six of the 10 deaths with NPC on the death certificate were from the Wallingford plant also studied by Marsh et al. (2007c).[61] Marsh et al. (2007b) hypothesized that the excess NPCs in the Wallingford plant could be due to external employment in metal-working industries. However, as noted by Beane Freeman et al. (2013), when Marsh et al. (2007b) adjusted for metal-working, the associations of NPC with formaldehyde for different metrics of exposure did not decrease.

Although smoking data were not available for the cohort, smoking is unlikely to explain the excesses in NPCs because there was no consistent increase for tobacco-related diseases, including lung cancer, across the same exposure metrics. No information was available on Epstein-Barr virus infections, a major risk factor for NPC, in the cohort.

[61]In the previous follow-up of the NCI cohort by Hauptmann et al. (2004), 10 NPCs were reported on death certificates and included in NCI's SMR analyses, but one of these cases was apparently misclassified on the death certificate, so only nine cases were used to estimate the RRs in the internal comparison analyses; the misclassified case was not from the Wallingford plant (Beane Freeman et al., 2013).

In the reporting of the previous follow-up, Hauptmann et al. (2004) noted that each of the seven formaldehyde-exposed workers who had died of NPC was also exposed to particulates and neither of the two workers who died of NPC but were not exposed to formaldehyde was exposed to particulates. Due to the complete collinearity of formaldehyde and particulate exposures, one cannot estimate the exposure-response slope in workers exposed only to formaldehyde. The exposure-response relationships observed for formaldehyde within the NCI cohort and the associations observed between formaldehyde exposure and NPC in workers not exposed to particulates indicate that there is a formaldehyde effect independent of particulates; however, one cannot rule out a possible modifying effect of particulates, which might, for example, enhance delivery of formaldehyde to the nasopharynx.

In summary, uncontrolled confounding could theoretically result in unit risk estimates that are either under- or overestimated; nevertheless, given the careful consideration paid to potential confounding, any quantitative impacts are expected to be minimal. However, a possible modifying effect of particulate exposure on NPC cannot be ruled out, which could overestimate the risk from formaldehyde alone to an unknown extent.

2.2.7. Previous IRIS Assessment: Inhalation Unit Risk

In the previous assessment (last updated in 1991), an inhalation unit risk of 1.3×10^{-5} per $\mu g/m^3$ was developed based on nasal SCCs in F344 rats from Kerns et al. (1983). The data were modeled from the estimates of the probability of death with tumor and its variance using a linearized multistage procedure.

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