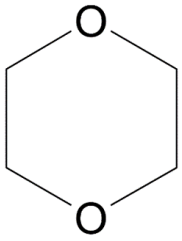
United States
Environmental Protection Agency

Office of Chemical Safety and
Pollution Prevention
December 2020

Summary of External Peer Review and Public Comments and Disposition for 1,4-Dioxane:

Response to Support Risk Evaluation of 1,4-Dioxane

December 2020



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This document summarizes the public and external peer review comments that the EPA's Office of Pollution Prevention and Toxics (OPPT) responses to the comments received for the draft risk evaluation. This document also summarizes the public comments and EPA/OPPT's responses to the comments received for the draft supplemental analysis to the draft risk evaluation of 1,4-dioxane. It also provides EPA/OPPT's response to the comments received from the public and the peer review panel.

EPA/OPPT appreciates the valuable input provided by the public and peer review panel. The input resulted in numerous revisions to the risk evaluation document.

The peer review and public comments are categorized by the 1,4-dioxane peer review charge questions, which align with the seven themes listed below (including the addition of a section for editorial comments). Within each theme, comments that cover similar issues are presented together.

1. Content and Organization
2. Systematic Review
3. Environmental Fate, Exposure & Effects
4. Exposure and Releases
5. Human Health
6. Risk Characterization
7. Editorial Comments
8. Supplemental Analysis

Abbreviations

ACC	American Chemistry Council
ACE	Acute-to-Chronic Estimation
ADC	Average daily concentration
AF	Assessment factor
AFL-CIO	American Federation of Labor and Congress of Industrial Organizations
AEGL	Acute Exposure Level Guidelines
AIHA	American Industrial Hygiene Association
AOP	Adverse outcome pathway
APF	Assigned protection factor
APHA	American Public Health Association
APHL	Association of Public Health Laboratories
AQMD	Air Quality Management District
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	Bioconcentration Factor
BMDL	Benchmark dose lower bound
BMDS	Benchmark Dose Software
BW	Bodyweight
CAA	Clean Air Act
CalEPA	California Environmental Protection Agency
CASRN	Chemical Abstracts Service Registry Number
CEM	Consumer Exposure Model
COU	Condition of use
CFD	Computational fluid dynamics
ChV	Chronic value
CNS	Central Nervous System
COC	Concentration of concern
CWA	Clean Water Act
DMR	Discharge Monitoring Report
EC_{50}	Effect Concentration at which 50% of test organisms exhibit the effect
ECEL	Existing Chemical Concentration Limit
EDF	Environmental Defense Fund
E-FAST	Exposure and Fate Assessment Screening Tool

EIA	Environmental Investigation Agency
EPI Suite™	Estimation Programs Interface suite of models
EPN	Environmental Protection Network
EXAMS	Exposure Analysis Modeling System
GHS	Globally Harmonized System
HAP	Hazardous air pollutant
HEC	Human equivalent concentration
HEI	Health Effects Institute
HERO	Health & Environmental Research Online
HUC	Hydrologic unit code
IARC	International Agency for Research on Cancer
IUR	Inhalation unit risk
K_{oa}	Octanol-Air Partition Coefficient
K_{oc}	Soil Organic Carbon-Water Partitioning Coefficient
LADC	Lifetime average daily concentrations
LC_{01}	Lethal Concentration at which 1% of test organisms die
LC_{10}	Lethal Concentration at which 10% of test organisms die
LC_{50}	Lethal Concentration at which 50% of test organisms die
LOAEL	Lowest Observed Adverse Effect Level
LOD	Limit of detection
MOA	Mode of Action
MOE	Margin of Exposure
NAICS	North American Industry Classification System
NAS	National Academies of Science
NATA	National Air Toxics Assessment
NEI	National Emissions Inventory
NESHAP	National Emission Standards for Hazardous Air Pollutants
NF	Near-field
NHANES	National Health and Nutrition Examination Survey
NIOSH	National Institute for Occupational Safety and Health
NOAEL	No Observed Adverse Effect Level
NOEC	No Observed Effect Concentration
NPDES	National Pollutant Discharge Elimination System

NTP	National Toxicology Program
OECD	Organisation for Economic Co-operation and Development
OES	Occupational exposure scenario
OPERA	Open Structure-activity/property Relationship App
OPPT	Office of Pollution Prevention and Toxics
ONU	Occupational non-user
OSHA	Occupational Safety and Health Administration
PBPK	Physiologically based pharmacokinetic
PESS	Potentially Exposed or Susceptible Subpopulations
PEL	Permissible exposure limits
PDM	Probabilistic Dilution Model
PF	Protection factor
POD	Point of departure
POTW	Publicly owned treatment works
PPE	Personal protective equipment
QSAR	Quantitative Structure-Activity Relationship
REL	Reference Exposure Level
RIOPA	Relationship between Indoor, Outdoor, and Personal Air
ROS	Regression on Order Statistics
RQ	Risk quotient
SACC	Science Advisory Committee on Chemicals
SCHF	Safer Chemicals Healthy Families
SDS	Safety Data Sheet
SIR	Standard incidence rates
SOCMA	Society of Chemical Manufacturers & Affiliates
STORET	STOrage and RETrieval database
TNO	The Netherlands Organisation for Applied Scientific Research
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TURI	Toxics Use Reduction Institute
TWA	Time-weighted average
UCSF PRHE	University of California, San Francisco Program on Reproductive Health and the Environment
UF	Uncertainty factor

U.S. BLS	United States Bureau of Labor Statistics
USGS	U.S. Geological Survey
WHO	World Health Organization

List of Comments

Risk Evaluation		
#	**Docket File**	**Submitter**
14	EPA-HQ-OPPT-2019-0238-0014	Gary A. Buchanan, Director, New Jersey Department of Environmental Protection (NJDEP)
15	EPA-HQ-OPPT-2019-0238-0015	Liz Hitchcock, Acting Director, Safer Chemicals Healthy Families et al.
19	EPA-HQ-OPPT-2019-0238-0019	Environmental Protection Network (EPN)
20	EPA-HQ-OPPT-2019-0238-0020	Ben Gann, Director, Chemical Products & Technology Division, American Chemistry Council's (ACC) North American Flame Retardant Alliance (NAFRA)
21	EPA-HQ-OPPT-2019-0238-0021	Jonathan Kalmuss-Katz, Staff Attorney, Earthjustice and Randy Rabinowitz, Executive Director, Occupational Safety & Health (OSH) Law Project
22	EPA-HQ-OPPT-2019-0238-0022	Stephen P. Risotto, Senior Director, American Chemistry Council (ACC)
23	EPA-HQ-OPPT-2019-0238-0023	Suzanne Hartigan, Senior Director, Regulatory and Technical Affairs, American Chemistry Council (ACC)
24	EPA-HQ-OPPT-2019-0238-0024	Richard A. Denison, Lead Senior Scientist, on behalf of Environmental Defense Fund (EDF)
30	EPA-HQ-OPPT-2019-0238-0030	Douglas M. Troutman, Sr. Vice President, Government Affairs, American Cleaning Institute (ACI) and Michael R. Gruber, Vice President, Government Affairs, Grocery Manufacturers Association (GMA)
31	EPA-HQ-OPPT-2019-0238-0031	Steve Risotto, American Chemistry Council (ACC)
32	EPA-HQ-OPPT-2019-0238-0032	Huntington Breast Cancer Action Coalition, Inc (HBCAC)
40	EPA-HQ-OPPT-2019-0238-0040	Brett Howard, Director, Regulatory & Technical Affairs American Chemistry Council
42	EPA-HQ-OPPT-2019-0238-0042	Emily Sutton, Haw Riverkeeper, Haw River Assembly
43	EPA-HQ-OPPT-2019-0238-0043	Catherine Neuschler, Manager, Water Assessment Section, Environmental Analysis and Outcomes Division, Minnesota Pollution Control Agency (MPCA) and Jim Kelly, Manager, Environmental Surveillance & Assessment, Environmental Health Division, Minnesota Department of Health (MDH)
44	EPA-HQ-OPPT-2019-0238-0044	James R. Fletchtner, Executive Director, Cape Fear Public Utility Authority (CFPUA)
45	EPA-HQ-OPPT-2019-0238-0045	Mack McKinley, Water Resources Engineer, City of Sanford, Florida

46	EPA-HQ-OPPT-2019-0238-0046	Jonathan Kalmuss-Katz, Staff Attorney, Earthjustice and Randy Rabinowitz, Executive Director, Occupational Safety & Health Law Project on behalf of American Federation of Labor and Congress of Industrial Organizations et al.
47	EPA-HQ-OPPT-2019-0238-0047	Sonya Lunder, Senior Toxics Policy Advisor Gender, Equity & Environment Program, Sierra Club
48	EPA-HQ-OPPT-2019-0238-0048	Suzanne Hartigan, Senior Director, Regulatory and Technical Affairs, American Chemistry Council (ACC)
49	EPA-HQ-OPPT-2019-0238-0049	G. Tracy Mehan III, Executive Director, Government Affairs, American Water Works Association (AWWA) and Diane VanDe Hei, Chief Executive Officer, Association of Metropolitan Water Agencies (AMWA)
50	EPA-HQ-OPPT-2019-0238-0050	Amble Johnson, Jean Zhuang and Kelly Moser, Attorneys, Southern Environmental Law Center (SELC)
51	EPA-HQ-OPPT-2019-0238-0051	Tosh Sagar, Senior Associate Attorney, Earthjustice
52	EPA-HQ-OPPT-2019-0238-0052	Brent Tracy, Senior Director and Associate General Counsel, Johns Manville (JM)
53	EPA-HQ-OPPT-2019-0238-0053	D. Peter
54	EPA-HQ-OPPT-2019-0238-0054	Amble Johnson, Jean Zhuang and Kelly Moser, Attorneys, Southern Environmental Law Center (SELC)
55	EPA-HQ-OPPT-2019-0238-0055	Liz Hitchcock, Acting Director, Safer Chemicals Healthy Families (SCHF) et al.
56	EPA-HQ-OPPT-2019-0238-0056	Swati Rayasam, Science Associate, Program on Reproductive Health and the Environment, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco et al.
57	EPA-HQ-OPPT-2019-0238-0057	Tosh Sagar, Senior Associate Attorney, Earthjustice on behalf of Achieving Community Tasks Successfully (ACTS)
58	EPA-HQ-OPPT-2019-0238-0058	Stephanie Schwarz, Legal Fellow, Environmental Defense Fund (EDF)
59	EPA-HQ-OPPT-2019-0238-0059	Stephen P. Risotto, Senior Director, American Chemistry Council (ACC)
60	EPA-HQ-OPPT-2019-0238-0060	Cape Fear River Watch (Part 1 of 3)
61	EPA-HQ-OPPT-2019-0238-0061	Cape Fear River Watch (Part 2 of 3)
62	EPA-HQ-OPPT-2019-0238-0062	Cape Fear River Watch (Part 3 of 3)
SACC	N/A	Science Advisory Committee on Chemicals (SACC)

Supplemental Analysis		
75	EPA-HQ-OPPT-2019-0238-0075	J. Alan Roberson, Executive Director, Association of State Drinking Water Administrators (ASDWA)
76	EPA-HQ-OPPT-2019-0238-0076	Diane VanDe Hei, Chief Executive Officer, Association of Metropolitan Water Agencies (AMWA)
77	EPA-HQ-OPPT-2019-0238-0077	Elizabeth Hitchcock, Safer Chemicals Healthy Families et al.
78	EPA-HQ-OPPT-2019-0238-0078	Michelle Roos, Environmental Protection Network (EPN)
79	EPA-HQ-OPPT-2019-0238-0079	Stephen Wieroniey, Director, American Chemistry Council's (ACC) Spray Foam Coalition (SFC)
80	EPA-HQ-OPPT-2019-0238-0080	Stephen P. Risotto, Senior Director, American Chemistry Council (ACC)
81	EPA-HQ-OPPT-2019-0238-0081	G. Tracy Mehan, III, Executive Director - Government Affairs, American Water Works Association (AWWA)
82	EPA-HQ-OPPT-2019-0238-0082	Vincent Cogliano, Deputy Director for Scientific Programs, California Office of Environmental Health Hazard Assessment
83	EPA-HQ-OPPT-2019-0238-0083	Richard Denison, Lead Senior Scientist, Environmental Defense Fund (EDF)
84	EPA-HQ-OPPT-2019-0238-0084	Kathleen Stanton, Associate Vice President, Technical & International Affairs, American Cleaning Institute (ACI) and Steven Bennett, Senior Vice President, Scientific & Regulatory Affairs, Household and Commercial Products Association (HCPA)
85	EPA-HQ-OPPT-2019-0238-0085	Letitia James, Attorney General of New York, Sarah Kam, Assistant Attorney General, Office of the Attorney General, New York State et al.
86	EPA-HQ-OPPT-2019-0238-0086	Meredith Williams, Director, Department of Toxic Substances Control, California Department of Toxic Substances Control (DTSC)
87	EPA-HQ-OPPT-2019-0238-0087	J. Alan Roberson, Executive Director, Association of State Drinking Water Administrators (ASDWA)
88	EPA-HQ-OPPT-2019-0238-0088	Jonathan Kalmuss-Katz and Rashmi Joglekar, Earthjustice, and Randy Rabinowitz, Executive Director, Occupational Safety & Health Law Project on behalf of American Federation of Labor and Congress of Industrial Organizations (AFL-CIO) et al.
89	EPA-HQ-OPPT-2019-0238-0089	Elizabeth Hitchcock, Safer Chemicals Healthy Families et al.
90	EPA-HQ-OPPT-2019-0238-0090	Suzanne Hartigan, Senior Director, Regulatory and Technical Affairs, American Chemistry Council (ACC)

1. Content and Organization

Charge Question 1.1: Please comment on the overall content, organization, and presentation of the draft risk evaluation of 1,4-dioxane. **Charge Question 1.2:** Please provide suggestions for improving the clarity of the information presented in the documents.		
#	**Summary of Comments for Specific Issues Related to Charge Question 1**	**EPA/OPPT Response**
General Comments		
SACC	• Provide a brief history and basis for why the chemical is under risk evaluation. While much of this information is introduced in the Scope and Problem Formulation, inclusion in the Evaluation would greatly enhance the final product. • Improve the clarity of the risk evaluation with careful review, editing, and inclusion of additional graphics. All section references (including appendices and their subheadings) should be formatted as hyperlinks to support easier review and reading. • EPA should provide definitions for all specific terms early in the main document, not just by giving a citation to other document. This could be done by incorporating a glossary of terms.	• A basis for the chemical risk evaluation is provided in the Introduction (Section 1). • Each of the recommendations to improve clarity within the risk evaluation have been accepted. • While EPA has not included a glossary, definitions have been provided for terms within the context of their use in the document.
58	**Information Authorities** • Why did EPA fail to use its information authorities under TSCA to require submission and/or development of relevant information to fill numerous data gaps, including an absence of sufficient environmental monitoring data; environmental fate data; ecotoxicity data; product/use and concentration data; inhalation exposure data; dermal exposure data; dermal toxicity data; and reproductive/developmental/ neurodevelopmental toxicity data?	EPA had sufficient information to complete the 1,4-dioxane risk evaluation using a weight of scientific evidence approach. EPA selected the first 10 chemicals for risk evaluation based in part on its assessment that these chemicals could be assessed without the need for regulatory information collection or development. When preparing this risk evaluation, EPA obtained and considered reasonably available information, defined as information that EPA possesses, or can reasonably obtain and synthesize for use in risk

		evaluations, considering the deadlines for completing the evaluation. In some cases, when information available to EPA was limited, the Agency relied on models; the use of modeled data is in line with EPA's final Risk Evaluation Rule and EPA's risk assessment guidelines. As further noted in the response to the comments on the scope documents, EPA conducted extensive and varied data gathering activities for each of the first 10 chemicals, including: • Extensive and transparent searches of public databases and sources of scientific literature, government and industry sector or other reports; • Searches of EPA TSCA section 8(e) Substantial Risk Reporting, Chemical Data Reporting, and Toxics Release Inventory databases and other EPA information holdings; and CBI submission holdings; • Searches for Safety Data Sheets (SDSs) using the internet, EPA Chemical and Product Categories (CPCat) data, the National Institute for Health's (NIH) Household Product Database, and other resources in which SDS could be found; • Preparation of a market analysis using proprietary databases and repositories; • Outreach meetings with chemical manufacturers, processors, chemical users, non-governmental organizations, trade

		organizations, and other experts, including other State and Federal Agencies (*e.g.*, Department of Defense, NASA, OSHA, NIOSH, FDA and CPSC); and • Publication of conditions of use documents, scope documents, and problem formulation documents to solicit information generally from industry, nongovernmental organizations, and the public.
24, 46, 48, 50, 54, 58	**Best Available Science** • In several instances, EPA failed to utilize the "best available science" "without consideration of costs or other non-risk factors" and all "reasonably available information" (15 U.S.C. § 2625(h)). o For example, EPA relied on outdated TRI data, choosing to use data from 2015, even though data from 2016 and 2017 are readily available; the rationale that incorporation of more recent reporting years was not expected to alter conclusions of the screening-level assessment is not acceptable.	• At the time of original project scoping, 2015 TRI data was the most current and complete dataset. EPA has updated the final risk evaluation document using 2018 TRI data in response to this comment and the elapsed time since original scoping. The 2018 TRI data is the most current and complete data set as of January 2020. EPA has updated the DMR dataset used in the risk evaluation to reflect the latest available data from 2018 as well.
85	**Environmental Justice** • EPA does not consider environmental justice despite Executive Order 12898, which mandates "disproportionately high and adverse human health or environmental effects of its programs, policies, and activities on minority populations and low-income populations" are identified and addressed. Executive Order 12898 does not contain exemptions for any type of agency "programs, policies, and activities." • EPA has acknowledged that it must analyze risks to environmental justice communities as part of its risk evaluation and include	TSCA § 6(b)(4) requires that EPA conduct a risk evaluation to "determine whether a chemical substance presents an unreasonable risk of injury to health or the environment, without consideration of cost or other non-risk factors, including an unreasonable risk to a potentially exposed or susceptible subpopulation identified as relevant to the risk evaluation by the Administrator, under the conditions of use." TSCA § 3(12) states that

	environmental justice communities in the development of the risk evaluation. EPA must determine if exposure to 1,4-dioxane will result in disproportionate risks to "minority populations and low-income populations." • Residents of low-income and communities of color may face greater exposure to 1,4-dioxane, making EPA's failure to comply with TSCA and EPA implementing regulations particularly egregious from the perspective of environmental justice.	"the term 'potentially exposed or susceptible subpopulation' means a group of individuals within the general population identified by the Administrator who, due to either greater susceptibility or greater exposure, may be at greater risk than the general population of adverse health effects from exposure to a chemical substance or mixture, such as infants, children, pregnant women, workers, or the elderly." EPA believes that the statutory directive to consider potentially exposed or susceptible subpopulations (PESS) and the statutory definition of PESS inherently include environmental justice populations. Thus, EPA's consideration of PESS in this risk evaluation addresses the requirements of the Executive Order. EPA considers both exposure (Section 2.4) and biological (Section 3.2.6.1) considerations in evaluating PESS. As discussed in Section 4.4, certain human subpopulations may be more susceptible to exposure to 1,4-dioxane than others. Some subpopulations may be more biologically susceptible to the effects of 1,4-dioxane due to genetic variability, pre-existing health conditions, lifestage, pregnancy, or other factors that alter metabolism or increase target organ susceptibility. Other susceptibility factors may include race/ethnicity and socioeconomic status. The variability in human susceptibility to 1,4-dioxane is reflected in the selection of the uncertainty factor for human variability included in the benchmark MOE. In addition,

		EPA accounts for exposures to PESS by using the high-end exposure value when making its unreasonable risk determinations. EPA seeks to achieve the fair treatment and meaningful involvement of any group, including minority and/or low income populations, in the development, implementation, and enforcement of environmental laws, regulations, and policies. To this end, the Agency has already sought input from specific populations and public health experts in implementing TSCA and will continue to do so. EPA will also consider environmental justice populations in accordance with the Executive Order as it develops risk management actions based on final TSCA section 6(b) risk evaluations.
Scope Comments - Excluded Conditions of Use		
SACC,24, 47, 58	**Byproducts** • The justifications for not including byproducts as a condition of use were inadequate, and in breach of TSCA mandates. There is a requirement to evaluate circumstances in which a chemical is intended, known, or reasonably foreseen to be manufactured, processed, distributed in commerce, used, or disposed § 2602(4). Byproducts (or impurities or contaminants) are considered conditions of use under TSCA. There is also a requirement to consider all available information on exposures resulting from the conditions of use of the chemical, without exception. See 15 U.S.C. § 2605(b)(4)(F)(i).	As explained in the scope document, 1,4-dioxane may be found as a contaminant in consumer products that are readily available for public purchase. In the final risk evaluation, eight consumer conditions of use are evaluated based on the uses identified in EPA's 2015 TSCA Work Plan Chemical Problem Formulation and Initial Assessment of 1,4-Dioxane (U.S. EPA, 2015). An additional systematic review effort was undertaken for consumer exposures to identify, screen, and evaluate relevant data sources. These conditions of use include use of 1,4-dioxane as a surface cleaner, antifreeze, dish soap,

		dishwasher detergent, laundry detergent, paint and floor lacquer, textile dye, and spray polyurethane foam (SPF). 1,4-Dioxane may be found in these products at low levels (0.0009 to 0.02%) based on its presence as a byproduct of other formulation ingredients (*i.e.*, ethoxylated chemicals). Inhalation exposures are estimated for consumers and bystanders and dermal exposures are estimated for users. Acute exposures are presented for all consumer conditions of use, while chronic exposures are presented for the conditions of use that are reasonably expected to involve daily use intervals (*i.e.*, surface cleaner, dish soap, dishwasher detergent, and laundry detergent). See Section 2.4.3 of the final risk evaluation.
51, 58	**Use and Disposal of Fuel/Fuel Additives** • EPA unlawfully excluded the use and disposal of 1,4- dioxane as a fuel or fuel additive because it determined that such uses had been discontinued. Exclusion of these so-called "legacy uses" and "legacy disposal" is unlawful under TSCA, because, even if these uses have been discontinued, the ongoing disposal of these products is still a circumstance under which the chemical is known or reasonably foreseen to be disposed of. See 15 U.S.C. § 2602(4).	• The use of 1,4-dioxane in the past as a racing fuel additive is not a "legacy" use. As described in EPA's Risk Evaluation Rule (82 FR 33726, 33729 (July 20, 2017)), a legacy use is an activity that does not reflect ongoing or prospective manufacturing, processing, or distribution in commerce for that application. The commenter appears to be describing associated disposal or legacy disposal. The example provided in the Risk Evaluation Rule for associated disposal is the future disposal of insulation that contains a chemical substance, which may be present in buildings after a chemical substance is no longer being manufactured, processed,

		or distributed for that use. In contrast, 1,4-dioxane in racing fuel is no longer being manufactured, processed, distributed in commerce, used, or disposed of, to the best of EPA's knowledge, which is based on EPA's research and outreach and review of reasonably available information; therefore, this does not fall under the definition of legacy use or associated disposal. Specifically, EPA received no information from any commenters or otherwise indicating that racing fuel products in the United States had been stockpiled or that use or disposal was ongoing. Finally, racing authorities have prohibited the use of 1,4-dioxane in racing fuels, and EPA has no information to suggest that it is, has been, or would be used in fuels other than racing fuels. Therefore, EPA does not consider use or disposal of 1,4-dioxane in racing fuel additive to be a condition of use of 1,4-dioxane. Any disposal associated with past use of 1,4-dioxane as a racing fuel additive would be considered a "legacy disposal" that has already occurred and would also not be considered a condition of use of 1,4-dioxane. See *Safer Chemicals, Healthy Families v. EPA*, 943 F.3d 397 (9th Cir. 2019).
48, 52	**Spray Polyurethane Foam** • EPA included spray foam in the risk evaluation; however, the manufacturer claims that 1,4-dioxane is not used in the	• The commenter appears to be referring to the Safety Data Sheet (SDS) and comments submitted by Johns Manville (JM), a manufacturer of spray polyurethane foam

	manufacturing of the product and disagrees with the level of 1,4-dioxane claimed to be in spray foam that was purportedly obtained from the SDS. The manufacturer indicates that the product SDS makes no mention of 1,4-dioxane and attempted to contact EPA regarding the source of the reported value and did not get a response.	(SPF), but this SDS was not used in the risk evaluation because the product no longer contains 1,4-dioxane. SDS from two other companies were used. The JM product is referenced, along with others, in the *Preliminary Information on Manufacturing, Processing, Distribution, Use, and Disposal: 1,4-Dioxane* document. The SDS, written in 2011 by JM, note concentrations of ~0.04% for 1,4-dioxane. In subsequent years it appears JM may have updated the product and/or SDS as the current 2019 revision does not list 1,4-dioxane as an ingredient (as the commenter and manufacturer have pointed out). Therefore, the risk evaluation does not include the JM product because it does not contain 1,4-dioxane. The risk evaluation includes SPF products that do contain 1,4-dioxane from other manufacturers as the basis of potential worker exposures.
Scope Comments - Excluded Exposure Pathways		
SACC, 19, 24, 42, 43, 44, 47, 50, 51, 54, 55, 56, 58, 60	• The justifications for excluding the general population, consumers, and susceptible subpopulations, and for not including byproducts as a condition of use, or evaluating risks to the environment were inadequate, and in breach of TSCA mandates. • Regulatory Nexus: Provide additional scientific basis for how general population, occupational and consumer exposures not currently assessed under TSCA are effectively managed under other regulatory authorities. TSCA authorizes EPA to consider its other statutory authorities only in the risk management phase. See 15 U.S.C. § 2608. • The risk evaluation should be revised to include these populations,	EPA found that exposures to the general population may occur from the conditions of use due to releases to air, water or land. The exposures to the general population via drinking water, ambient air and sediment pathways falls under the jurisdiction of other environmental statutes administered by EPA, *i.e.*, CAA, SDWA, and RCRA. As explained in more detail in section 1.4.2, EPA believes it is both reasonable and prudent to tailor TSCA risk evaluations when other EPA offices have

	or EPA needs to address each relevant TSCA mandate and provide credible justification with empirical evidence that demonstrates the exposures in question are irrelevant and, therefore, not covered under TSCA law. • The risk evaluation should be revised to include the air and drinking water exposure pathways, and also evaluation of ingestion of contaminated food products.	expertise and experience to address specific environmental media, rather than attempt to evaluate and regulate potential exposures and risks from those media under TSCA. EPA has therefore tailored the scope of the risk evaluations for 1,4-dioxane using authorities in TSCA sections 6(b) and 9(b)(1). EPA did not evaluate hazards or exposures to the general population via certain pathways in the risk evaluation, and as such the unreasonable risk determinations for relevant conditions of use do not account for exposures to the general population for certain pathways. However, the final risk evaluation includes an evaluation of general population exposures through recreational activities (*i.e.*, swimming) in ambient water bodies. See Section 1.4.2 of the final risk evaluation. As explained in the scope document, 1,4-dioxane may be found as a contaminant in consumer products that are readily available for public purchase. In the final risk evaluation, eight consumer conditions of use are evaluated based on the uses identified in EPA's 2015 TSCA Work Plan Chemical Problem Formulation and Initial Assessment of 1,4-Dioxane (U.S. EPA, 2015). An additional systematic review effort was undertaken for consumer exposures to identify, screen, and evaluate relevant data sources. These conditions of use include use of 1,4-dioxane as a surface cleaner, antifreeze, dish soap,

		dishwasher detergent, laundry detergent, paint and floor lacquer, textile dye, and spray polyurethane foam (SPF). 1,4-Dioxane may be found in these products at low levels (0.0009 to 0.02%) based on its presence as a byproduct of other formulation ingredients (*i.e.*, ethoxylated chemicals). See Section 2.4.3 of the final risk evaluation. TSCA section 3(2) defines "chemical substance" to exclude any food or food additive as the terms are defined in section 201 of the Federal Food, Drug, and Cosmetic Act, when manufactured, processed, or distributed in commerce for use as a food or food additive. Therefore, EPA believes that the ingestion of contaminated food products falls under the jurisdiction of FDA.
Exposure Assumptions		
SACC, 21, 22, 46, 58	EPA's consideration of compliance with OSHA's worker protection standards is not clear. Specific examples and citations are required. EPA evaluated worker risk assuming PPE is used to mitigate exposure and risk. To comply with TSCA's worker protection mandate, EPA must evaluate 1,4-dioxane without assuming any PPE use.	The OSHA regulations at 29 CFR 1910.132 require employers to assess a workplace to determine if hazards are present or likely to be present which necessitate the use of personal protective equipment (PPE). If the employer determines hazards are present or likely to be present, the employer must select the types of PPE that will protect against the identified hazards, require employees to use that PPE, communicate the selection decisions to each affected employee, and select PPE that properly fits each affected employee. OSHA has established a permissible exposure limit (PEL) of 100 ppm (8-hour TWA) for 1,4-dioxane.

		However, as noted on OSHA's website, "*OSHA recognizes that many of its permissible exposure limits (PELs) are outdated and inadequate for ensuring protection of worker health. Most of OSHA's PELs were issued shortly after adoption of the Occupational Safety and Health (OSH) Act in 1970, and have not been updated since that time*." OSHA provides an annotated list of PELs on its website, including alternate exposure levels. For 1,4-dioxane, the alternates provided are the California OSHA PEL of 0.28 ppm and the ACGIH TLV of 20 ppm. (https://www.osha.gov/dsg/annotated-pels/tablez-1.html) EPA's approach for evaluating risk to workers and ONUs is to use the reasonably available information and professional judgement to construct exposure scenarios that reflect the workplace practices involved in the conditions of use of the chemicals . When appropriate, in the risk evaluation, EPA will use exposure scenarios both with and without engineering controls and/or PPE that may be applicable to particular worker tasks on a case-specific basis for a given chemical. Thus, while EPA has evaluated worker risk with and without PPE, as a matter of policy, EPA does not believe it should assume that workers are unprotected by PPE where such PPE might be necessary to meet federal regulations, unless it has evidence that workers are unprotected.

		For the purposes of determining whether or not a condition of use presents unreasonable risks, EPA incorporates assumptions regarding PPE use based on information and judgement underlying the exposure scenarios. These assumptions are described in the unreasonable risk determination for each condition of use, in section 5.2 of the risk evaluation. Additionally, in consideration of the uncertainties and variabilities in PPE usage, EPA uses the high-end exposure value when making its unreasonable risk determination in order to address those uncertainties. EPA has also outlined its PPE assumptions in section 5.1 of the risk evaluation. Further, in the final risk evaluation for 1,4-dioxane, EPA has determined that most conditions of use pose an unreasonable risk to workers even with the assumed PPE.
Risk Characterization Comments		
55	• There is a requirement to consider aggregate exposure. See TSCA Section 6(b)(4)(F).	TSCA section 6(b)(4)(F)(ii) directs EPA to "describe whether aggregate or sentinel exposures to a chemical substance under the conditions of use were considered, and the basis for that consideration" in risk evaluations. EPA defines aggregate exposures as the combined exposures to an individual from a single chemical substance across multiple routes (*i.e.*, dermal, inhalation, or oral) and across multiple pathways (*i.e.*, exposure from different sources). 40 CFR 702.33. EPA defines sentinel exposures as the exposure from a single chemical substance that represents the

		plausible upper bound of exposure relative to all other exposures within a broad category of similar or related exposures. 40 CFR 702.33. EPA considered the reasonably available information and used the best available science to determine whether to consider aggregate or sentinel exposures for a particular chemical. EPA has determined that using the high-end risk estimate for inhalation and dermal risks separately as the basis for the unreasonable risk determination is a best available science approach. There is low confidence in the result of aggregating the dermal and inhalation exposures and risks for this chemical if EPA uses an additive approach, due to the uncertainty in the data that could be reliably modeled into the aggregate exposure such as would occur with a PBPK model. Using an additive approach to aggregate exposure and risk in this case would result in an overestimate of risk. Given all the limitations that exist with the data, EPA's approach is the best available approach.
Risk Determination Comments		
48	• It is unclear how EPA's risk characterization supports its risk determination. The risk characterization summary discussion requires a description of how new information impacts the risk characterization.	• See the Executive Summary, updated Risk Characterization (Section 4), and updated Risk Determination (Section 5) for more clarification on how these sections support each other and how new information is incorporated.
SACC, 47	• Provide a clear scientific rationale for the determination of "reasonable" risk for conditions of use that require personal protective equipment for such determination to be appropriate.	While EPA believes that discussions of the rationale for the determination of unreasonable risk is outside the scope of the SACC, EPA is

	There is a requirement to make risk determinations based on hazard and exposure, not consideration of "nonrisk" factors. See 15 U.S.C. § 2605(b)(4)(A), (F)(iii).	committed to providing the public with sufficient information on the basis for that determination. TSCA requires EPA to determine whether chemicals in the marketplace present unreasonable risks to health or the environment. While the law does not specifically define this term unreasonable risk, during the risk evaluation process EPA weighs a variety of factors including the effects of the chemical on human health or the environment, populations exposed (including any sensitive subpopulations), the severity of the hazard, and uncertainties. This approach is outlined in EPA's 2017 *Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act* rule ("Risk Evaluation Rule") preamble on how risk evaluations will be conducted. [82 FR 33726, at 33735 (July 20, 2017)] Each draft risk evaluation details those factors and describes for the public which conditions of use were preliminarily identified to have unreasonable risk for a chemical. For 1,4-dioxane, these factors included a range of workplace exposures. EPA's approach for developing exposure assessments for workers is to use the reasonably available information and expert judgment. When appropriate, in the risk evaluation, EPA will use exposure scenarios both with and without engineering controls and/or personal protective equipment (PPE)

		that may be applicable to particular worker tasks on a case-specific basis for a given chemical. Again, while EPA has evaluated worker risk with and without PPE, as a matter of policy, EPA does not believe it should assume that workers are unprotected by PPE where such PPE might be necessary to meet federal regulations, unless it has evidence that workers are unprotected. For the purposes of determining whether a condition of use presents unreasonable risks, EPA incorporates assumptions regarding PPE use based on information and judgment underlying the exposure scenarios. These assumptions are described in the unreasonable risk determination for each condition of use, in Section 5.2. For example, in the case of 1,4-dioxane, which is manufactured, processed, and used in industrial settings, where there are typically strong industrial hygiene programs that include training and oversight, EPA believes that it is reasonable to assume a protection factor (PF) of 10 or 20 for dermal protection (gloves) and assigned protection factor (APF) of 25 or 50 for inhalation protection (respirators). For 1,4-dioxane, each condition of use includes a characterization of risks at the central tendency and high-end exposures and also when PPE was considered at these exposure levels. EPA presented each of these risk estimates to the public in the draft risk evaluation, and refined them with additional information for the final risk

		evaluation. For the purposes of determining whether or not a condition of use presents an unreasonable risk, EPA incorporates assumptions regarding PPE use based on information and judgement underlying the exposure scenarios. These assumptions are described in the unreasonable risk determination for each condition of use, in section 5.2. Additionally, in consideration of the uncertainties and variabilities in PPE usage, EPA uses the high-end exposure value when making its unreasonable risk determination in order to address those uncertainties. In the final risk evaluation, EPA has determined that most of the conditions of use present unreasonable risks to workers even with the assumed PPE.
SACC, 22	Incorporate the tabular format for the risk determination as done in Section 6. The final risk determination sections should be clarified. EPA should cite the relevant supporting scientific information (section/page/table numbers from the draft risk evaluation) for each decision made under the risk determination section.	• While EPA is unable to add such extensive citations, the formatting and clarity changes to the unreasonable risk determination section from draft to final should provide the reader with an understanding of which risk characterization tables are relevant for each condition of use. Similarly, the new summary table in the risk characterization chapter (section 4) provides a unified crosswalk between major pieces of information throughout the risk evaluation for each condition of use.
Clarity Comments		
22, 40, 48, 58	• The tiered assessment approach used for exposure assessment should be described more clearly. • A clear statement indicating whether or not EPA had access to the full study reports for all of the studies cited is needed.	• EPA added language to Executive Summary of the risk evaluation describing its approach for exposure assessment, which is also discussed in section 2.4.

	• EPA's assumptions in modeling exposures to 1,4-dioxane would benefit from additional documentation.	EPA's approach for developing exposure assessments for workers and ONUs is to use the reasonably available information and professional judgment. When appropriate in the risk evaluation, EPA has used exposure scenarios both with and without engineering controls and/or PPE that may be applicable to particular worker tasks on a case-specific basis for a given chemical. While EPA has evaluated worker risk with and without PPE, as a matter of policy, EPA does not believe it should assume that workers are unprotected by PPE where such PPE might be necessary to meet federal regulations, unless it has evidence that workers are unprotected. For the purposes of determining whether or not a condition of use presents unreasonable risks, EPA incorporates assumptions regarding PPE use based on information and judgment underlying the exposure scenarios. These assumptions are described in the unreasonable risk determination for each condition of use, in section 5.2. Additionally, in consideration of the uncertainties and variabilities in PPE usage, EPA uses the high-end exposure value when making its unreasonable risk determination in order to address those uncertainties. EPA has also outlined its PPE assumptions in section 5.1. Further, in the final risk evaluation for 1,4-dioxane, EPA has determined that most conditions

		of use pose an unreasonable risk to workers even with the assumed PPE. • EPA provides detailed explanations and sample calculations for modeled exposures in Appendix G. This appendix provides a rational and basis for the parameters used, assumptions made, and a narrative of the various models. All parameters, equations, and methods are cited where applicable for further analysis and review.

2. Systematic Review

Charge Question 2.1: Please comment on the approaches and/or methods used to support and inform the gathering, screening, evaluation, and integration of data/information used in the Draft Risk Evaluation for 1,4-Dioxane.

Charge Question 2.2: Please also comment on the clarity of the information as presented related to systematic review and suggest improvements as warranted.

#	Summary of Comments for Specific Issues Related to Charge Question 2	EPA/OPPT Response
SACC, 48,56, 58	**General Comments** • The application of systematic review criteria is inconsistent. There is a reliance on some sources that do not go through the systematic review process, while other sources are excluded "on the basis of the systematic review process." The inclusion or exclusion of sources appears in some cases to be based on the decision about whether or not to apply the systematic review process, and these decisions are not fully explained or justified. • All cited data sources should be made publicly available.	• While some sources did not go through the initial inclusion/exclusion process, all data used in the risk evaluation went through data evaluation criteria and received a data quality rating. • To the extent possible, EPA makes the studies it relies on publicly accessible via the EPA HERO database. Each citation in the risk evaluation is hyperlinked to its HERO database entry. Most journal article entries in HERO have a link to a DOI (Digital Object Identifier). This link will direct you to a journal or publisher website. If the article is free to the public, or you have a subscription to the journal, you can download the PDF. If not, you will usually be offered an option to purchase the individual article. Copyright law prohibits EPA from distributing copyrighted material.
ECHA Dossiers		
58	• It is not clear why studies cited in ECHA dossiers would bypass the data screening step and move directly to the data evaluation step. • It is not transparent whether full studies were obtained, or whether EPA has relied on industry-prepared	• Studies previously identified by authoritative sources such as ECHA were automatically identified as relevant for consideration. Additional studies were identified through systematic review searches. All studies then went through data quality evaluation to determine

	summaries without access to the full studies. EPA should request full studies from the submitters. • A clear distinction must be made between industry data that have not been evaluated, industry data that have been evaluated by ECHA or other government authorities in the EU, and information that ECHA has itself developed or provided.	whether they are acceptable for inclusion in the risk evaluation, regardless of how they were initially identified. EPA only used complete study reports as key and supporting studies and did not rely on industry-prepared summaries. On their own, the robust summaries available through ECHA do not provide sufficient information to receive an "acceptable" rating in EPA's data quality evaluation process. While EPA relies on previous assessments to help identify potentially useful sources of data, it does not rely on previous assessments to determine the quality of those sources. EPA evaluated all of the key and supporting studies it relied on in this risk evaluation using its own data quality evaluation process.
Data Quality Evaluation		
22, 24, 48, 56, 58, 59	• There is no empirical basis for the current scoring method to exclude research based on a single reporting, or methodological limitation. • Submitters disagree with OPPT's systematic review methodology wherein if a single metric is assigned a score of Unacceptable, the entire study is dismissed. • Professional judgement was used to upgrade or downgrade overall study scores for animal toxicity data in four instances. • Efforts need to be taken to calibrate the reviews of different reviewers, as some inconsistencies in data quality evaluation both within and across chemicals seems apparent. ○ Staff doing the data quality evaluations must have appropriate subject matter expertise and be trained on general data quality review methods.	• Appendix A of the Application of Systematic Review in TSCA Risk Evaluations explains the basis for EPA/OPPT's development of a numerical scoring system to inform the characterization of the data/information sources during the data integration phase. The intent is to provide transparency and consistency to the evaluation process along with creating evaluation strategies that meet the TSCA science standards for various data/information streams. • EPA/OPPT's quality evaluation method was developed following identification and review of various published qualitative and quantitative scoring systems to inform our own fit-for-purpose tool. The development process involved reviewing various evaluation tools/frameworks (*e.g.,* NTP's Office of

	○ Efforts being made to do internal quality checks on the data quality evaluations for individual studies and risk evaluations must be disclosed.	Health Assessment and Translation (OHAT) Risk of Bias tool, Criteria for Reporting and Evaluating Ecotoxicity Data (CRED), etc.; see Table 1 and Appendix A of the Application of Systematic Review in TSCA Risk Evaluations and references therein), as well as soliciting input from scientists based on their expert knowledge about evaluating various data/information sources for risk assessment purposes. While there are many published systematic review tools available for human health and environmental health hazard assessment, no systematic review tools were identified that encompass either exposure assessment (*e.g.*, general population exposures, occupational exposures and industrial releases) or fate and transport assessment. The data quality evaluation results published with each risk evaluation provides the lists of references EPA/OPPT evaluated for the first 10 TSCA risk evaluations. • In order to ascertain the quality of the available data, EPA/OPPT used a numerical scoring system to assign a qualitative rating. The goal of this approach was to add consistency and transparency to the evaluation process. Scores were used for the purpose of assigning the confidence level rating of High, Medium, Low, or Unacceptable, and informed the characterization of data/information sources during the data integration phase. The data quality evaluation results for the first ten TSCA Risk Evaluations are posted on chemical specific websites. In all evaluation strategies, professional judgment was employed to determine the adequacy or appropriateness of the qualitative rating

		assigned by the numerical scoring system. • The TSCA evaluation strategies consider methodological design and implementation and reporting within the existing domains and metrics. Since it is difficult to have high confidence in data where the underlying methods are unreported or poorly reported, EPA assesses reporting and methodological quality simultaneously. However, EPA recognizes the challenge of discerning between a deficit in reporting and a problem in the underlying methodological quality of the data/information source. Developing a reporting checklist, guidance document or a separate reporting quality domain may be a future solution for consideration in optimizing the evaluation strategies. EPA also designed evaluation criteria that consider risk of bias and Bradford Hill aspects when assessing the quality of animal toxicity and epidemiological studies. Refer to Appendices F, G and H of the Application of Systematic Review in TSCA Risk Evaluations for more information. • Relevant data sources are evaluated for data quality following title/abstract and full-text screenings for the first 10 and next 20 TSCA risk evaluations, after a pilot period to calibrate criteria and revise as needed. Generally, each study evaluation is conducted by at least two reviewers, with a process for comparing and resolving differences. This helps ensure quality assurance. However, based on assessment needs, the assessment team should make decisions about how many reviewers are needed. While more than one reviewer is ideal, there may be times when one

		reviewer is acceptable, such as when the assessment needs to be conducted under a rapid timeframe and the outcome being reviewed is unlikely to be a driver for the assessment. These quality assurance methods are the same as used by EPA's IRIS Program. Other EPA Offices (such as Office of Research and Development and the Office of Science Coordination and Policy) partnered with OPPT in developing innovations in searching and screening for the next 20 chemical evaluations (see response to Q5) and continues to support OPPT in scoping and SR efforts. • The data evaluation is conducted in a tool (*e.g.,* Excel, Access, DistillerSR) that tracks and records the evaluation for each data/information source including reviewer's comments. The evaluation results for each study evaluated under TSCA were released publicly with each draft risk evaluation to validate the evaluation tools and explore potential differences in professional judgment that may arise from multiple reviewers (both internal and external stakeholders). This documentation approach also increased transparency of professional judgment calls to stakeholders and the public for the first 10 TSCA risk evaluations. EPA/OPPT plans to use these evaluation strategies, including pre-determined criteria, documented in EPA's Application of Systematic Review in TSCA Risk Evaluations document, for the next 20 TSCA risk evaluations. However, refinements to the evaluation strategies are likely to occur. EPA already made changes to the physical chemical properties, environmental hazard, and epidemiological criteria since the Application of

		Systematic Review in TSCA Risk Evaluations document was published. These changes were due to validation and improvement efforts to ensure that the most relevant studies were included in the TSCA risk evaluations, and the most up-to-date data quality evaluation criteria are used for the next 20 TSCA risk evaluations
SACC, 56, 58, 59	**Potential Bias** • EPA relies on voluntary submissions for much of its exposure data. There is concern that this could lead to a collection of biased data or submission of data that is "cherry picked." Additional steps should be taken to ensure that the information received is accurate and complete. A process should be in place for vetting statements and assertions made by entities with a financial interest in the outcome of the risk assessment.	• EPA evaluated data submitted using the data evaluation criteria. However, in the future, EPA will put all data submitted to the Agency through a screening process and then an evaluation process that utilizes the same criteria as data identified from literature searches.
24, 56, 58	**Epidemiological Data Quality Criteria** • Under the new criteria, epidemiological studies can no longer receive high scores for all study metrics, making it difficult for epidemiological studies to be scored overall as high quality. o Some metrics (#18-22) no longer allow a score of unacceptable. o No explanations or empirical support was provided for the revisions to the systematic review data quality criteria for epidemiological studies.	• EPA/OPPT's quality evaluation method was developed following identification and review of various published qualitative and quantitative scoring systems to inform our own fit-for-purpose tool. The development process involved reviewing various evaluation tools/frameworks (*e.g.*, OHAT Risk of Bias tool, CRED, etc.; see Appendix A of the Application of Systematic Review in TSCA Risk Evaluations document and references therein), as well as soliciting input from scientists based on their expert knowledge about evaluating various data/information sources specifically for risk assessment purposes. • The epidemiologic criteria were later revised to more stringently distinguish between High, Medium and Low studies. After additional piloting of the criteria, EPA

		found that the initial iteration of the epi data quality criteria (as published in the Application of Systematic Review in TSCA Risk Evaluations) was inadvertently skewing quality scores toward the tail ends of the scoring spectrum (High and Unacceptable). In order to have the criteria represent a more accurate depiction of the quality levels in the epi literature, the criteria were revised using 2 methods. • The first method was to make the unacceptable metrics less stringent. This was accomplished by either rewording the metrics to allow for more professional judgement in the interpretation of the unacceptable criterion, or in some cases, completely removing the unacceptable bin from metrics that EPA determined were not influential enough to completely disqualify a study from consideration (mostly metrics in the Analysis and Biomonitoring domain). EPA found that these criteria changes greatly reduced the type one error in the Unacceptable scoring. No acceptable studies were inaccurately classified as Unacceptable. • The second method was to reduce the number of studies that received an overall High rating. The majority of overall scores in EPA's initial evaluations during piloting tended to be High. Therefore, EPA strived to revise the criteria to provide more gradation in the scoring to more accurately and objectively distinguish studies of the highest quality from medium and low quality studies. To do this, EPA removed the High criterion from some metrics, particularly in dichotomous metrics (High/Low or High/Unacceptable) that were primarily being binned as High by reviewers

		across the majority of the studies. These dichotomous metrics were contributing to the overall quality scores being skewed towards High. To address this, EPA shifted some of the dichotomous metrics such that the highest metric score possible (for all studies) is a Medium. The change led to the dichotomous metrics having less significant impact to the numerical scoring and the overall quality rating for each study. • With the aforementioned changes to the criteria, EPA observed fewer studies with Unacceptable ratings and more studies shifting from High to Medium, with only the highest quality studies receiving a High overall rating. Out of the ~200 relevant epidemiologic studies and cohorts evaluated for data quality for the first 10 TSCA chemicals, the majority (~80%) still scored as High or Medium. The remaining ~20% of studies scored Low or Unacceptable. EPA is confident that no studies of acceptable quality were inappropriately assigned as Unacceptable. EPA is also confident that the revised criteria bins the quality levels of these epi studies more appropriately than the previous iteration. Additional refinements to the epidemiologic data evaluation criteria are likely to occur as EPA's validation and process improvement efforts continue.
Data Integration		
24, 48, 58	• The approach to evaluation of quality is clearly addressed in the supplemental documents for the risk evaluation, but the approaches for evaluation of consistency, relevance, coherence, and biological plausibility are not as clearly documented. • While EPA provides the overall study quality ratings for	• EPA will work with the National Academy of Sciences, Engineering, and Medicine (NASEM) TSCA Committee to consider revisions to the data quality evaluation criteria and options regarding integrating evidence within and across evidence streams (human, animal, mechanistic data). EPA proposes to use a more

	the pertinent studies for each endpoint, it is not clear how final conclusions were reached for all hazard endpoints. • The failure to provide a pre-established protocol for evidence integration and instead relying on a "weight-of-the-scientific evidence narrative" does not align with best practices shared by leading systematic review methods. • A specific weight-of-evidence methodology should be presented. • EPA should more clearly and transparently present biologically robust, weight of evidence assessments where data integration is required, such as the Organization for Economic Cooperation and Development (OECD) Adverse Outcome Pathway (AOP) methodology or the mode of action (MOA) approach initially championed by the World Health Organization (WHO)/International Program on Chemical Safety (IPCS).	structured framework for evidence integration for the next set of chemicals evaluated under TSCA.

3. Environmental Fate, Exposure & Effects

Charge Question 3.1: Please comment on the data, approaches and/or methods used to characterize exposure to aquatic receptors in surface water. What other additional information, if any, should be considered?		
#	**Summary of Comments for Specific Issues Related to Charge Question 3**	**EPA/OPPT Response**
Dismissal of Available Environmental Exposure Data		
SACC	The Committee recommended inclusion of all reasonably reliable data for aqueous 1,4-Dioxane concentrations, 1,4-Dioxane concentrations in sediment, and aquatic toxicity results with aggregate weighting factors related to the quality of each study. This approach will reward studies of the highest quality, while not ignoring studies that may be outliers or that were performed in an era when the current record keeping rules were not established. For example, extant data describing 1,4-Dioxane in surface water could be used rather than modeled surface water concentrations.	In EPA's 2018 Problem Formulation, ambient surface water monitoring data from STORET and NWIS were noted to range from 0.568 to 100 µg/L. EPA also conducted screening-level aquatic exposure modeling during problem formulation that informed the decision not to further analyze the pathway during risk evaluation. Predicted levels of 1,4-dioxane in surface water from this screen were as high as 11,500 µg/L that was linked to releases from facilities. EPA included additional sources, as identified in SACC and public comments, in the risk evaluation to better characterize surface water levels of 1,4-dioxane that aquatic species could be exposed to. While none of these reported levels exceeded levels predicted from EFAST modeling, they are now referenced for a more robust characterization of 1,4-dioxane in surface waters in the risk evaluation.
24, 58	For environmental exposure data, EPA did not use the best available science as directed by TSCA. Available empirical data were not always considered, and in some instances, there was a reliance on outdated or incorrect data. Exclusion of reasonably available information is contrary to TSCA policy.	EPA conducted qualitative and quantitative analyses in the problem formulation stage that informed the level of environmental analysis in the risk evaluation. Based on this effort during problem formulation, environmental exposure pathways for ecological receptors were not further analyzed during risk evaluation. However, EPA incorporated the analysis in the final risk evaluation with updates to correct TRI release information, incorporate indirect dischargers, and apply an updated acute COC. Reasonably available surface water discharge,

Charge Question 3.1: Please comment on the data, approaches and/or methods used to characterize exposure to aquatic receptors in surface water. What other additional information, if any, should be considered?		
#	**Summary of Comments for Specific Issues Related to Charge Question 3**	**EPA/OPPT Response**
		environmental fate, and ecological toxicity data were utilized during problem formulation to support the decision to conduct no further analysis for environmental exposure pathways.
42, 43, 60, 61, 62	Submitters provided multiple data monitoring points indicating 1,4-dioxane levels in rivers, drinking water, ground water, and surface water that are orders of magnitude above EPA advisory levels; these empirical data were not considered in the Risk Evaluation. This includes 105 site investigation reports measuring 1,4-dioxane's presence in the environment. • Samples were collected from: wastewater treatment plant discharges, Cape Fear River, Haw River, intake water for Pittsboro's drinking water treatment plant, ground water and landfill leachate in Minnesota, and treated wastewater effluent. • Available data reporting 1,4-dioxane levels in sludge from a manufacturing facility in Fayetteville, NC report high levels, establishing exposure from biosolids can be significant. These data were not considered.	Drinking water exposures to the general population via surface and/or groundwater sources were not within the scope of this evaluation (See Section 1.4.2 of the final risk evaluation). However, these data in surface water were used in the final risk evaluation to estimate incidental oral and dermal exposure to the general population from recreational activities (*i.e.*, swimming) in ambient water. Regarding the aquatic exposure assessment, while the referenced surface water data may indicate levels in the environment above EPA and/or state advisory levels, they were not greater than the predicted (modeled) estimates used during problem formulation to determine that no further analysis on the aquatic exposure assessment to ecological receptors was warranted during risk evaluation. Predicted levels of 1,4-dioxane in surface water, as reported in the final problem formulation and the final risk evaluation, are as high as 11,500 µg/L for acute scenarios, whereas the highest level of 1,4-dioxane reported in the submitted surface water sources is 1,405 µg/L. • EPA included additional surface water monitoring data sources as identified in SACC and public comments, to better characterize surface water levels

Charge Question 3.1: Please comment on the data, approaches and/or methods used to characterize exposure to aquatic receptors in surface water. What other additional information, if any, should be considered?		
#	Summary of Comments for Specific Issues Related to Charge Question 3	EPA/OPPT Response
		of 1,4-dioxane that aquatic species could be exposed to. These data cover measured levels of 1,4-dioxane in the Cape Fear Watershed; Cape Fear, Deep, and Haw Rivers (including near the Pittsboro drinking water intake), and Minnesota surface waters. While none of these reported levels exceeded levels predicted from EFAST modeling, they are now referenced for a more robust characterization of 1,4-dioxane in surface waters. The referenced Minnesota landfill leachate data were not utilized based on the scope of the evaluation (See Section 1.4.2). • The value of 20.4 ppm measured in North Carolina likely represents an extreme case, and was measured in sludge, not dewatered and processed biosolids. Even so, it is only somewhat higher than the chronic aquatic COC of 14.5 ppm (an aqueous concentration, so comparison with the sludge value would require correction for moisture content). So, while a hypothetical direct exposure to this sludge may be associated with ecological risk, the risk for the indirect pathway of runoff from land-applied biosolids is extremely low.
24, 58	• The 2015 data used did not include indirect discharges to water. The justification for excluding this data was insufficient and did not meet the TSCA mandate to use "the best available science." • 2016-2018 TRI data, which report higher water release values than the 2015 document, were not included in the risk evaluation. This resulted in an underestimation of the	• EPA's first-tier aquatic exposure modeling effort initially did not include indirect discharges or transfers off-site for waste treatment. In response to public comment, EPA has augmented this first-tier analysis to include indirect dischargers (*i.e.*, facilities reporting off-site transfers to POTW for treatment) for the years analyzed (2014-2015).

Charge Question 3.1: Please comment on the data, approaches and/or methods used to characterize exposure to aquatic receptors in surface water. What other additional information, if any, should be considered?		
#	**Summary of Comments for Specific Issues Related to Charge Question 3**	**EPA/OPPT Response**
	impact from water releases.	• The modeling done during problem formulation to conduct the analysis of environmental exposure for aquatic species used the two most recent complete years of TRI reporting at the time of problem formulation – 2014 and 2015. EPA's risk evaluation was informed by the decision not to further analyze environmental pathways set forth in its problem formulation.
24, 58	• Air, land, and disposal or other release data from the 2015 Toxic Releases Inventory (TRI) data were not considered under the false assumption that these would be regulated by other environmental statutes. • Air emission values reported for 1,4-dioxane through the National Emissions Inventory (NEI), which are much higher than those reported under the TRI, were not cited or evaluated. • According to the 2018 Toxics Release Inventory data, a number of manufacturing facilities emit 1,4- dioxane to the air and release it to the water. These releases were not included in the risk evaluation.	• Section 1.4.2 in the risk evaluation provides details as to why certain pathways were not included in the risk evaluation. However, because there is no nationally recommended Ambient Water Quality Criteria under the CWA, EPA included exposures to the general population via ambient surface water. EPA evaluated hazards and exposures to the general population from ambient surface water for the conditions of use in the risk evaluation. The final risk evaluation includes 1,4-dioxane water releases based on 2018 TRI and DMR reporting. These releases were used to model ambient water concentrations and estimate incidental oral and dermal exposure to the general population from recreational activities (*i.e.,* swimming). • Air releases were not included in the scope of the risk evaluation, as stated in Section 1.4.2. • In its revision, EPA included a release assessment describing releases to water. EPA has augmented its original first-tier aquatic exposure assessment to include additional facilities releasing and reporting to

Charge Question 3.1: Please comment on the data, approaches and/or methods used to characterize exposure to aquatic receptors in surface water. What other additional information, if any, should be considered?		
#	**Summary of Comments for Specific Issues Related to Charge Question 3**	**EPA/OPPT Response**
		TRI for the years analyzed during problem formulation (2014-2015). The revised first-tier aquatic exposure assessment includes the direct and indirect discharging facilities.
43	EPA did not consider data from the Third Unregulated Contaminant Monitoring Rule ("UCMR3") that includes comprehensive monitoring data.	Data from UCMR3, which provides nationally representative data on the occurrence of contaminants in drinking water, were not utilized in the aquatic exposure assessment due to a focus on ambient surface water levels since general population drinking water exposures were not included in the scope of the risk evaluation (see Section 1.4.2).
SACC	On page 46: Clarity is increased by listing the "conservative" assumptions in estimating values for surface water in a bulleted form. Unregulated Contaminant Monitoring Rule (UCMR-3) data can serve this purpose (Adamson *et al.*, 2017). Similarly, surface water values (secondary and tertiary wastewater values) from the State of California can also be used for Measured Environmental Concentrations (MEC) (Anderson *et al.*, 2018). Estimated concentrations can be placed in context by using UCMR data. Additionally, Simonich *et al.*, (2013) determined that 38 of 40 wastewater treatment plant (WWTP) discharges contained detectable 1,4-Dioxane amounts, but at lower concentrations than modeled. This suggests that sorption or volatilization from WWTPs may not have been adequately assessed to protect workers and the broader population from 1,4-dioxane inhalation or exposure to biosolids.	Data from UCMR3, which provides nationally representative data on the occurrence of contaminants in drinking water, were not utilized in the aquatic exposure assessment due to a focus on ambient surface water levels since general population exposures via drinking water were not included in the scope of the risk evaluation (see Section 1.4.2). In its revision of the draft risk evaluation, EPA included additional sources to characterize surface water levels of 1,4-dioxane that aquatic species could be exposed to. While none of these reported levels exceeded levels predicted from EFAST modeling, they are now referenced for a more robust characterization of 1,4-dioxane in surface waters. Removal by volatilization may vary depending on WWTP design, but exposures via air are out of scope for

Charge Question 3.1: Please comment on the data, approaches and/or methods used to characterize exposure to aquatic receptors in surface water. What other additional information, if any, should be considered?		
#	**Summary of Comments for Specific Issues Related to Charge Question 3**	**EPA/OPPT Response**
		this risk evaluation because 1,4-dioxane is regulated under the Clean Air Act (See Section 1.4.2). EPA expects that sorption of 1,4-dioxane to sludge will be negligible in every WWTP due to its organic carbon-water partition coefficient (log K_{OC} = 0.4), but 1,4-dioxane is expected to be present in the biosolids-associated water at concentrations similar to the bulk water in the sludge settling tank. Direct human exposures to biosolids are not expected, but exposures resulting from land-applied biosolids are expected to be via air from volatilized 1,4-dioxane or via drinking water as a result of surface runoff from biosolids-treated land. However, exposures via air and drinking water are out of scope for this risk evaluation because 1,4-dioxane is regulated under the Clean Air Act and Safe Drinking Water Act (see Section 1.4.2).
58	272 on-topic studies identified as relevant to analyzing aquatic exposures were not evaluated.	As described in the caption to Figure 2-6 in the draft risk evaluation, EPA determined during problem formulation that environmental exposure pathways for ecological receptors were within scope but would not be further analyzed based on quantitative and qualitative analyses covering ecological pathways (U.S. EPA, 2018c). These analyses were made ahead of the data screening stage for these data sources, and therefore, the environmental exposure references were excluded, as they did not meet the risk evaluation PECO statement.
58	EPA cannot disregard data (or consider it to be zero) where the analytical sample values have extremely high method detection limits (MDLs).	EPA thanks the commenter for pointing out this consideration of the STORET data cited in the draft risk evaluation. While EPA did consider the referenced range

Charge Question 3.1: Please comment on the data, approaches and/or methods used to characterize exposure to aquatic receptors in surface water. What other additional information, if any, should be considered?		
#	**Summary of Comments for Specific Issues Related to Charge Question 3**	**EPA/OPPT Response**
	• The justification for discarding MDLs that were nearly double the chronic aquatic COC was invalid.	from STORET for years 2007 through 2017 in its draft risk evaluation, the RQs presented in Table 5-2 are dependent on results of the screening-level modeling analysis. Additionally, though some of the sampling MDLs were higher than the chronic COC, EPA did not use unreported/unknown levels below such MDLs as the basis for an RQ or unreasonable risk determination. In response, EPA has augmented its discussion of uncertainty in Section 4.3.2 with a discussion of this point.
SACC	Using measured surface water concentrations is particularly important. The surface water data range of 0.5-100 µg/L appears to be erroneously low. Information published in 2016 by Sun, Loez, and Knappe, found 543 µg/L in one sample from the Cape Fear River, North Carolina and over 1,400 ug/L in WWTP effluent. The 543 µg/L concentration in surface water was determined using an EPA method (Sun *et al.,* 2016). These surface water measurements exceed the Agency exposure estimate for surface water by a factor of 4.4-5.4. The Committee recommended including these data in the estimates of chronic exposure and factoring these into the final risk. These values are useful in estimating the distribution function used in estimating higher percentile concentrations.	The measured surface water concentrations cited from STORET would not include individual published data sources, such as those noted by the SACC panel. Therefore, they may reflect lower levels than those reported elsewhere based on differences in sampling methods and sampling location, *e.g.*, proximity to sources of 1,4-dioxane in surface water. EPA did not conduct a comprehensive review of surface water monitoring data for 1,4-dioxane on the basis that the screening-level modeling conducted during problem formulation supported performing no further analysis. The 543 µg/L cited from Sun *et al.,* (2016) does not exceed either the chronic or acute concentrations of concern (COCs) derived in the ecological hazard assessment for 1,4-dioxane, which are 57,500 and 14,500 µg/L, respectively. 543 µg/L is also less than the high-end exposure concentrations estimated in EFAST, which included a maximum estimate of 11,500 µg/L for a 10-day, acute release scenario.

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		In its revision of the draft risk evaluation, EPA included additional sources to characterize surface water levels of 1,4-dioxane that aquatic species could be exposed to. While none of these reported levels exceeded levels predicted from EFAST modeling, they are now referenced for a more robust characterization of 1,4-dioxane in surface waters.
Unsupported Assumptions Related to Environmental Exposure		
24, 55, 58	The data to support the following claims were not provided in the risk evaluation: • "Recent monitoring data on ambient surface water levels indicate relatively low levels." (p. 213) • EPA acknowledges "[T]here are relatively fewer data available on 1,4-dioxane levels in surface water," (p. 28), indicating a data gap that EPA apparently will do nothing to address. • "Limited sediment monitoring data for 1,4-dioxane that are available, suggest that 1,4-dioxane is present in sediments." (pp. 131, 211).	• In Section 3.3.1, EPA states "National-scale monitoring data from EPA's STOrage and RETreival (STORET) and National Water Information System (NWIS) for the past ten years, shows that 1,4-dioxane is detected in surface water. The data points show a detection rate of approximately 6% for this media, with detections ranging from 0.568 to 100 μg/L." • EPA acknowledges that it did not include additional references to ambient surface water levels based on its approach using a screening-level aquatic exposure assessment during problem formulation supportive of not doing further analysis during risk evaluation. In its revision of the draft risk evaluation, EPA included additional sources to characterize surface water levels of 1,4-dioxane that aquatic species could be exposed to. While none of these reported levels exceeded levels predicted from EFAST modeling, they are now referenced for a more robust characterization of 1,4-dioxane in surface waters.

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		• As described in Section 3.1 and Section 5.1.1, EPA's assessment of the fate of 1,4-dioxane in sediment was based on a qualitative consideration of its physical-chemical properties. Based on its log K_{OW} and water solubility, 1,4-dioxane in sediment will be present primarily in the sediment porewater as opposed to sorbed to the solids.
SACC	In the Evaluation (page 21, and also Table 2-8 in the Problem Formulation document (U.S. EPA 2018), EPA states it "did not identify any exceedances of benchmarks to aquatic vertebrates, aquatic invertebrates, and aquatic plants from exposures to 1,4-Dioxane in surface waters." Missing from this list is discussion of toxicity to benthic organisms. Adverse effects were assessed for only one aquatic invertebrate species (Evaluation page 80). The absence of benthic organism data represents a serious data gap, as does the absence of multiple chronic toxicity studies for any species or guild (Kaviraj *et al.*, 2004, Bernot *et al.*, 2005, Saha *et al.*, 2006, Dobbins *et al.*, 2009, Guo *et al.*, 2012, Chen *et al.*, 2018, Liu *et al.*, 2018, Yang *et al.*, 2018, Ibrahim and Sayed 2019, Kang *et al.*, 2019). Sediment organisms have quite different sensitivities to many toxicants than are surface invertebrates, and bivalves are often much more sensitive (Kaviraj *et al.*, 2004, Liu *et al.*, 2018, Dobbins *et al.*, 2009). The assumption of similar toxicity to other species has questionable merit. Please note that the needed data can be obtained within the time frame of risk assessment finalization.	EPA recognizes that benthic/sediment-dwelling organisms are highly sensitive to various xenobiotics and the hazard could be very different from those that dominate in the water column. However, after examining the physical/chemical properties of 1,4-dioxane, EPA concludes that the toxicity will be low to sediment-dwelling organisms that are exposed to pore water and sediment-dwelling species that were characterized for hazard in the surface water can be used as a surrogate species. EPA stands by the rationale for using the toxicity profile for *Daphnia magna* and *Gammarus pseudolimnaeus* to read-across for 1,4-dioxane's effects to sediment dwelling organisms. It has been well documented that *D. magna* has been used to study the effects of hazardous chemicals to pore water and sediment contaminants such as metals and organic compounds (Giesy *et al.*, 1998; Othoudt *et al.*, 1991; Ristola *et al.*, 1995; Coen and Janssen, 1998; Suedel and Rodgers 1996; CPA, 2004; Parkak *et al.*, 2010). Other surface water species such as *Brachionus calyciflorus* and *Thamnocephalus plaxyurus* (Heida and Oost, 1996) have also been used to determine the effects of

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		hazardous chemicals in pore water. Although these procedures and protocols have been updated, the results from these studies have been used for establishing benchmark dose levels for sediment toxicity.
24, 50, 55, 58	It is unclear how EPA can state that there is a lack of unreasonable risks to the environment (pp. 21, 156) when significant data gaps were identified, including ecotoxicity data for soil or sediment dwelling organisms, plants, terrestrial species, and avian species, and a lack of aquatic chronic toxicity data except for fish. • EPA should use its information authorities through TSCA to address identified data gaps.	EPA derived environmental concern levels based on hazard values from highly acceptable studies and reported exposure levels in the environment. EPA stands by the analysis that was conducted to determine the hazard and risk of 1,4-dioxane to the environment. After a complete analysis of the hazard data of 1,4-dioxane, EPA is confident that the risks of this chemical are low to the aquatic and terrestrial organisms. These conclusions are supported by other countries that have investigated the hazard of 1,4-dioxane. EPA recognizes that benthic/sediment-dwelling organisms are highly sensitive to various xenobiotics and the hazard could be very different from those that dominate in the water column. However, after examining the physical/chemical properties of 1,4-dioxane, EPA concludes that the toxicity will be low to sediment-dwelling organisms that are exposed to pore water and sediment-dwelling species that were characterized for hazard in the surface water can be used a surrogate species. EPA stands by the rationale for using the toxicity profile for *Daphnia magna* and *Gammarus pseudolimnaeus* to read-across for 1,4-dioxane's effects to sediment-dwelling organisms. It has been well documented that *D. magna* has been used to

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		study the effects of hazardous chemicals to pore water and sediment contaminants such as metals and organic compounds (Giesy *et al.,* 1998; Othoudt *et al.,* 1991; Ristola *et al.,* 1995; Coen and Janssen, 1998; Suedel and Rodgers 1996; CPA, 2004; Parkak *et al.,* 2010). Other surface water species such as *Brachionus calyciflorus* and *Thamnocephalus plaxyurus* (Heida and Oost, 1996) have also been used to determine the effects of hazardous chemicals in pore water. Although these procedures and protocols have been updated, the results from these studies have been used for establishing benchmark dose levels for sediment toxicity.
24, 58	The water release value reported in the risk evaluation is not the total water release value of 56,935 lbs as reported in TRI 2015. EPA removed discharges to sewage treatment plants from the total water release; an explanation for this decision should be provided.	EPA's intention was not to exclude indirect discharges or transfers to wastewater treatment sites (*e.g.,* POTWs) from its first-tier screening level aquatic exposure assessment as described in the problem formulation. In response to this comment, EPA compared the TRI release information (direct and indirect discharges) used during problem formulation to TRI release information extracted from EPA's TRI Explorer website and identified some inconsistencies. EPA found that some of the site-specific off-site waste transfers to POTWs for treatment were of a greater magnitude than the site-specific direct discharges modeled for years 2014-2015 during problem formulation. Additionally, some of the facilities originally included as direct dischargers were also identified as errors. Therefore, EPA has corrected its initial modeling assessment of TRI direct dischargers and added sites reporting off-site waste transfers to

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		POTWs for treatment. The modeling is still done on a site-specific basis. The updates and corrections are shown in Appendix E of the final risk evaluation.
58	It was assumed that no exposures were expected to occur during distribution because chemicals are packaged in closed system containers. Data/documentation to support this assumption must be provided. • Are drums, bottles, and pails that may be opened still considered "closed" systems?	The chemical packagers and end-users incorporated closed systems into their chemical management solutions. Closed system containers, unless otherwise intentionally opened, are sealed during transport, distribution and handling to prevent accidental releases. Thus, closed system containers under normal operation will not result in exposure to 1,4-dioxane.
58	EPA states that 1,4-dioxane "is not likely to accumulate in wastewater biosolids…" (p. 45), and that "exposures to surface water from biosolids are estimated to be low" (p. 131, 212); support for this assumption should be provided. • To accurately assess impacts to the environment from land-applied biosolids, a total accounting of the 1,4-dioxane in the biosolids should be developed. • The assumption that land-applied biosolids are only generated through wastewater treatment plants (WWTP) is incorrect. ○ Available data reporting 1,4-dioxane levels in sludge from a manufacturing facility in Fayetteville, NC report high levels, establishing exposure from biosolids can be significant. These data were not considered. • It cannot be assumed that, just because 1,4-dioxane does not partition strongly to organic material, that there is no	• EPA's assessment of the fate of 1,4-dioxane in land-applied biosolids was based on a qualitative consideration of its physical-chemical properties, combined with a comparison to the scenario of direct surface water discharge. Given its high water solubility and low Henry's law constant and log K_{OC}, 1,4-dioxane in wastewater treatment influent will be associated primarily with the water phase and will not volatilize or adsorb to solids. 1,4-Dioxane in biosolids will be present in the porewater of the material. The production of biosolids from waste streams involves dewatering processes, which will fractionate 1,4-dioxane and result in lower volume concentrations of the compound in biosolids compared to those found in influent and effluent waters. Less than 2% of 1,4-dioxane in wastewater treatment plant influent is expected to be present in

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	pathway for exposure via sediment or land-applied biosolids. The empirical fact that 1,4-dioxane is present in these media must be considered.	biosolids. Thus, while leaching from land-applied biosolids does represent a plausible pathway for transport of 1,4-dioxane, fractionation in wastewater treatment and environmental dilution mean that the masses introduced via this pathway will be far lower than those associated with direct discharge to surface water. As assessed elsewhere in the risk evaluation, surface water concentrations are predicted to be well below the chronic COC for aquatic organisms. The value of 20.4 ppm (in solids) measured in North Carolina likely represents an extreme case, and was measured in sludge, not fully processed biosolids. Even so, it is only somewhat higher than the chronic aquatic COC of 14.5 ppm (an aqueous concentration, so comparison with the sludge value would require correction for moisture content). So, while a hypothetical direct exposure to this sludge may be associated with ecological risk, the risk for the indirect pathway of runoff from land-applied biosolids is extremely low. • Based on its log K_{OC} (0.4) and water solubility (>800 mg/L), 1,4-dioxane does not partition to soil and sediment. In a Level III fugacity model assuming 100% of emissions to soil, it is estimated that 7% of 1,4-dioxane will be in soil at equilibrium, 93% will be in air, and <0.1% will be in water or sediment. Thus, based on physical/chemical and fate properties, 1,4-dioxane may be expected to be present in soil and sediment, but exposure from soil

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		and sediment is likely to be negligible compared to exposure via air.
43, 50	The risk evaluation states the physical-chemical properties of 1,4-dioxane were used to determine that sediment, soil and biosolids were not relevant pathways. It is not clear that any investigations were done to identify empirical monitoring data. If concentrations were detected in these media, then the pathways should have been evaluated. • Industrial biosolids delivered to a North Carolina composting plant contained 1,4-dioxane at 20,000 parts per billion—a high level considering that EPA's health advisory for the chemical is 35 parts per billion in drinking water.	EPA conducted qualitative and quantitative analyses in the problem formulation stage that informed the level of environmental analysis in the draft risk evaluation. Based on this effort during problem formulation, environmental exposure pathways for ecological receptors were not further analyzed during risk evaluation. • The production of biosolids from waste streams involves dewatering processes, which will fractionate 1,4-dioxane and result in lower volume concentrations of the compound in biosolids compared to those found in influent and effluent waters. Less than 2% of 1,4-dioxane in wastewater treatment plant influent is expected to be present in biosolids. Thus, while leaching from land-applied biosolids does represent a plausible pathway for transport of 1,4-dioxane, fractionation in wastewater treatment and environmental dilution mean that the masses introduced via this pathway will be far lower than those associated with direct discharge to surface water. The value of 20.4 ppm (in solids) measured in North Carolina likely represents an extreme case, and was measured in sludge, not fully processed biosolids.
24, 58	EPA states that measured and estimated levels of 1,4-dioxane in the environment are sufficiently below the acute and chronic	This conclusion was based on the comparison of estimated (modeled) surface water levels of 1,4-dioxane

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	aquatic concentrations of concern (COCs) without providing analysis to support this conclusion.	to acute and chronic COCs, included in Section 4.1 of the draft risk evaluation. EPA disagrees with the commenter's conclusion that the analysis for deriving the concern levels in the aquatic environment are not supported. EPA has made revisions in the environmental hazard section of the risk assessment that clarifies the methods used to derive the acute and chronic concentrations of concern. Also, during problem formation, EPA conducted a preliminary assessment regarding the hazard and risk of 1,4-dioxane to aquatic receptors. EPA identified the following sources of environmental hazard data for 1,4-dioxane: (Health Canada, 2010; ECJRC, 2002; OECD, 1999; NICNAS, 1998); and the European Chemicals Agency (ECHA) Database. Studies published since 2003 were identified in the literature search for 1,4-dioxane and were reviewed as described in Application of Systematic Review in TSCA Risk Evaluations (U.S. EPA, 2018a) and Strategy for Assessing Data Quality in TSCA Risk Evaluations (U.S. EPA, 2018b). These studies have been summarized in section 2.4 Hazards (Effects) of the risk evaluation. The data show that 1,4-dioxane's toxicity is low to aquatic organisms. Based on the physical/chemical properties of 1,4-dioxane, the chemical is expected to migrate through soil and the final fate will be to groundwater. These conclusions have been in the environmental fate, hazard and risk characterization sections of the risk evaluation.

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24, 58	EPA's modeling of surface water concentrations includes assumptions that are not necessarily conservative, despite EPA's claims to the contrary. • For example, EPA points to the surface water modeling assumption that "[w]astewater treatment removal is assumed to be 0% for this exercise" (p. 29); yet its own modeling of wastewater treatment removal efficiency using EPISuite STP module indicates removal rates will be very low, on the order of 2% (p. 24). Far from being a conservative assumption, this use of 0% is a reasonable conclusion based on the available data. • Despite a promised "full table of results, see Appendix E" (p. 29), that table provides only EPA's conclusions and none of its analysis.	• EPA states that "wastewater treatment removal is assumed to be 0% for all direct discharges, as reported direct loadings/releases are assumed to account for any pre-release treatment" in Appendix E of the final risk evaluation. This is not a claim of conservatism, but an explanation of modeling inputs. • Table E-3 in Appendix E includes the values needed to cross-check results using the publicly available model used. Additionally, the supplemental file published along with the draft risk evaluation contains detailed facility information for additional context. All sites modeled are shown, along with release inputs and key results (concentration based on low-flow 7Q10 conditions and predicted days of exceedance of the chronic COC for non-acute release scenarios [*i.e.*, those with 20 days or more of release]). Because the predicted surface water concentrations based on the low-flow (7Q10) conditions are typically used by OPPT to assess ecological risk, this was the only predicted concentration in Tables E-3 through E-5. EPA understands that the table does not show certain elements that would be more comprehensive. Therefore, in the final risk evaluation, EPA has included an EFAST output report for a modeled scenario as an example of the source of the values in the result table. EPA has also included in its final risk evaluation a column showing the conversion from reported annual loads in lbs/year to kg/year,

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		which were used in EFAST modeling. These updates are included in the supplemental file: Aquatic Exposure Screen Facility Information.
Environmental Assessment Methodology		
SACC	The rationale for using modeled surface water data rather than measured data is unclear. The relative contribution of "estimated" and "predicted" modeling values seem to describe similar processes and are simply different tools to model concentrations that are unknown or assumed to be unknown. It is also unclear how ambient data were used to confirm model estimates. Given the databases available, there would be greater certainty to use Measured Environmental Concentrations (MECs) rather than Predicted Environmental Concentrations (PECs) for risk assessments.	EPA did not conduct a comprehensive review of surface water monitoring data for 1,4-dioxane on the basis that the screening-level modeling conducted during problem formulation supported no further analysis during risk evaluation. In this way, the modeling done during problem formulation was treated as a first-tier of a tiered assessment approach. In Section 3.3.1, EPA states "National-scale monitoring data from EPA's STOrage and RETreival (STORET) and National Water Information System (NWIS) for the past ten years, shows that 1,4-dioxane is detected in surface water. The data points show a detection rate of approximately 6% for this media, with detections ranging from 0.568 to 100 µg/L." EPA acknowledges that it did not include additional references to ambient surface water levels based on its approach using a screening-level aquatic exposure assessment during problem formulation supportive of not doing further analysis during risk evaluation. In the final risk evaluation, EPA included additional sources to better characterize surface water levels of 1,4-dioxane that aquatic species could be exposed to. While none of these reported levels exceeded levels predicted from EFAST

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		modeling, they are now referenced for a more robust characterization of 1,4-dioxane in surface waters.
SACC	While Monte Carlo analyses was used to incorporate variability and examine uncertainty in estimates obtained from models for inhalation exposure estimates. Monte Carlo methods were not similarly used in the examination of estimates of environmental exposures. No reasons were given for this decision. Regardless of whether Monte Carlo methods were used, uncertainty in the estimates presented for environmental exposures needs to be addressed in the Evaluation. • Monte Carlo analyses should be included in environmental estimates, and this will require a robust data set.	In Section 4.3.2 of the risk evaluation, EPA characterizes uncertainty surrounding the prediction of surface water concentrations using EFAST. While EPA did not conduct a quantitative uncertainty analysis for the model itself, the risk evaluation discusses uncertainty of the key inputs and incorporates variability by modeling multiple release day scenarios for each facility modeled, resulting in a range of surface water estimates. The key modeling input that drives surface water concentration estimates is the release volume (kg/site/day). Many of the facility discharges are reported in TRI or DMR as a single annual loading estimate; there may not be an available range to consider modeling to capture site-specific variability in release volume. Therefore, from facilities reporting these data on a site-specific basis. The variability stems from the uncertainty surrounding possible annual release days, which EPA did consider by modeling 1, 20, and 250 days of release for direct dischargers. EPA's approach is conservative, as the risk characterization relied on the highest modeled surface water concentrations (*i.e.*, those associated with the lowest release day scenario for a given discharger). • EPA develops Monte Carlo analyses in environmental estimates when it is appropriate. For 1,4-dioxane, first-tier analyses indicated that

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		a more comprehensive analysis (*i.e.,* Monte Carlo) was not warranted.
SACC	The Agency erroneously avoided using the aqueous concentration upper bound (11,500 µg/L: Table E-3) for the chronic aquatic environmental exposure assessment. The 11,500 µg/L value is not an acute value it was a 10-day average (Table E-3; footnote b) and it approaches the chronic toxicity threshold (14,500 µg/L effect). Unlike all other facilities for which releases were modeled, the DAK facility was not considered for the single day release. Considering only the 10-day release scenario decreased acute surface concentration estimates by factor of 10. Thus, neither a worst case nor high percentile estimate is presented in this assessment. Using the upper bound is an appropriate choice given the modeled nature of this exposure estimate. Using 10 x 11,500 µg/L (to account for the unmodeled single day release rather than the modeled 10-day release) would produce an acute RQ of 0.46.	As the SACC panel pointed out, a footnote explains that a 10-day scenario was utilized for this site based on engineering assumptions related to the lowest number of operating days for a site falling within this standard industrial category. However, based on EPA's standard procedures for new chemicals, a 10-day release scenario is still considered acute in nature and would still be compared against the acute COC. Only releases of 20 days per year or more are compared against the chronic COC.
Scope of Environmental Exposure Assessment		
SACC	Exposure scenarios that include consumers should be included in the 1,4-dioxane hazard determination. The presence of 1,4-Dioxane in plastic, other commercially available products, surface water, drinking water, groundwater, and in sediments is well documented and the risks to human health are as yet unassessed by the Agency. The American Grocers and the Cleaning Products Institute (both trade associations) agree.	Regarding consumers, as explained in the scope document for 1,4-dioxane, 1,4-dioxane may be found as a contaminant in consumer products and/or commercial products that are readily available for public purchase. However, it is present as a result of byproduct formation during manufacture of ethoxylated chemicals that are subsequently formulated into products. EPA did not evaluate exposures to consumers and bystanders from byproduct or contaminant exposure in this risk evaluation. In the final risk evaluation, eight consumer conditions of use are evaluated based on the uses

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		identified in EPA's 2015 TSCA Work Plan Chemical Problem Formulation and Initial Assessment of 1,4-Dioxane (U.S. EPA, 2015). An additional systematic review effort was undertaken for consumer exposures to identify, screen, and evaluate relevant data sources. These conditions of use include use of 1,4-dioxane as a surface cleaner, antifreeze, dish soap, dishwasher detergent, laundry detergent, paint and floor lacquer, textile dye, and spray polyurethane foam (SPF). 1,4-Dioxane may be found in these products at low levels (0.0009 to 0.02%) based on its presence as a byproduct of other formulation ingredients (*i.e.*, ethoxylated chemicals). Inhalation exposures are estimated for consumers and bystanders and dermal exposures are estimated for users. Acute exposures are presented for all consumer conditions of use, while chronic exposures are presented for the conditions of use that are reasonably expected to involve daily use intervals (*i.e.*, surface cleaner, dish soap, dishwasher detergent, and laundry detergent). See Section 2.4.3 of the final risk evaluation. Please refer to section 1.4.2 in the risk evaluation which provides details as to why certain pathways of exposure to the general population were not included in the scope of the risk evaluation.
SACC	General human population and biota exposure must be assessed by the Agency for inhalation, ingestion, and dermal routes of exposure within the defined time limit for a TSCA assessment.	Environmental exposures via surface water, sediment, and biosolids pathways were quantitatively or qualitatively assessed during problem formulation. Please refer to section 1.4.2 in the risk evaluation which

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	This appropriately broader population should include different sensitive or highly exposed sub-populations. The Agency should consider human exposures from: lawn watering, public pools, and dust abatement at construction sites or on roads. The concentrations of 1,4-Dioxane in sediments should be explicitly summarized or tabulated, not noted as present and dismissed (Problem Formulation: page 41).	provides details as to why certain pathways of exposure to the general population were not included in the scope of the risk evaluation. These excluded pathways include human exposures from the activities such as lawn care, etc. which would be covered by SDWA. However, because there is no nationally recommended Ambient Water Quality Criteria under the CWA, EPA included exposures to the general population via ambient surface water. EPA evaluated hazards and exposures to the general population from ambient surface water for the conditions of use in the risk evaluation. The final risk evaluation includes 1,4-dioxane water releases based on 2018 TRI and DMR reporting. These releases were used to model ambient water concentrations and estimate incidental oral and dermal exposure to the general population from recreational activities (*i.e.*, swimming).
SACC	Exposure assessment through groundwater and other environmental pathways must be evaluated. Data on these pathways should be generated if unavailable. Groundwater is regulated by the Clean Water Act only if it is used for municipal purposes. Omission of groundwater in the exposure assessment means that risks to consumers of groundwater are unknown. Data are available to define the numbers of individuals consuming groundwater from private wells for drinking water and/or irrigation of crops. These data can be used in conjunction with subsurface injection site location information to provide estimates of the numbers of potentially exposed individuals. In many areas, groundwater is directly	Please refer to section 1.4.2 in the risk evaluation which provides details as to why certain pathways of exposure to the general population were not included in the scope of the risk evaluation. Exposures to the general population via drinking water, which includes finished surface and ground water are covered under SDWA. In addition, 1,4-dioxane is a hazardous waste injected into Class 1 underground injection hazardous wells under the jurisdiction of RCRA. Section 1.4.2 in the risk evaluation provides details as to why these pathways were not included in the risk evaluation.

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	recharged from surface waters (example: Edwards Aquifer in Texas) further increasing the numbers of potentially exposed. On page 46, the Agency should determine to what extent groundwater is contaminated by the million pounds of 1,4-Dioxane injected into subsurface zones over the past several years (Table E-1: Class 1 Underground injection column). This human exposure must be considered, given the current use and the fact that millions of U.S. citizens and residents consume and otherwise utilize groundwater from unregulated wells.	
SACC	The frequency of detects in drinking water is less important than the number of persons who are exposed to those concentrations (Problem Formulation: page 43). A population exposure estimate should be provided in the assessment. To accomplish this, data would be needed for large, medium and small water management facilities as well as differing water types, soft, moderately hard, near brackish, effluent dominated, so forth. This should have been pointed out as a data need in the problem formulation process. The omission of exposure through drinking water leaves the 1,4-Dioxane Evaluation incomplete.	Please refer to section 1.4.2 in the risk evaluation which provides details as to why this pathway was not included in the risk evaluation.
19, 24, 43, 50, 58	EPA's reasoning for the exclusion of some environmental exposure pathways is based on the assumption that they will be adequately assessed and managed through other statutes or regulations (including the Resource Conservation and Recovery Act [RCRA], the Clean Air Act [CAA], the Clean Water Act [CWA], the Safe Drinking Water Act [SDWA], and various state programs). However: • EPA did not show or establish that these regulations eliminate any unreasonable risk.	EPA found that exposures to the general population may occur from the conditions of use due to releases to air, water or land. The exposures to the general population via drinking water, ambient air and land pathways falls under the jurisdiction of other environmental statutes administered by EPA, *i.e.*, CAA, SDWA, CERCLA, and RCRA. As explained in more detail in section 1.4.2, EPA believes it is both reasonable and prudent to tailor TSCA risk evaluations when other EPA offices have

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	• No statute that addresses groundwater as a source of exposure was identified, and groundwater or groundwater discharge to surface water are not identified as exposure pathways in the risk evaluation. • Disposal is not limited to RCRA Subtitle C landfills. • Many of these statutes and regulations vary by state and/or are not adequately enforced (*e.g.*, RCRA). • EPA recognized that 1,4-dioxane has been detected in landfill leachate but fails to identify adequate management under state or federal laws.	expertise and experience to address specific environmental media, rather than attempt to evaluate and regulate potential exposures and risks from those media under TSCA. EPA has therefore tailored the scope of the risk evaluations for 1,4-dioxane using authorities in TSCA sections 6(b) and 9(b)(1). EPA did not evaluate hazards or exposures to the general population via drinking water, ambient air, or sediment pathways in the risk evaluation, and as such the unreasonable risk determinations for relevant conditions of use do not account for exposures to the general population. However, because there is no nationally recommended Ambient Water Quality Criteria under the CWA, EPA included exposures to the general population via ambient surface water. EPA evaluated hazards and exposures to the general population from ambient surface water for the conditions of use in the risk evaluation. The final risk evaluation includes 1,4-dioxane water releases based on 2018 TRI and DMR reporting. These releases were used to model ambient water concentrations and estimate incidental oral and dermal exposure to the general population from recreational activities (*i.e.*, swimming).
58	To justify its exclusion of exposures from air emission pathways, in the problem formulation EPA merely provides a list of technology-based standards for certain source categories. EPA provides no analysis whatsoever as to: the extent to which the standards cover the full range of stationary sources of this chemical; the extent and magnitude of releases of the chemical allowed under each of the standards; the duration, intensity, frequency, and number of exposures resulting from those allowable emissions (as required under TSCA section 6(b)(4)(F)(iv)); or any other factors that would be necessary to analyze and determine the extent and nature of potential risk allowed under the standards. EPA has not acknowledged, let alone analyzed, the overall risks to the general population or to vulnerable subpopulations due to the combination of exposures arising from the various sources for which standards exist, not to mention additional emission sources not subject to any standard. EPA has made no attempt to reconcile any such risk with that allowed under TSCA. In the absence of such analyses, there is no basis whatsoever for EPA to assert that air	

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	releases of this chemical have been adequately assessed or that any risks have been effectively managed under TSCA's standards.	
43	Aquatic species were evaluated by using estimated discharges of 1,4-dioxane to surface water from wastewater facilities; this does not include releases from spills or leaching from contaminated sites into groundwater and subsequent transport to surface water. It also does not include data available for wastewater releases.	Spills and leaks generally are not included within the scope of a TSCA risk evaluation because in general they are not considered to be circumstances under which a chemical substance is intended, known or reasonably foreseen to be manufactured, processed, distributed, used, or disposed of. To the extent there may be potential exposure from spills and leaks, EPA is also declining to evaluate environmental exposure pathways addressed by other EPA-administered statutes and associated regulatory programs. First, EPA does not identify 1,4-dioxane spills or leaks as "conditions of use." EPA does not consider 1,4-dioxane spills or leaks to constitute circumstances under which 1,4-dioxane is manufactured, processed, distributed, used, or disposed of, within TSCA's definition of "conditions of use." Congress specifically listed discrete, routine chemical lifecycle stages within the statutory definition of "conditions of use" and EPA does not believe it is reasonable to interpret "circumstances" under which 1,4-dioxane is manufactured, processed, distributed, used, or disposed of to include uncommon and unconfined spills or leaks for purposes of the statutory definition. Further, EPA does not generally consider spills and leaks to constitute

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		"disposal" of a chemical for purposes of identifying a COU in the conduct of a risk evaluation. In addition, even if spills or leaks of 1,4-dioxane could be considered part of the listed lifecycle stages of 1,4-dioxane, EPA has "determined" that spills and leaks are not circumstances under which 1,4-dioxane is intended, known or reasonably foreseen to be manufactured, processed, distributed, used, or disposed of, as provided by TSCA's definition of "conditions of use," and EPA is therefore exercising its discretionary authority under TSCA Section 3(4) to exclude 1,4-dioxane spills and leaks from the scope of the 1,4-dioxane risk evaluation. The exercise of that authority is informed by EPA's experience in developing scoping documents and risk evaluations, and on various TSCA provisions indicating the intent for EPA to have some discretion on how best to address the demands associated with implementation of the full TSCA risk evaluation process. Specifically, since the publication of the Risk Evaluation Rule, EPA has gained experience by conducting ten risk evaluations and designating forty chemical substances as low- and high-priority substances. These processes have required EPA to determine whether the case-specific facts and the reasonably available information justify identifying a particular activity as a "condition of use." With the experience EPA has gained, it is better situated to discern circumstances that are appropriately considered to be outside the bounds of "circumstances… under

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		which a chemical substance is intended, known, or reasonably foreseen to be manufactured, processed, distributed in commerce, used, or disposed of" and to thereby meaningfully limit circumstances subject to evaluation. Because of the expansive and potentially boundless impacts that could result from including spills and leaks as part of the risk evaluation, (*e.g.*, due to the unpredictable and irregular scenarios that would need to be accounted for, including variability in volume, frequency, and geographic location of spills and leaks; potential application across multiple exposure routes and pathways affecting myriad ecological and human receptors; and far-reaching analyses that would be needed to support assessments that account for uncertainties but are based on best available science), which could make the conduct of the risk evaluation untenable within the applicable deadlines, spills and leaks are determined not to be circumstances under which 1,4-dioxane is intended, known or reasonably foreseen to be manufactured, processed, distributed, used, or disposed of, as provided by TSCA's definition of "conditions of use." Exercising the discretion to not identify spills and leaks of 1,4-dioxane as a COU is consistent with the discretion Congress provided in a variety of provisions to manage the challenges presented in implementing TSCA risk evaluation. See *e.g.*, TSCA Sections 3(4), 3(12), 6(b)(4)(D), 6(b)(4)(F). In particular, TSCA Section

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		6(b)(4)(F)(iv) instructs EPA to factor into TSCA risk evaluations "the likely duration, intensity, frequency, and number of exposures under the conditions of use…," suggesting that activities for which duration, intensity, frequency, and number of exposures cannot be accurately predicted or calculated based on reasonably available information, including spills and leaks, were not intended to be the focus of TSCA risk evaluations. And, as noted in the preamble to the Risk Evaluation Rule, EPA believes that Congress intended there to be some reasonable limitation on TSCA risk evaluations, expressly indicated by the direction in TSCA Section 2(c) to "carry out [TSCA] in a reasonable and prudent manner." For these reasons, EPA is exercising this discretion to not consider spills and leaks of 1,4-dioxane to be COUs. Second, even if 1,4-dioxane spills or leaks could be identified as exposures from a COU in some cases, these are generally not forms of exposure that EPA expects to consider in risk evaluation. TSCA Section 6(b)(4)(D) requires EPA, in developing the scope of a risk evaluation, to identify the hazards, exposures, conditions of use, and potentially exposed or susceptible subpopulations the Agency "expects to consider" in a risk evaluation. This language suggests that EPA is not required to consider all conditions of use, hazards, or exposure pathways in risk evaluations. EPA has chosen

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		to tailor the scope of the risk evaluation to exclude spills and leaks in order to focus analytical efforts on those exposures that present the greatest potential for risk. In the problem formulation documents for many of the first 10 chemicals undergoing risk evaluation, EPA applied the same authority and rationale to certain exposure pathways, explaining that "EPA is planning to exercise its discretion under TSCA 6(b)(4)(D) to focus its analytical efforts on exposures that are likely to present the greatest concern and consequently merit a risk evaluation under TSCA...." This approach is informed by the legislative history of the amended TSCA, which supports the Agency's exercise of discretion to focus the risk evaluation on areas that raise the greatest potential for risk. See June 7, 2016 Cong. Rec., S3519-S3520. In addition to TSCA Section 6(b)(4)(D), the Agency also has discretionary authority under the first sentence of TSCA Section 9(b)(1) to "coordinate actions taken under [TSCA] with actions taken under other Federal laws administered in whole or in part by the Administrator." TSCA Section 9(b)(1) provides EPA authority to coordinate actions with other EPA offices, including coordination on tailoring the scope of TSCA risk evaluations to focus on areas of greatest concern rather than exposure pathways addressed by other EPA-administered statutes and regulatory programs, which

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		does not involve a risk determination or public interest finding under TSCA Section 9(b)(2). EPA has already tailored the scope of this risk evaluation using such discretionary authorities with respect to exposure pathways covered under the jurisdiction of other EPA-administered statutes and associated regulatory programs (see section 1.4.3). Following coordination with EPA's Office of Land and Emergency Management (OLEM), EPA has found that exposures of 1,4-dioxane from spills and leaks fall under the jurisdiction of RCRA. See 40 CFR 261.33(d) (defining in part a hazardous waste as "any residue or contaminated soil, water or other debris resulting from the cleanup of a spill into or on any land or water of any commercial chemical product or manufacturing chemical intermediate having the generic name listed [40 CFR 261.33(e) or (f)], or any residue or contaminated soil, water or other debris resulting from the cleanup of a spill, into or on any land or water, of any off-specification chemical product and manufacturing chemical intermediate which, if it met specifications, would have the generic name listed in [40 CFR 261.33(e) or (f)]"); 40 CFR 261.33(f) (listing 1,4-dioxane as hazardous waste no. U108). As a result, EPA believes it is both reasonable and prudent to tailor the TSCA risk evaluation for 1,4-dioxane by declining to evaluate potential exposures from spills and leaks, rather than attempt to evaluate and regulate potential exposures

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		from spills and leaks under TSCA. See Section 2.4.1 in the final risk evaluation for further explanation on a COU basis.
24, 55	The risk evaluation does not evaluate 1,4-dioxane's presence as a byproduct or contaminant; therefore, exposure as a result of its presence in personal care and cleaning products was not evaluated. Down-the-drain discharges and industrial discharges to sewage treatment plants can contribute to groundwater and surface water contamination.	As explained in the scope document, 1,4-dioxane may be found as a contaminant in consumer products that are readily available for public purchase. In the final risk evaluation, eight consumer conditions of use are evaluated based on the uses identified in EPA's 2015 TSCA Work Plan Chemical Problem Formulation and Initial Assessment of 1,4-Dioxane (U.S. EPA, 2015). An additional systematic review effort was undertaken for consumer exposures to identify, screen, and evaluate relevant data sources. These conditions of use include use of 1,4-dioxane as a surface cleaner, antifreeze, dish soap, dishwasher detergent, laundry detergent, paint and floor lacquer, textile dye, and spray polyurethane foam (SPF). 1,4-Dioxane may be found in these products at low levels (0.0009 to 0.02%) based on its presence as a byproduct of other formulation ingredients (*i.e.*, ethoxylated chemicals). Inhalation exposures are estimated for consumers and bystanders and dermal exposures are estimated for users. Acute exposures are presented for all consumer conditions of use, while chronic exposures are presented for the conditions of use that are reasonably expected to involve daily use intervals (*i.e.*, surface cleaner, dish soap, dishwasher detergent, and laundry detergent). See Section 2.4.3 of the final risk evaluation.

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SACC, 58	• The exclusion of subsurface and land disposal from the Evaluation (Problem Formulation: page 44): leaves this TSCA Evaluation incomplete. The Agency must assess the concentrations of 1,4-Dioxane found in air and water (surface and ground) near these injection facilities. This determination cannot be made in the absence of such data. • On page 209: The rationale for no further evaluation of the disposal life stage seems to be tied to the comment in Table B2 that states "2015 TRI data indicates 3 sites reporting 13,422 lbs to landfills. However, 1,4-Dioxane has low sorption to soil." If 1,4-Dioxane is not sorbed to soils it must be released as a vapor or transported to groundwater. Both events produce risks that should be evaluated for human and environmental health. • Sludge or biosolids associated with disposed waste or wastewater treatment facilities other than WWTPs must be included in EPA's analysis of releases to land.	As described in Section 3.1 and Section 5.1.1, based on its water solubility and log K_{OW} 1,4-dioxane in soil, sediment, and biosolids is expected to be in pore water rather than sorbed to the solid fraction of the media. Similarly, 1,4-dioxane released via surface or subsurface disposal is not expected to sorb to soil but will migrate to groundwater or surface water or, in relatively dry conditions, will volatilize to air. As described in Section 2.5.3.3 of the 1,4-dioxane problem formulation (US EPA, 2018), ambient air, drinking water, and ambient water exposure pathways were not assessed in the 1,4-dioxane risk evaluation because those media are addressed under the Clean Air Act, Safe Drinking Water Act, and Clean Water Act.
SACC	The decision not to further analyze background levels of 1,4-Dioxane in any matrix (Problem Formulation: page 47) cannot be supported by any risk assessment principle. Any current use scenarios increase exposures over those currently being experienced.	Exposures pathways, including routes of exposure through drinking water and ambient air, covered under other EPA-administered statutes were not included in the scope of the risk evaluation (see Section 1.4.2 of the final risk evaluation).
Environmental Fate Parameters		
58	• The organic carbon-water partitioning coefficient (KOC) has been estimated, not measured for 1,4-dioxane. Justification is required for the decision to use the lower, less conservative, KOC value when a more protective value	• There are two K_{OC}-estimation methods included in the EPI Suite™ KOCWIN module. The value produced by the molecular connectivity index (MCI) method was presented in the risk evaluation but is

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	was also reported. • An analysis of how the two values may affect uncertainty in the predictive model outputs should be done. ○ Using the lower value, EPA concluded that "1,4-Dioxane is not expected to adsorb to soil and sediment due to its low partitioning to organic matter (estimated log KOC = 0.4)" (p. 212)	similar to the value estimated using the log K_{OW} method (log K_{OC} = 0.4 by MCI and 0.6 by K_{OW}). The MCI method was presented in the risk evaluation because it produced a slightly better fit to measured values for the validation set (MCI r^2 = 0.85, K_{OW} method r^2 = 0.78). • The discrepancy in values is negligible and does not produce uncertainty in the evaluation. Both values lead to the conclusion that 1,4-dioxane will have low potential to sorb to soil, sediment, or biosolids particles.
58	Predictive modeling was used for environmental exposures instead of available empirical environmental monitoring and fate data. This is in violation of TSCA mandates. • EPA identified only one study providing measured values for environmental fate and transport. • In instances where empirical data are not available, uncertainty analysis must be performed to understand the confidence that can be put into the models, specifically soil partitioning modeling and fugacity models, and to understand the impact of uncertainty and variability on estimated risks. • There are circumstances under which fugacity models cannot accurately predict fate and transport of a chemical such as 1,4-dioxane without empirical data or more extensive modeling. • For example, depending on groundwater flow and	• As described in the risk evaluation document, systematic review of fate literature was undertaken only for those environmental pathways and media remaining in the environmental conceptual model after the regulatory overlay was applied. Because EPA determined during problem formulation that no environmental pathways to ecological receptors would be further analyzed in risk evaluation, EPA limited data extraction and evaluation to key data sources used in the 2015 EPA assessment of 1,4-dioxane. The publication about biodegradation in soil microcosms was the only publication used in that risk assessment, so all other fate parameters were estimated using EPI Suite™. • The fugacity and STP removal models in EPI Suite™ rely on p-chem properties for which

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	hydrostatic conditions, there is some evidence that 1,4-dioxane, when present in water as a contaminant, can effectively be stored in place in the pore water and will persist there. This is consistent with the conclusion in the ATSDR Toxicological Profile that "1,4-Dioxane is expected to persist in both water and soil."	measured values were collected (*e.g.*, Henry's law constant and vapor pressure) in conjunction with the organic carbon-water partition coefficient (log K_{OC}) which was estimated using a molecular connectivity index (MCI) method with high reliability. EPI Suite™ also includes a method of estimation log K_{OC} based on log K_{OW}, and the result of that estimation method is similar to the MCI method result. Thus, although measured values were not obtained for some fate endpoints, the uncertainty surrounding fugacity model results is relatively low. • The persistence of 1,4-dioxane in water and soil as described by ATSDR is not inconsistent with the results of the fugacity models in EPI Suite™. The summary statement about the fate of 1,4-dioxane (Section 3.1, pg. 52) was modified to clarify the expected environmental persistence of 1,4-dioxane.
Environmental Risk Characterization		
24, 58	The words "conservative approach" and "conservative assumptions" are inappropriately associated with assessment factors in developing aquatic COCs. Assessment factors cannot be construed as "safety factors" that yield conservative estimates.	EPA has revised the hazard assessment section of the risk evaluation. The updated section includes a weight-of-evidence approach for selecting the most relevant species for the surface water environment. The receptor that is the most relevant on the population level for short-term exposure to 1,4-dioxane in the aquatic environment is the algal endpoint. EPA has modified the calculations for deriving the COC for this endpoint. The COC for algae is derived by dividing the hazard value by an assessment factor of ten. For the chronic endpoint, the most relevant species on the population level is the fish

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		endpoint. The method for deriving the chronic COC has not changed. EPA acknowledges that there are some limitations in applying assessment factors for certain species. However, EPA stands by the analysis that was conducted to determine the environmental hazard, exposure and risk of 1,4-dioxane to the environment. After a complete analysis of the hazard data and exposure assessment of 1,4-dioxane, EPA is confident that the risks of this chemical are low to aquatic organisms. These conclusions are supported by other countries that have investigated the risk of 1,4-dioxane.
23	• EPA compares both monitoring data and modeling data predicting surface water concentrations near discharging facilities to the acute and chronic COCs to generate risk quotients. Why does EPA need to use both modeling and monitoring data? o EPA may want to consider developing guidance or a flow chart describing how both monitoring and modeling data should be handled to inform a tiered approach to assessment. • The above comparison should be re-done using the corrected acute COC calculated from the lowest toxicity value in Table F-1 (575 mg/L).	• Section 4.1.1 of the draft risk evaluation only utilizes the predicted surface water levels obtained from the first-tier aquatic exposure screen. Because it was decided during problem formulation based on this first-tier assessment not to further analyze this pathway, EPA utilized modeled data derived from known releasers to derive risk quotients as part of the risk characterization. • EPA inadvertently calculated the short term (acute) concentrations of concerns (COCs) for fish rather than for the algal endpoint. EPA has since updated the COC for the correct endpoint. In addition, EPA has updated the calculations used for determining the assessment factor for the acute endpoint.
24, 58	With little analysis and based on limited data, EPA asserts that "[m]easured and estimated levels of 1,4-dioxane in the	• EPA has revised the hazard assessment section of the risk evaluation. The updated section includes a

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	environment are sufficiently below the acute and chronic aquatic COCs [concentrations of concern]," plans no further analysis, and implies it has concluded that any associated risks can be ignored (p. 41). Yet: • EPA's predicted concentrations in surface water for acute and chronic scenarios are up to 58% and 40% of the COCs, leaving little room for error. • EPA implies that its calculations of COCs are conservative at least in part because of its use of assessments factors (pp. 29, 70, 81). The use of such factors is not conservative: They account for real-world sources of variability as well as database limitations, and cannot be construed as "safety factors" that yield conservative estimates.158 As EPA states: "The application of AFs [assessment factors] provides a lower bound effect level that would likely encompass more sensitive species not specifically represented by the available experimental data. AFs are also account for differences in inter- and intra-species variability, as well as laboratory-to-field variability." (p. 70) • EPA's calculated acute COC is inconsistently reported. In the text, it is listed as 59,800 ppb (p. 35), while in Appendix C it is listed as 20,000 ppb (p. 70).	weight-of-evidence approach for selecting the most relevant species for the surface water environment. The species that is the most relevant on the population level for short-term exposure to 1,4-dioxane in the aquatic environment is the algal endpoint. EPA has modified the calculations for deriving the COC for this endpoint. The COC is for algae is derived by dividing the hazard value by an assessment factor of ten instead of four. For the chronic endpoint, the most relevant species on the population level is the fish endpoint. The method for deriving the chronic COC has not changed. The assessment factor is ten. • EPA stands by the analysis that was conducted to determine the environmental hazard and risk of 1,4-dioxane to the environment. After a complete analysis of the hazard data of 1,4-dioxane and the quantitative and qualitative exposure analyses conducted during problem formulation, EPA is confident that the risks of this chemical are low to aquatic organisms. These conclusions are supported by other countries that have investigated the hazard of 1,4-dioxane. • EPA inadvertently calculated the short term (acute) concentrations of concerns (COCs) for fish rather than for the algal endpoint. EPA has since updated the COC for the correct endpoint. In addition, EPA has updated the calculations used for determining the

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		assessment factor for the acute endpoint. The assessment factor is ten (10).

4. Exposure and Releases

Charge Question 4.1: Please comment on the characterization of occupational inhalation exposure for workers for each of the identified conditions of use. What other additional information, if any, should be considered?

Charge Question 4.2: Please comment on the characterization of occupational inhalation exposure for occupational non-users for each of the identified conditions of use. What other additional information, if any, should be considered?

Charge Question 4.3: Please comment on the characterization of occupational dermal exposure for workers. What other additional information, if any, should be considered?

Charge Question 4.4: Please comment on the approach for characterizing the different use scenarios. Are there any additional 1,4-dioxane specific data and/or information that should be considered?

#	**Summary of Comments for Specific Issues Related to Charge Question 4**	**EPA/OPPT Response**
SACC	• Include members on the assessment team with a strong industrial hygiene background relative to modeling and the setting and comparing of occupational exposure limits to estimated levels of potential exposure.	• The EPA multidisciplinary team includes an industrial hygienist who has reviewed and/or contributed to this risk evaluation document.
SACC	• Add more information concerning the context (*e.g.*, measurement and methodology details) of monitoring data used in the Evaluation.	• EPA provides reasonable context for the data in the current risk evaluation. Evaluation criteria can be found in the supplemental document titled *Application of Systematic Review in TSCA Risk Evaluations.* The scores and rationale for each score can be found in the supplemental document titled *Data Quality Evaluation of Environmental Releases and Occupational Exposure*

		Data. Monitoring test protocols and results were assessed for quality of data, including quality of measurement and methodology.
SACC	• Obtain, using TSCA authority, additional monitoring and specific scenario data on workers and ONUs linked to the specific drivers within the scenarios causing that exposure that would help to reduce uncertainties associated with this assessment.	EPA used reasonably available information to construct exposure scenarios for workers and ONUs for the conditions of use of 1,4-dioxane. Assumptions regarding worker and ONU exposures were discussed in Section 2.4.1. Additional clarifications are also included: Workers that are directly handling 1,4-dioxane and/or perform activities near sources of 1,4-dioxane are in the near field and are called workers throughout this risk evaluation. The near-field is defined as a volume of air within one-meter in any direction of the worker's head and the far-field comprised the remainder of the room {Tielemans, 2008, 2599270}. The source areas/exposure zones are conceptualized and delineated by several factors such as the quantity of 1,4-dioxane releases, ventilation of the facility, vapor pressure and emission potential of the chemical, process temperature, size of the room, job tasks, and modes of chemical dispersal from activities {Leblanc, 2018, 4140533}. Corn and Esmen {1979, 29525} indicated that the assignment of zones is a professional judgment and not a scientific exercise.
SACC	• The hierarchy for breathing zone exposure potential should be reformulated to put modeling ahead of monitoring for poorly described scenarios.	EPA used model and relevant parameter data for Occupational Exposure Scenarios (OESs) for inhalation (personal breathing zones) and dermal exposure conditions as listed in Table 4-13. EPA did not find reasonably available data for modeling of breathing zones for other OESs. In addition, the breathing zone exposure models cannot be validated using the full range of possible exposure concentrations.
SACC	• The steady-state breathing-zone concentration model used by the Agency for interior rooms should be	• Computational fluid dynamics or other advanced models could perform better simulation of airflow and transport of

	discarded as out-of-date. A team member (see #2 above) with knowledge of contemporary AIHA models should handle the modeling in this document.	1,4-dioxane in occupied spaces. To capture these behaviors with a high degree of accuracy requires spatial (grid) resolution and time step refinement that can directly simulate appropriate scenario. This was certainly not achieved here, as the simulation could not be validated via tests data. Model results work well or poorly depending on data and known constraints for their applications, even when the application is limited to a point source in a room under general ventilation. Numerous researchers, including National Research Council (see *Using Modeling and Simulation in Test Design and Evaluation* by Panel on Statistical Methods for Testing and Evaluating Defense Systems, 1998. DOI: https://doi.org/10.17226/6037), agreed that no simulations, experiments, or field tests will fully represent the universe of possible scenarios to which these models could be reasonably applied by industrial hygienists. This is a limitation shared by scientists for any method of model evaluation. Inhalation exposures in the current assessment were evaluated using modeled data along with personal breathing zone (PBZ) samples. Assumptions of steady-state air concentrations were necessary and associated with the development of this risk evaluation. EPA may consider the use of alternate and more sophisticated modelling in conjunction with validated monitoring data in future risk evaluation work.
SACC	• Add a spill scenario to this assessment.	Spills and leaks generally are not included within the scope of a TSCA risk evaluation because in general they are not considered to be circumstances under which a chemical substance is intended, known or reasonably foreseen to be manufactured, processed, distributed, used, or disposed of. To

		the extent there may be potential exposure from spills and leaks, EPA is also declining to evaluate environmental exposure pathways addressed by other EPA-administered statutes and associated regulatory programs. First, EPA does not identify 1,4-dioxane spills or leaks as "conditions of use." EPA does not consider 1,4-dioxane spills or leaks to constitute circumstances under which 1,4-dioxane is manufactured, processed, distributed, used, or disposed of, within TSCA's definition of "conditions of use." Congress specifically listed discrete, routine chemical lifecycle stages within the statutory definition of "conditions of use" and EPA does not believe it is reasonable to interpret "circumstances" under which 1,4-dioxane is manufactured, processed, distributed, used, or disposed of to include uncommon and unconfined spills or leaks for purposes of the statutory definition. Further, EPA does not generally consider spills and leaks to constitute "disposal" of a chemical for purposes of identifying a COU in the conduct of a risk evaluation. In addition, even if spills or leaks of 1,4-dioxane could be considered part of the listed lifecycle stages of 1,4-dioxane, EPA has "determined" that spills and leaks are not circumstances under which 1,4-dioxane is intended, known or reasonably foreseen to be manufactured, processed, distributed, used, or disposed of, as provided by TSCA's definition of "conditions of use," and EPA is therefore exercising its discretionary authority under TSCA Section 3(4) to exclude 1,4-dioxane spills and leaks from the scope of the 1,4-dioxane risk evaluation. The exercise of that authority is informed by EPA's experience in developing scoping documents and risk evaluations, and on various TSCA provisions indicating the intent for EPA to have some

		discretion on how best to address the demands associated with implementation of the full TSCA risk evaluation process. Specifically, since the publication of the Risk Evaluation Rule, EPA has gained experience by conducting ten risk evaluations and designating forty chemical substances as low- and high-priority substances. These processes have required EPA to determine whether the case-specific facts and the reasonably available information justify identifying a particular activity as a "condition of use." With the experience EPA has gained, it is better situated to discern circumstances that are appropriately considered to be outside the bounds of "circumstances… under which a chemical substance is intended, known, or reasonably foreseen to be manufactured, processed, distributed in commerce, used, or disposed of" and to thereby meaningfully limit circumstances subject to evaluation. Because of the expansive and potentially boundless impacts that could result from including spills and leaks as part of the risk evaluation, (*e.g.*, due to the unpredictable and irregular scenarios that would need to be accounted for, including variability in volume, frequency, and geographic location of spills and leaks; potential application across multiple exposure routes and pathways affecting myriad ecological and human receptors; and far-reaching analyses that would be needed to support assessments that account for uncertainties but are based on best available science), which could make the conduct of the risk evaluation untenable within the applicable deadlines, spills and leaks are determined not to be circumstances under which 1,4-dioxane is intended, known or reasonably foreseen to be manufactured, processed, distributed, used, or disposed of, as provided by TSCA's definition of "conditions of use." Exercising the discretion to not identify spills and leaks of

		1,4-dioxane as a COU is consistent with the discretion Congress provided in a variety of provisions to manage the challenges presented in implementing TSCA risk evaluation. See *e.g.,* TSCA Sections 3(4), 3(12), 6(b)(4)(D), 6(b)(4)(F). In particular, TSCA Section 6(b)(4)(F)(iv) instructs EPA to factor into TSCA risk evaluations "the likely duration, intensity, frequency, and number of exposures under the conditions of use…," suggesting that activities for which duration, intensity, frequency, and number of exposures cannot be accurately predicted or calculated based on reasonably available information, including spills and leaks, were not intended to be the focus of TSCA risk evaluations. And, as noted in the preamble to the Risk Evaluation Rule, EPA believes that Congress intended there to be some reasonable limitation on TSCA risk evaluations, expressly indicated by the direction in TSCA Section 2(c) to "carry out [TSCA] in a reasonable and prudent manner." For these reasons, EPA is exercising this discretion to not consider spills and leaks of 1,4-dioxane to be COUs. Second, even if 1,4-dioxane spills or leaks could be identified as exposures from a COU in some cases, these are generally not forms of exposure that EPA expects to consider in risk evaluation. TSCA Section 6(b)(4)(D) requires EPA, in developing the scope of a risk evaluation, to identify the hazards, exposures, conditions of use, and potentially exposed or susceptible subpopulations the Agency "expects to consider" in a risk evaluation. This language suggests that EPA is not required to consider all conditions of use, hazards, or exposure pathways in risk evaluations. EPA has chosen to tailor the scope of the risk evaluation to exclude spills and leaks in order to focus analytical efforts on those exposures

		that present the greatest potential for risk. In the problem formulation documents for many of the first 10 chemicals undergoing risk evaluation, EPA applied the same authority and rationale to certain exposure pathways, explaining that "EPA is planning to exercise its discretion under TSCA 6(b)(4)(D) to focus its analytical efforts on exposures that are likely to present the greatest concern and consequently merit a risk evaluation under TSCA...." This approach is informed by the legislative history of the amended TSCA, which supports the Agency's exercise of discretion to focus the risk evaluation on areas that raise the greatest potential for risk. See June 7, 2016 Cong. Rec., S3519-S3520. In addition to TSCA Section 6(b)(4)(D), the Agency also has discretionary authority under the first sentence of TSCA Section 9(b)(1) to "coordinate actions taken under [TSCA] with actions taken under other Federal laws administered in whole or in part by the Administrator." TSCA Section 9(b)(1) provides EPA authority to coordinate actions with other EPA offices, including coordination on tailoring the scope of TSCA risk evaluations to focus on areas of greatest concern rather than exposure pathways addressed by other EPA-administered statutes and regulatory programs, which does not involve a risk determination or public interest finding under TSCA Section 9(b)(2). EPA has already tailored the scope of this risk evaluation using such discretionary authorities with respect to exposure pathways covered under the jurisdiction of other EPA-administered statutes and associated regulatory programs (see section 1.4.3). Following coordination with EPA's Office of Land and

		Emergency Management (OLEM), EPA has found that exposures of 1,4-dioxane from spills and leaks fall under the jurisdiction of RCRA. See 40 CFR 261.33(d) (defining in part a hazardous waste as "any residue or contaminated soil, water or other debris resulting from the cleanup of a spill into or on any land or water of any commercial chemical product or manufacturing chemical intermediate having the generic name listed [40 CFR 261.33(e) or (f)], or any residue or contaminated soil, water or other debris resulting from the cleanup of a spill, into or on any land or water, of any off-specification chemical product and manufacturing chemical intermediate which, if it met specifications, would have the generic name listed in [40 CFR 261.33(e) or (f)]"); 40 CFR 261.33(f) (listing 1,4-dioxane as hazardous waste no. U108). As a result, EPA believes it is both reasonable and prudent to tailor the TSCA risk evaluation for 1,4-dioxane by declining to evaluate potential exposures from spills and leaks, rather than attempt to evaluate and regulate potential exposures from spills and leaks under TSCA. See Section 2.4.1 in the final risk evaluation for further explanation on a COU basis.
SACC	• Add a fugitive emissions scenario to this assessment.	EPA did not include the emission pathways to ambient air from commercial and industrial stationary sources, because stationary source releases of 1,4-dioxane to ambient air are under the jurisdiction of and addressed by Section 112 of the Clean Air Act (CAA). The resulting exposure pathways were out of scope as described in Section 1.4.2.
SACC	• Add scenarios in which respirators are not used for an entire 8-hour work shift.	The risk evaluation already presents exposure and risk estimates with and without PPE, which includes no respirators. As previously noted, 1,4-dioxane is manufactured, processed, and used in industrial settings, where there are typically strong industrial hygiene programs that include training and oversight. It is not reasonable to assume no respirator use in these settings. For situations in which

		workers do not use respirators for an entire shift, EPA used the high-end exposure value when considering worker risks in order to address the uncertainties and variability in PPE usage
SACC	• Consider scenarios in which acute exposures occur on time frames of less than 8 hours.	Exposures at different facilities could occur for a variety of conditions of use and those scenarios are discussed in the risk evaluation document based on the reasonably available information. EPA assessed occupational exposure scenarios less than 8-hour as well as full shift depending on conditions of use. Examples of less than 8-hour work shift includes 15-minute TWA (Evaporator Dump) for manufacturing, short (15-minute) duration degassing for laboratory use; and the 30-minute exposure for repackaging into drums.
SACC	• Present worst-case inhalation exposures for workers with estimates from scenarios assuming no use of PPE.	The risk evaluation presents exposure and risk estimates with no use of PPE as worst-case for various occupational exposure scenarios.
SACC	• In addition to a qualifier for the quality of data used for estimating inhalation exposures, EPA should add a qualifier for the overall confidence in the final exposure estimates (in addition to the description of uncertainties).	The quality and quantity of monitoring data, surrogate, modeling and other information were listed in Table 2-19. The Table 2-19 also provides confidence ranking for various COUs.
SACC	• Clarify how ONU exposures compare to both unprotected and protected user exposures.	EPA considers occupational non-users (ONUs) to be a subset of workers for whom the potential inhalation exposures may differ based on proximity to the exposure source. For the majority of 1,4-dioxane conditions of use, the difference between ONU exposures and workers directly handling the chemical cannot be quantified. EPA assumed an absence of PPE for ONUs, since ONUs do not directly handle the chemical and are instead doing other tasks in the vicinity of 1,4-dioxane use. EPA also assumed that, in most cases, ONU inhalation exposures are lower than inhalation exposures for workers directly handling the chemical substance. For dermal exposures, because ONUs are not dermally exposed to 1,4-

		dioxane, dermal risks to ONUs were not identified. For inhalation exposures, EPA, where possible, estimated ONU exposures and described the risks separately from workers directly exposed. To account for those instances where, based on EPA's analysis, the monitoring data or modeling data for worker and ONU inhalation exposure could not be distinguished, EPA considered the central tendency risk estimate when determining ONU risk.
SACC	• Engage an expert in dermal exposure assessment from within the Agency or a consultant to provide quantitative estimates of the amount of 1,4-Dioxane absorbed systemically in reasonably anticipated scenarios.	• Dermal exposure assessments have been updated by using sensitivity analysis; and comparing test results performed at different facilities. Peer-reviewed references are cited as appropriate.
SACC	• Strengthen the discussion and analysis for uncertainty for dermal exposure by quantitatively defining the assumptions made in each scenario using a Monte Carlo simulation.	• Monte Carlo simulation and other sensitivity analysis have been performed as applicable for the inhalation and dermal exposures. The operating variables and constraints for those conditions along with the assumptions, citations of the references for the data used are already included in the risk evaluation.
SACC	• Clearly state the estimated exposures to gloved and ungloved Users.	The risk evaluation presents exposure and risk estimates for workers with and without PPE, including gloves. As previously noted, ONUs do not handle the chemical; therefore, dermal exposures were not assessed for ONUs.
SACC	• Contrast ONU estimated exposures to estimated exposures of gloved and ungloved Users.	EPA has updated several sub-sections in Section 4.1.4 to show risk estimates for workers with PPE and without PPE, and risk estimates for ONUs, who EPA assumes do not have PPE. As previously noted, ONUs do not handle the chemical; therefore, dermal exposures were not assessed for ONUs.
SACC	• Resolve the large discrepancy between the theoretical predictions of high dermal doses and apparently low systemic uptake as reported by experimental	As indicated earlier in this response to comment document, the dermal exposure calculations have been updated and validated by using sensitivity analysis and by comparing test results reported by the researchers at the Kansas State University, Manhattan, Kansas; and at the University

	observations.	Erlangen-Nuremberg, Erlangen, Germany, and the citations are included in the revised risk evaluation document (see Section 2.4.1.14 - Dermal Exposure Assessment).
SACC	• Conduct in vitro testing (OECD 2004) of the dermal absorption of 1,4-Dioxane.	The peer-reviewed publications that reported test results (in-vivo and ex-vivo) using 1,4-dioxane and human skin are discussed, as appropriate, in the revised dermal exposure assessments of the risk evaluation. The researchers at the Kansas State University, Manhattan, Kansas and at the University Erlangen-Nuremberg, Erlangen, Germany performed in-vitro and ex-vivo dermal absorptions using 1,4-dioxane and these results with interpretations are included in the Section 2.4.1.14 (Dermal Exposure Assessment) with citations.
SACC	• Define scenarios as exposure settings that have a comprehensive set of the determining factors that cause the exposure. When these are matched to monitoring data, it is a very powerful tool for assessing exposure and risk. Without monitoring data, models should be used with these scenarios.	Modeling and monitoring data were used to compare the validity of the assessment, as appropriate. When model calibration data and monitoring data needed for performance evaluation and validation of mathematical models are not available, the limitations are recognized, assumptions are specified, and literature data (or surrogate data) are identified during the interpretation of scenarios.
24, 30, 43, 50, 55 58	**Consumer Exposure** • EPA claims it "did not find evidence of any current consumer uses for 1,4-dioxane and is excluding consumer uses from the scope of the risk evaluation." "Contamination of industrial, commercial and consumer products or presence as a byproduct are not intended conditions of use for 1,4-dioxane and therefore will not be evaluated." • EPA must account for this pathway of exposure now as part of the cumulative exposure to the general population and workers. • Exclusion of evaluation of exposure from consumer uses is in violation of TSCA requirements.	As explained in the scope document, 1,4-dioxane may be found as a contaminant in consumer products that are readily available for public purchase. In the final risk evaluation, eight consumer conditions of use are evaluated based on the uses identified in EPA's 2015 TSCA Work Plan Chemical Problem Formulation and Initial Assessment of 1,4-Dioxane (U.S. EPA, 2015). An additional systematic review effort was undertaken for consumer exposures to identify, screen, and evaluate relevant data sources. These conditions of use include use of 1,4-dioxane as a surface cleaner, antifreeze, dish soap, dishwasher detergent, laundry detergent, paint and floor lacquer, textile dye, and spray polyurethane foam (SPF). Regarding body care and cosmetic products, they are

	• Many consumer uses were correctly recognized in the scoping document, but not evaluated. • 1,4-dioxane as a residual contaminant has been detected in paints, coatings, lacquers, ethylene glycol-based antifreeze coolants, spray polyurethane foam, household detergents (dish and laundry), cosmetics/toiletries including shampoo, body wash, baby wipes, soaps, lotions, sunscreen and toothpaste, textile dyes, clothing, baby bibs, blankets/throws, bath and pool water toys, pharmaceuticals, foods, agricultural and veterinary products, magnetic tape and adhesives, and in compost sold for home and garden use. • The justification for excluding consumer uses based on presence of 1,4-dioxane as a "byproduct" or a contaminant, rather than an intentional use, is unacceptable. • TSCA does not distinguish between intentional and unintentional presence of a chemical in a product. • Deliberate uses reported in the 2002 EU risk assessment were ignored. • For cleaning agents and paint as end uses, the EU risk assessment found reasonable worst case to be 50 mg/m3 and the typical concentration to be 15 mg/m3, which are considerably higher than the Central Tendency average daily concentration (ADC) and High-End ADCs EPA relies on for all of its exposure scenarios (see Table 5-5 on p. 137). • According to the reports submitted to FracFocus, 1,4-dioxane is not just present as an impurity or by-product. Companies reported over 400 instances where 1,4-dioxane was used as an ingredient, representing 77% of the reported cases in this time period.	excluded from the definition of "chemical substance" per TSCA section 3(2) and are outside the scope of this risk evaluation. 1,4-Dioxane may be found in these products at low levels (0.0009 to 0.02%) based on its presence as a byproduct of other formulation ingredients (*i.e.,* ethoxylated chemicals). Inhalation exposures are estimated for consumers and bystanders and dermal exposures are estimated for users. Acute exposures are presented for all consumer conditions of use, while chronic exposures are presented for the conditions of use that are reasonably expected to involve daily use intervals (*i.e.,* surface cleaner, dish soap, dishwasher detergent, and laundry detergent). See Section 2.4.3 of the final risk evaluation. • EPA has reviewed the list of FracFocus reports on 1,4-dioxane submitted by the commenter as well as the three individual job reports submitted by the commenter. In one individual job report, the 1,4-dioxane is specifically noted as an impurity. In the other two, the percentage of 1,4-dioxane reported was low, indicating that the 1,4-dioxane is likely present as an impurity in the ethoxylated alcohols that are also named in the same reports. EPA initially excluded production of 1,4-dioxane as a by-product from certain other chemicals and presence as a contaminant in industrial, commercial and consumer products from the scope of the risk evaluation using EPA's discretion under TSCA section 6(b)(4)(D). While EPA has addressed some conditions of use related to 1,4-dioxane as a byproduct in this risk evaluation, EPA expects that 1,4-dioxane exposures associated with the use of ethoxylated alcohols used in hydraulic fracturing fluids would be considered in the scope of a risk evaluation for ethoxylated alcohols. In cases like this,

	• The choice to exclude 1,4-dioxane's presence as a byproduct as a condition of use in the risk evaluation provides no basis for EPA not to include 1,4-dioxane's presence as an intentionally added substance. • 1,4-Dioxane has been detected in landfill leachate (ATSDR, 2012); this suggests that it may be coming from consumer products containing it.	EPA believes its regulatory tools under TSCA section 6(a) are better suited to addressing any unreasonable risks that might arise from these activities through regulation of the activities that generate 1,4-dioxane as an impurity or cause it to be present as a contaminant than they are to addressing them through direct regulation of 1,4-dioxane. This case-by-case approach for byproducts exposures is consistent with the various scenarios explained in the Risk Evaluation Rule, 82 FR at 33730. As described in Section 1.4.2 of the risk evaluation, EPA believes it is both reasonable and prudent to tailor TSCA risk evaluations when other EPA offices have expertise and experience to address specific environmental media, including landfill leachate under RCRA, rather than attempt to evaluate and regulate potential exposures and risks from those media under TSCA. EPA has therefore tailored the scope of the risk evaluation for 1,4-dioxane using authorities in TSCA Sections 6(b) and 9(b)(1).
24, 58	**Occupational/Workplace Exposure** **Reliance on Limited or Questionable Data** • Overall, EPA's sources of workplace exposure data are from selective, unrepresentative sources; lack critical detail on which processes, exposure sources and worker activities they represent; are insufficient to understand the distribution of exposures in a given setting; and reliable occupational exposure data are limited. EPA should require the production of reasonable exposure data. • Oral exposure should be assessed as an exposure pathway. • For its Manufacturing scenario, EPA chose to use data it received from BASF, comprised of 30 samples from	• EPA received monitoring data from industry consortium (Halogenated Solvents Industry Alliance, Inc., Arlington, Virginia), Department of Defense, National Institute for Occupational Safety and Health (NIOSH), Occupational Safety and Health Administration (OSHA), and Kansas City National Security Campus (KCNSC), Kansas City, Missouri. These monitoring data were discussed and interpreted in the risk evaluation and supporting documents. • There are two known manufacturers in the U.S., and one of these sites is representative of the U.S. manufacturing. One of the two manufacturers (BASF) provided information that is more relevant and recent compared in comparison to other source that lacks monitoring data (see

	a single manufacturing site, and assumed these data to be representative of all U.S. manufacturing. The data also lacked specific descriptions of worker tasks, exposure sources, and possible engineering controls to provide context. ○ EPA assumed that the 2016 BASF data are PBZ measurements relevant to worker activities and are also 8-hour TWA measurements. This assumption could underestimate exposures. The sampling rate was missing for some of the 2016 data, so EPA assumed the same sampling rate was applied for other data in the set. These assumptions were not included in the "assumptions and key sources of uncertainty section." ○ It was also noted that access to the original data source was not provided, and no link was provided for the HERO entry. • Regarding open system functional fluids: EPA claims it derived fluid concentrations from available SDSs (p. 62), but none of the relevant cited SDSs that are publicly accessible makes any mention of 1,4-dioxane as a constituent. EPA's cited source (Burton and Driscoll 1997) is a NIOSH site report, motivated by worker concern over fungi- and bacteria- contaminated synthetic metal–working fluids (MWF). It entailed no direct measurements of 1,4-dioxane, only synthetic MWF and it is not clear the fluids at this site even contained the chemical (p. 61). • Regarding printing inks: EPA's analysis of worker exposure to printing inks is *based on a single air sample reported in a 2016 paper*; despite the fact that the authors and other researchers note that the	details in Section 4.1.4 of the risk evaluation). EPA updated additional discussion about considerations made in the *Assumptions and Key Sources of Uncertainty* section in response to sub-comment 3a. EPA has additionally corrected the HERO entry for the BASF, 2016 citation (HERO ID 5079874) so that the original data source can be accessed. • Citations with appropriate references including Burton and Driscoll (1997) are detailed in Appendix G of the risk evaluation. Though Burton and Driscoll (1997) do not address 1,4-dioxane in metalworking fluids (MWF), they indicated "*PBZ and area measurements of water-soluble synthetic metalworking fluids and oil mists from conventional metalworking fluids*." This pertinent information along with the SDS information were used to address potential exposure to 1,4-dioxane from metal working fluids. • The "basis for single air sample reported in a 2016 paper" is provided in the Key Uncertainties section: "*Additionally, the sample provided is not a PBZ sample. Since the sample was taken within the 3D printing enclosure, the exposure value is likely higher than a worker would typically experience while operating the 3D printer*." • Regarding the Industrial Uses related "explanation for considering highest exposure point", EPA provides the explanation for considering the 184mg/m^3 datapoint as an outlier in the Appendix G. In response to this comment, EPA further clarified the explanation in the Appendix G - Section 6.3). • Regarding "1,4-dioxane mists," *Table G-17, 1997 NIOSH HHE PBZ and Area Sampling Data for Metalworking Fluids* in Appendix G of the risk evaluation provides the

	concentration could well be an underestimate (p. 70), EPA asserts it is likely an overestimate (p. 71). The basis for this assertion should be provided. • For Industrial Uses, EPA excludes the highest exposure point (184 mg/m3) from the 2002 EU Risk Assessment. An explanation for considering this value "likely an outlier" (p. 264) should be provided. • EPA draws the conclusion that exposure to 1,4-dioxane mists would be negligible; supporting analysis or data should be provided. • An available workplace monitoring study (OSHA 2016) was inappropriately scored as unacceptable, EPA should attempt to collect this potentially useful data.	complete rationale and approach for determining worker exposure to 1,4-dioxane from mists generated during metalworking. EPA used data from the analysis outlined here to develop the conclusions on 1,4-dioxane mists. • EPA converted the OSHA 2016 document into a file format that was legible and re-examined the data. The data is OSHA sampling data from 2016 and all of the entries are non-detects. As described by Hornung and Reed (1990), the method for estimating non-detects depends upon the degree to which the data are skewed and the proportion of the data that is below detection limits. If the geometric standard deviation of the monitoring data set is less than 3.0, nondetectable values should be replaced by the limit of detection divided by the square root of two ($L/\sqrt{2}$).If the data are highly skewed, with a geometric standard deviation of 3.0 or greater, nondetectable values should be replaced by half the detection limit (L/2). The scoring for the document has been changed from unacceptable to medium. Per OSHA recommendation, EPA did not use non-detects from OSHA (2016). The uncertainties of OSHA (2016) data quality has been also recognized due to the lack of clarity - whether the source areas from where the samples were collected contained 1,4-dioxane.
21, 24 46, 48, 55, 58,	**Use of PPE** EPA assumes that PPE equipment is a) provided to all workers, b) used by all workers (properly), and c) that PPE equipment used would provide adequate protection such that there are few unreasonable risks to workers. Support for these assumptions should be provided. • OSHA previously informed EPA that it "consider[s] the use of respirators to be the least satisfactory approach to exposure control." EPA has not published	• The quote from the commenter does not reflect OSHA review of this risk evaluation; rather, it cites to a comment on a 2014 proposed SNUR. OSHA participated in review of EPA's draft risk evaluation and final risk evaluation of 1,4-dioxane. EPA has recognized in the draft and final risk evaluation documents regarding OSHA's hierarchy of controls and recognized that there can be reliability issues associated with PPE. EPA's risk evaluation characterizes risks with and without PPE considerations, with

	the results of OSHA's review of the draft 1,4-dioxane risk evaluation. • EPA assumes that the three general OSHA standards – the Personal Protective Equipment Standard, the Respiratory Protection Standard, and the Hazard Communication Standard – will ensure that workers have access to and use appropriate PPE. • EPA overstates OSHA's authorities and requirements, claiming that OSHA requires employers to provide PPE (p. 48), requires the use of respirators for 1,4-dioxane (p. 52), and that the OSHA requirement for safety data sheets (SDSs) is sufficient to ensure use of protective measures such as PPE by all downstream users of 1,4-dioxane (p. 60). • OSHA regulations do not require that persons comply with SDSs and rely heavily on employers to adhere to other requirements. • OSHA does not require employers to use the same regulatory thresholds as EPA. • EPA made no attempts to coordinate with any of these other statutes to assure measures to mitigate risk were being taken. • If a chemical presents a significant risk, OSHA and NIOSH manage that risk using the "hierarchy of controls," under which hazard elimination, substitution, engineering and administrative controls are all prioritized over the use of PPE. Assuming PPE use ignores this hierarchy. • Under section 5 of the OSH Act, employers are required to comply with OSHA standards and provide a workplace free from recognized hazards. However, employers have no obligation to protect workers from chemical hazards that are not the subject of an OSHA	considerations of engineering and administrative controls. Additionally, in consideration of the uncertainties and variabilities in PPE usage, EPA uses the high-end exposure value when making its unreasonable risk determination in order to address those uncertainties. EPA has also outlined its PPE assumptions in section 5.1. • Information reasonably available to EPA, including data submitted by chemical manufacturers and processors, indicates that PPE is generally used. EPA does not assume that inclusion of PPE on SDSs is sufficient to ensure PPE use and while EPA considers the information on SDSs, EPA does not make PPE use assumptions based solely on SDSs. EPA is not yet at the risk management stage for this chemical, where the hierarchy of controls would be considered. OSHA's hierarchy of controls is a method for eliminating workplace hazards. While EPA has assessed the extent to which certain exposure reduction tools that it assumes to be in place may be reducing risks to workers, application of the methodology of the hierarchy of controls is not relevant to risk evaluations. EPA will manage unreasonable risks presented by chemical substances when the Agency undertakes regulatory action for COUs determined to have unreasonable risk. Utilization of the hierarchy of controls to recommend or require risk management actions in the risk evaluation would be premature and inappropriate. • 1,4-Dioxane is the subject of an OSHA standard. OSHA has established a permissible exposure limit (PEL) of 100 ppm (8-hour TWA) for 1,4-dioxane. However, as noted on OSHA's website, "OSHA recognizes that many of its permissible exposure limits (PELs) are outdated and inadequate for ensuring protection of worker health. Most

	standard unless the employer has actual knowledge that the chemical poses a risk to workers. OSHA has never recognized a government risk assessment as the basis for finding that an employer has actual knowledge of a chemical hazard, and the standards for evaluating hazards under the OSH Act are very different than those used to evaluate unreasonable risks under TSCA. • TSCA requires the assessment of risk to workers in the absence of PPE, and if risks are identified, it can then be considered whether the risks would or would not be mitigated by PPE. • TSCA § 9(b) provides that EPA "shall coordinate actions taken under [TSCA] with actions taken under other Federal laws administered in whole or in part by the Administrator" (15 U.S.C. § 2608(b)). While EPA is supposed to coordinate the "actions" under each statute, this provision does not contemplate EPA excluding exposures from the risk analyses prepared under TSCA. The remaining language of TSCA § 9(b) highlights that Congress intended for EPA to prepare risk evaluations analyzing all exposures, including those that might be addressed under another authority. • The risk evaluation does not take into consideration instances where PPE might NOT be used. • "[i]ndividuals with impaired lung function due to asthma, emphysema, or chronic obstructive pulmonary disease … may be physically unable to wear a respirator." • Workers may choose to forego respirators because they "may also present communication problems, vision problems, worker fatigue, and reduced work efficiency."	of OSHA's PELs were issued shortly after adoption of the Occupational Safety and Health (OSH) Act in 1970 and have not been updated since that time." OSHA provides an annotated list of PELs on its website, including alternate exposure levels. For 1,4-dioxane, the alternates provided are the California OSHA PEL of 0.28 ppm and the ACGIH TLV of 20 ppm. (https://www.osha.gov/dsg/annotated-pels/tablez-1.html) EPA's approach for developing exposure assessments for workers and ONUs is to use the reasonably available information and expert judgment. When appropriate, in the risk evaluation, EPA will use exposure scenarios both with and without engineering controls and/or PPE that may be applicable to particular worker tasks on a case-specific basis for a given chemical. Thus, while EPA has evaluated worker risk with and without PPE, as a matter of policy, EPA does not believe it should assume that workers are unprotected by PPE where such PPE might be necessary to meet federal regulations, unless it has evidence that workers are unprotected. For the purposes of determining whether or not a condition of use presents unreasonable risks, EPA incorporates assumptions regarding PPE use based on information and judgment underlying the exposure scenarios. These assumptions are described in the unreasonable risk determination for each condition of use, in section 5.2. Additionally, in consideration of the uncertainties and variabilities in PPE usage, EPA uses the high-end exposure value when making its unreasonable risk determination in order to address those uncertainties. EPA has also outlined its PPE assumptions in section 5.1. Further, in the final risk evaluation for 1,4-dioxane, EPA has determined that most conditions of use pose an unreasonable risk to workers

	• On p. 135, EPA claims that an APF=10 respirator is sufficient to eliminate even high-end inhalation non-cancer risk "during industrial use." This is not accurate: EPA found that an APF=25 respirator is necessary to get the acute high-end MOE above the benchmark MOE (Table 5-4) and that even an APF=50 respirator is not sufficient to get the chronic high-end MOE above the benchmark MOE (Table 5-5).	even with the assumed PPE. • EPA did assess the risk to workers in the absence of PPE and with PPE; are in Tables 4-4 through 4-11 in Section 4, Risk Characterization. • EPA has corrected the typographical error that appeared on page 135 of the draft risk evaluation.
24, 30, 47, 52, 58	**Other Conditions of Use** • 1,4-dioxane has been reported more than 500 times as an ingredient (not as an impurity or byproduct) used in hydraulic fracturing fluids across several states. EPA failed to identify this as a condition of use. Worker exposure to hydraulic fracturing fluids and wastewater must be evaluated. • EPA did include spray foam; however, the manufacturer claims that it's presence should be considered an impurity or a byproduct and therefore recommends EPA remove spray foam as a category in the risk evaluation. o EPA lacks monitoring data on spray foam use. o Regarding spray foam use, it was also claimed that EPA: 1) does not consider use of PPE in its exposure scenarios, 2) overestimates the number of workers on a per job basis, and 3) does not account for ventilation activities, or re-entry and re-occupancy times. o EPA should work with the SPF industry to develop more appropriate exposure estimates for potentially exposed workers. • 1,4-Dioxane may be produced as a reaction byproduct, particularly in chemicals which are produced by ethoxylation. EPA should evaluate those	• EPA disagrees with the commenter. While 1,4-dioxane has been reported many times to FracFocus, the national hydraulic fracturing chemical registry, the reported concentrations are very low, and the reports include presence of 1,4-dioxane with chemicals like ethoxylated alcohols. The reported 1,4-dioxane is present as an impurity or in the produced water. EPA initially excluded production of 1,4-dioxane as a by-product from certain other chemicals and presence as a contaminant in industrial, commercial and consumer products from the scope of the risk evaluation using EPA's discretion under TSCA section 6(b)(4)(D). While EPA has addressed some conditions of use related to 1,4-dioxane as a byproduct in this risk evaluation, EPA expects that 1,4-dioxane exposures associated with the use of ethoxylated alcohols used in hydraulic fracturing fluids would be considered in the scope of a risk evaluation for ethoxylated alcohols. In cases like this, EPA believes its regulatory tools under TSCA section 6(a) are better suited to addressing any unreasonable risks that might arise from these activities through regulation of the activities that generate 1,4-dioxane as an impurity or cause it to be present as a contaminant than they are to addressing them through direct regulation of 1,4-dioxane. This case-by-case approach for byproducts exposures is

	COU in this risk evaluation, not in the future risk evaluations for the ethoxylated chemicals.	consistent with the various scenarios explained in the Risk Evaluation Rule, 82 FR at 33730. • The commenter appears to be referring to submitted comments from Johns Manville, a distributor/manufacturer of spray polyurethane foam (SPF). EPA acknowledges that Johns Manville claims that the 1,4-dioxane's presence is as an impurity or byproduct. EPA has also noted that there are many other manufacturers of SPF products and patented technologies exist. EPA has found data from other manufacturers that suggests 1,4-dioxane might not always be a byproduct or impurity. Due to contradicting and limited information and the potential for worker exposure, EPA maintains its assessment of SPF use as an occupational exposure scenario. • In the final risk evaluation, eight consumer conditions of use are evaluated based on the uses identified in EPA's 2015 TSCA Work Plan Chemical Problem Formulation and Initial Assessment of 1,4-Dioxane (U.S. EPA, 2015). An additional systematic review effort was undertaken for consumer exposures to identify, screen, and evaluate relevant data sources. These conditions of use include use of 1,4-dioxane as a surface cleaner, antifreeze, dish soap, dishwasher detergent, laundry detergent, paint and floor lacquer, textile dye, and spray polyurethane foam (SPF). 1,4-Dioxane may be found in these products at low levels (0.0009 to 0.02%) based on its presence as a byproduct of other formulation ingredients (*i.e.*, ethoxylated chemicals). Inhalation exposures are estimated for consumers and bystanders and dermal exposures are estimated for users. Acute exposures are presented for all consumer conditions of use, while chronic exposures are presented for the conditions of use that are reasonably

		expected to involve daily use intervals (*i.e.,* surface cleaner, dish soap, dishwasher detergent, and laundry detergent). See Section 2.4.3 of the final risk evaluation.

22, 24, 48, 58, 59	**Occupational Dermal Exposure**
	• EPA needs to clarify what absorption values and assumptions were applied to each scenario for estimating dermal exposures.
	  ○ Risk values for the scenarios without gloves are reduced exactly by the protection factor (PF) EPA assumed for the three scenarios with gloves. See Table 5-10 on p. 144 and Table 5-11 on p. 145. This should not be the case if EPA applied different values for skin absorption for the scenarios with and without gloves.
	  ○ It is not clearly stated why EPA did not choose the more conservative absorption rate (3.2%) for non-occluded/no glove scenarios supported in Marzulli *et al.,* (1981).
	  ○ EPA reports that there are numerous ways in which glove use could increase skin exposure through occlusion; however, it is not clear how EPA's analysis accounted for this.
	  ○ It is not clear why EPA cited risk estimates for the 20x PFs in the risk determination section but ignored higher risks found with no gloves or gloves with lower PFs.
	• EPA needs to provide a more thorough analysis surrounding the limitations and protections offered by glove use and should also account for more recent data, such as Dennerlein *et al.,* (2013).
	• Tables 5-4, 5-5, 5-9, 5-10, and 5-11 do not distinguish between high-end and central tendency exposures.
		• The absorption values without gloves are discussed in Section 2.4.1.14 (Dermal Exposure Assessment). Materials of constructions of gloves and their suitability for 1,4-dioxane are described under sub-section Dermal Exposure Estimation. Since the absorption and penetration data for 1,4-dioxane through various materials of gloves are not available, the protection factor was used in computation of risk values.
		• As indicated in this response to comments document, the dermal exposure calculations have been updated and validated by using sensitivity analysis and by comparing test results reported by the researchers at the Kansas State University, Manhattan, Kansas; and at the University Erlangen-Nuremberg, Erlangen, Germany. The above-mentioned references are cited in the revised risk evaluation document (see Section 2.4.1.14 - Dermal Exposure Assessment). The revised risk evaluation document has been updated by deleting Bronaugh (1982) and the relevant paragraph as the Bronaugh (1982) cited data are not used in the dermal exposure assessment. The dermal calculations have been updated in the revised risk evaluation by including a conceptual diagram, tiered analysis using: a) updated calculations; b) sensitivity analysis to evaluate chemical fluxes at various fractional absorption varying from negligible (~0) to complete absorption (1.0); c) overall comparison of modeled chemical fluxes with in-vitro and ex-vivo test data reported in the literature.
		• EPA included a thorough analysis on incorporation of glove protection, limitations and protections of glove use,

	Some cancer risks exceed benchmarks even with respirator/glove use. • Although assumptions regarding glove use were clearly stated for dermal calculations, the empirical basis for the protection factors needs empirical justification. For example, the "fraction absorbed" into the stratum corneum was based on a "large dose" assumption not verified in the analysis. • EPA must explain why it relies on the in vitro dermal absorption study by Bronaugh (1982), which is a secondary source book chapter, to estimate dermal absorption. ○ This study is not publicly available and has not been subject to any quality review, yet information from this source is used in calculating (HEDs), which are themselves used as a basis for reducing the interspecies uncertainty value from 10 to 3 (pp. 111, 118). • EPA cites the fractional absorption potential for 1,4-dioxane to be 0.86 or 0.78, depending on the setting, based on Kasting and Miller (2006). EPA then adjusts the 0.86 or 0.78 values by the 0.3% or 3.2% values based on Bronaugh (1982). Through this "double" adjustment, potential dermal risk is underestimated. • EPA also relies on Marzulli *et al.*, (1981), which examined absorption in adult rhesus monkeys. But the vehicles employed were methanol and skin lotion, and it is not clear how representative they are of absorption under the conditions of use in this risk evaluation. Moreover, the authors describe their results as providing only "crude estimates." • EPA failed to review a dermal absorption study conducted by Dennerlein *et al.,* (2013). This study	potential for occlusion in Appendices E (E5 and E6), and G. Additional information are also included in Supplemental document (Engineering Assessment of Occupational Exposure for 1,4-Dioxane). • Analysis and interpretations have been updated in the revised risk evaluation document including citations of Dennerlein *et al.*, and other recent publications (see Section 2.4.1.14 for details on the multiple citations). • EPA updated dermal tables 5-9, 5-10, and 5-11 to include central tendency and clearly delineate between high-end and central tendency exposures. • A sensitivity analysis has been performed with respect to fraction sorbed. The double adjustment is no longer applicable. The citation of Bronaugh (1982) was included to provide general description on dermal absorption. EPA no longer relies on this source as the basis for any quantitative analysis. The revised risk evaluation document has been updated (to be done) by deleting the relevant paragraph as these data are not used in the revised assessment. In the final risk evaluation, Bronaugh (1982) is briefly referenced in the discussion of toxicokinetics to provide a more complete picture of the reasonably available information on dermal absorption, but data from the Bronaugh (1982) is not used in subsequent analysis. While EPA is unable to post the copyrighted material, the book is publicly available. • The dermal calculations have been updated by including a conceptual diagram, tiered analysis using: a) updated calculations; b) sensitivity analysis to evaluate chemical fluxes at various fractional absorption varying from negligible (~0) to complete absorption (1.0); c) overall comparison of modeled chemical fluxes with in-vitro and ex-vivo test data reported in the literature. There is no

	could not be found in either the Risk Evaluation or the Systematic Review Supplemental File and should be made available for public review.
	• Some of the assumptions applied in the dermal exposure models were not well supported by the weight of scientific evidence. It is suggested that EPA revisit these models and ensure the assumptions properly reflect occupational working conditions.
	  ○ No justification was provided for the assumption that dermal exposures occur as one event/day.
	• Contradictory assumptions about the absorption of a "large dose" were identified:
	  ○ In one section, it was assumed "the chemical amount forms a residual layer (or pool) on the top of the skin… [that] acts as a reservoir to replenish top layers [of skin] as the chemical permeates into the lower layer."
	  ○ Elsewhere, also regarding "large doses", it was stated "Only a fraction of the 1,4-dioxane that contacts the skin will be absorbed as the chemical readily evaporates from the skin," given its volatile nature. It is not clear whether the evaporated fraction was considered in the inhalation exposure.
		double adjustment in the updated calculations in the revised risk assessment document.
		• Marzulli *et al.,* (1981) and Bronaugh (1982) were only toxicological section. The revised document has been updated by deleting the relevant paragraph for dermal exposure as these data are not used in the assessment.
		• The Dennerlein *et al.,* (2013) reference has undergone systematic review and the results can be found in the Systematic Review Supplemental File. The source can be found in HERO (HERO ID: 3537857).
		• A section describing the general approaches and methods for dermal exposures of 1,4-dioxane from the outer surface of the skin to the inner layers of the skin are included in the revised document (see Section 2.4.1.14 - Dermal Exposure Assessment).
		• A search of the document text shows that the commenter is referring to a passage in section 3.4.1.14 and a passage in Appendix G.7.1. The comment noting that contradictory assumptions exist is inaccurate has been clarified and the statements in the revised risk evaluation document are accurate.
		
		Section 3.4.1.14 is a summary that is dermal contact with 1,4-dioxane and despite the commenter's statements, never refers to a "large dose" or similar concept. This section is talking about dermal exposure in a general sense, noting that because of 1,4-dioxane's volatility, not all of the applied chemical will be absorbed into the skin.
		
		The passage in Appendix G.7.1 is referring to a section describing the mathematical basis for the dermal model. In this section, titled ***Large Doses (Case 2: M0 > Msat),*** it is clearly describing a "large dose" as one where the initial

		dose is greater than that required to saturate the upper layers of the stratum corneum. This is the only section where the term "large dose" appears in the risk evaluation. The passage goes on to say that "*in this case, absorption and evaporation approach steady-state values as the dose is increased…*", showing agreement with the general statement presented in section 3.4.1.14.

58	**Aggregate Exposures**
	• EPA should consider total daily intake by combining exposures from inhalation and dermal, as well as oral, routes.
	  o Worker exposure and risk are understated because risk levels for dermal and inhalation exposure were determined separately.
	  ▪ On the other hand, it was noted that for inhalation exposure calculations, none of the exposure estimates considered active ventilation controls which could yield an overestimate.
	  o EPA assumed there are no oral exposures to workers, however, hand-to-mouth exposure is likely common.
	• Combined inhalation and dermal exposures were also not considered (review Take *et al.,* 2012).
	• EPA is required to evaluate exposures from combinations of activities. Exposure to workers in occupational settings should be added to exposure of those workers in non-occupational settings.
		• TSCA section 6(b)(4)(F)(ii) directs EPA to "describe whether aggregate or sentinel exposures to a chemical substance under the conditions of use were considered, and the basis for that consideration" in risk evaluations. EPA defines aggregate exposures as the combined exposures to an individual from a single chemical substance across multiple routes (*i.e.*, dermal, inhalation, or oral) and across multiple pathways (*i.e.*, exposure from different sources). 40 CFR 702.33. EPA defines sentinel exposures as the exposure from a single chemical substance that represents the plausible upper bound of exposure relative to all other exposures within a broad category of similar or related exposures. 40 CFR 702.33. EPA considered the reasonably available information and used the best available science to determine whether to consider aggregate or sentinel exposures for a particular chemical. EPA has determined that using the high-end risk estimate for inhalation and dermal risks separately as the basis for the unreasonable risk determination is a best available science approach. There is low confidence in the result of aggregating the dermal and inhalation risks for this chemical if EPA uses an additive approach, due to the uncertainty in the data. EPA does not have data that could be reliably modeled for the aggregate exposure, such as would occur with a PBPK model. Using an additive approach to aggregate risk in this case could result in an

		overestimate of risk. Given all the limitations that exist with the data, EPA's approach is the best available science. EPA has added language to the Key Assumptions and Uncertainties section describing these assumptions and uncertainties.

24, 46, 48, 58	**Other comments related to worker exposure**
	• EPA's risk determinations for workers emphasize central tendency exposure levels and give less weight to high-end exposures. How is the central tendency scenario more protective of workers?
	• EPA, for each category of worker, must identify and evaluate the worker whose exposure represents the plausible upper bound of exposure (sentinel exposure).
	  • EPA defines "sentinel exposure" to "mean the exposure from a single chemical substance that represents the plausible upper bound of exposure relative to all other exposures within a broad category of similar or related exposures."
	  • This definition was not applied throughout the risk evaluation.
	• Baseline exposure to workers via consumption of drinking water and product use, as well as environmental releases to air, water, and land, should be incorporated into worker risk calculations.
	• The agency assumes that all workers are "healthy" in its risk characterization (p. 132), but also acknowledges that there may be numerous worker subpopulations that may have pre-existing conditions that affect the liver or other organs targeted by 1,4-dioxane (p. 108). These sensitive subpopulations are not included in its analysis of risk.
	• In the Monte Carlo analyses to determine percentile of
		• EPA examines the totality of risk estimates for a condition of use when making a determination of unreasonable risk. EPA makes one determination for each condition of use and describes the basis in terms of risks to workers and ONUs. In the risk evaluation for 1,4-dioxane, EPA used the high-end exposure value when considering worker risks in order to address the uncertainties and variability in PPE usage. For inhalation exposures, EPA, where possible, estimated ONU exposures and described the risks separately from workers directly exposed. To account for those instances where, based on EPA's analysis, the monitoring data or modeling data for worker and ONU inhalation exposure could not be distinguished, EPA considered the central tendency risk estimate when determining ONU risk. EPA considered sentinel exposure the highest exposure given the details of the conditions of use and the potential exposure scenarios. Sentinel exposures for workers are the high-end no PPE scenario within each OES. In presenting the inhalation results, high intensity use was characterized by the model iteration that utilized the 95th percentile duration of use and mass of product used and the maximum weight fraction derived from product specific SDS, when available. Dermal exposures for workers for high intensity use were characterized by the model iteration that utilized the 95th percentile duration of use and maximum weight fraction.
		• Please refer to section 1.4.2 in the risk evaluation which provides details as to why exposures related to drinking

	exposure distribution, EPA should select parameters based on an assessment of present-day conditions, with a clear description of the underlying assumptions and present-day information reviewed. • The higher upper bound for the saturation factor parameter is not sufficiently justified. • The assigned parameters are outdated and should be re-evaluated. • EPA lumps together a highly diverse set of uses as "industrial uses" (p. 58) and asserts that all such operations "are expected" to be similar. Support for this assumption should be provided. • EPA uses single scenarios to represent each of the following activities despite their varied nature: all processing scenarios other than repackaging (p. 163); all intermediate use scenarios (p. 165); all open system functional fluid use scenarios (p. 166); all laboratory chemicals use scenarios (p. 168); and all disposal scenarios (p. 175). • No data or analysis was provided to show these scenarios are representative of other scenarios within a grouping or that this provides a health-protective approach. • EPA should provide support for the assumption that exposure via the selected scenario is representative of all potential worker scenarios, and that the selected exposure scenario was the most significant. • EPA assumed that occupational non-users (ONUs) would have lower exposure levels because they do not typically directly handle the chemical. No exposure	water as well as other exposure pathways related to environmental releases were not included in the risk evaluation. • For worker exposures, EPA does account for exposures to potentially exposed or susceptible subpopulations (PESS) by using the high-end exposure value when making its unreasonable risk determination for workers. • The model parameter values used represent EPA's current state of knowledge of the various parameters (*e.g.*, saturation factor, ventilation rate, etc). All parameters are cited and discussed in the Appendix G. • EPA has categorized the different industrial users based on where sufficient process information is known. While EPA recognizes the limitations of grouping the conditions of use enumerated in this comment. the current grouping is sufficient to represent general exposure within each use category. • EPA recognizes that sufficient data does not exist for a more quantitative assessment of ONU exposures. The risk evaluation takes known process descriptions, facility designs, and other factors into account when assessing the exposure potential for ONUs. The risk evaluation and supplemental documents note that while ONU inhalation exposures are assumed to be lower than inhalation exposures for workers directly handling the chemical substance, in some cases ONUs may have higher exposures than workers when workers wear PPE and the ONUs do not. Further, EPA has also used a different approach in the final 1,4-dioxane risk evaluation for making unreasonable risk determinations on ONU

	data for ONUs were evaluated, and it was noted that this assumption is likely only valid if the ONUs were also wearing PPE. • ONU exposures were not quantitatively assessed due to "lack of data". • The risk level for the entire worker population is set at the same level that EPA set for the most exposed individual in a population. This resulted in the determination that the majority of conditions of use posed no risk to workers. This approach must be rejected on scientific, as well as legal, grounds. • The range of workers that EPA defines as ONUs is too large to support a single classification. Supervisors and managers have very different exposure patterns than skilled trade workers, yet all three are assumed to face similar risks under EPA's ONU categorization.	exposures, *i.e.,* looking to the central tendency risk for workers where EPA is unable to separately calculate worker and ONU risks. • As noted in the draft risk evaluation, EPA relied on Agency precedent and NIOSH guidance when choosing the 10^{-4} cancer risk benchmark to evaluate risks to workers from 1,4-dioxane exposure. • The standard cancer benchmarks used by EPA and other regulatory agencies range from 1 in 1,000,000 to 1 in 10,000 (*i.e.*, $1x10^{-6}$ to $1x10^{-4}$) depending on the subpopulation exposed. • EPA, consistent with 2017 NIOSH guidance, used $1x10^{-4}$ as the benchmark for the purposes of this unreasonable risk determination for individuals in industrial and commercial work environments, including workers and ONUs $1x10^{-4}$ is not a bright line and EPA has discretion to make unreasonable risk determinations based on other benchmarks as appropriate. See section 5.1.1.2 of the risk evaluation for additional information. • EPA recognizes the commenter's request for further granulation of the ONU category but also recognizes that every workplace is different with an array of worker types experiencing varying types and degrees of exposures based on site design, equipment, company culture, etc. Without reasonably available information about each facility EPA cannot produce further divisions of ONU designations.
48, 58, 59	**Modeling** • EPA should verify model outputs by using a tiered approach towards exposure to ensure model outputs represent exposure levels in line with real-world conditions. • Dermal modeling with ChemSTEER could be	• Tiered approach has been considered using published test results and sensitivity analysis in the revised version. • The revised risk evaluation document has been updated with inclusion of several dermal exposure scenarios of 1,4-dioxane from the IHSkinPerm© (developed by American Industrial Hygiene Association, AIHA) output

	validated with other, higher-tier, modeling programs, such as IHSkinPerm. This method would be consistent with techniques discussed in the trichloroethylene problem formulation. A tiered approach to exposure modeling would be helpful to triangulate accurate risk levels and confirm underlying assumptions, such as the paragraph on p. 76 that states that dermal exposure with gloves will have higher measured absorption values, despite 1,4-dioxane's highly volatile nature. • It is suggested that EPA add a sensitivity analysis to identify the key factor(s) to pinpoint overly conservative assumptions. • A clearer description about the assumptions contained within each model is required. Nested assumptions and uncertainties can lead the models to provide unrealistic exposure levels. This is particularly true in the dermal exposure calculations, where model inputs are not supported by the weight of scientific evidence. • Regarding modeling, it is suggested that EPA provide added clarity when modeling exposures by organizing assumptions into a table and discussing the rationale for each assumption in the corresponding modeling section. • For inhalation exposure models, the lower ventilation rate assumption used in the models was created in the 1980s and does not reflect modern day design standards and facilities. Thus, it is impossible to conclude with confidence that the high-end exposure predicted by the EPA model is less than the 99.9th percentile. • Factors viewed as modeling errors: o Extrapolation from inhalation to dermal risks without considering flux dynamics that are	are summarized in Section 2.4.1.1.12. Description of conceptual diagram, synopsis of existing tools/models, interpretations, and citations of references are also included in the revised risk evaluation document. • Sensitivity analysis and evaluations with respect to chemical flux have been included in the revised version of risk evaluation document. • EPA recognizes the need for a clear and simple way to understand the assumptions made within each model and the associated rationale. The approach, assumptions, and mathematical calculations are addressed in Appendix G. • A Monte Carlo simulation was performed using wide variations of recent engineering published data to cover applicable ranges for saturation factor, ventilation rate, mixing factor and others. There is no additional ventilation (*e.g.*, fan) modeled in this scenario. • Revisions have been made by introducing a conceptual diagram, general approaches and methods for dermal exposures of 1,4-dioxane from the outer surface of the skin to the inner layers of the skin, tiered analysis using a sensitivity analysis and comparing calculated chemical fluxes from the model used and dermal test data from in vitro and ex vivo studies (see Section 2.4.1.14 - Dermal Exposure Assessment). A diagram in the revised risk evaluation document (Figure 2-2) shows the comparative transdermal flux parameters for 1,4-dioxane across human skin at various exposure conditions.

	uniquely applicable to dermal absorption. ○ Assumption that time equals infinity in dermal modeling (which overestimates evaporation and underestimates absorption). ○ Crucial mistakes in dermal dose equation calculations (not further elaborated). ○ Use of fixed glove PFs of 5x, 10x, and 20x.	
Exposure-Related Systematic Review		
24, 58, 59	**Inappropriate Scoring** • A highly relevant OSHA monitoring study was inappropriately excluded because the data were in a text file instead of an Excel file (see p. 105 of the 1,4-dioxane Supplemental File: Data Quality Evaluation of Environmental Releases and Occupational Exposure Data). The study was scored as unacceptable because [the data are] "all smooshed together in a text file and not useful." This is arbitrary and illustrates inconsistent application of scoring criteria; file format is not one of the criteria for scoring a study as unacceptable. EPA should have worked with OSHA to obtain the data. • **2016 BASF Data**: Why did EPA assign a score of 1 to "Sample Size" and include a note indicating "Representative sample size," when the data set comprised only 28 samples from a single site? In the Risk Evaluation itself, EPA acknowledges that these data are unlikely to be representative: "It is uncertain to what extent the limited monitoring data used to estimate inhalation exposures for this scenario that could be representative of occupational exposures in other manufacturing facilities of 1,4-dioxane" (p. 55). Sampling rate was missing in some cases, so it was assumed that reported rates applied to all measures.	• EPA converted the document into a file format that was intelligible and re-examined the data. The data is OSHA sampling data from 2016 and all of the entries are non-detects. The scoring for the document was upgraded from unacceptable to medium. Per OSHA recommendation, however, EPA policy is to not use non-detects from OSHA because neither OSHA nor EPA can determine if the samples were collected from an environment actually containing 1,4-dioxane. Using these samples may underestimate occupational exposure. Given that all of the data points were non-detects for 1,4-dioxane, the current monitoring data used in the risk evaluation does not change. • Document scores are determined before the risk evaluation and in isolation relative to other sources, in other words scores are purely based on the merits of the document itself. The scoring rubric in the *Application of Systematic Review in TSCA Risk Evaluations* provides the following description for a score of 1 in the Sample Size category; "Statistical distribution of samples is fully characterized." The 2016 BASF data is only from one site, but the statistical distribution of samples from that site are fully characterized and representative of the site. Furthermore, because there are only two known manufacturers or importers in the USA, the data is

	• **2017 BASF Data**: Why did EPA assign a score of 2 to "Sample Size," when the data set comprised only four data points from a single site?	representative of the entire industry. • The scoring metrics for "Samples Size" in the monitoring data scoring rubric of the *Application of Systematic Review in TSCA Risk Evaluations* is defined by how well a range of samples are presented, not the actual number of samples. The title of the metric is misleading in this way, but the underlying definitions are clear. A document with a score of 2 if defined as the "distribution of samples is characterized by a range with uncertain statistics". Furthermore, when scoring documents, all metrics are based solely on the quality of the data within the document. In this case, the 4 data points fall into the Medium (score = 2) category.

5. Human Health

Charge Question 5.1: Please comment on the evaluation of human health hazards including evaluation of portal of entry and systemic toxicity for cancer. Are there any additional 1,4-dioxane specific data and/or information that should be considered?

Charge Question 5.2: Please comment on the evaluation of human health hazards including evaluation of portal of entry and systemic toxicity for non-cancer. Are there any additional 1,4-dioxane specific data and/or information that should be considered?

Charge Question 5.3: Please comment on any other aspects of the human health risk characterization that have not been mentioned.

Charge Question 5.4: Please comment on the mode of action discussion and provide feedback on mode of action analysis.

Charge Question 5.5: Please provide comment on the presented approaches. Please provide comment on any additional model consideration that EPA could include for cancer characterization.

#	Summary of Comments for Specific Issues Related to Charge Question 5	EPA/OPPT Response
SACC, 22, 58, 59	**Genotoxicity- Narrative and Weight of Evidence** **SACC Recommendation:** Clarify the reasoning leading to the weight of evidence statement on page 96. Immediately after discussing a study in which a significant increase in point mutations was seen, the TSCA document states: "Therefore, EPA concluded that the weight-of-the- scientific evidence supports that 1,4-Dioxane is not mutagenic but may elicit clastogenicity in vivo at high doses." The study does provide some evidence that 1-4- Dioxane is mutagenic. However, because the evidence for the induction of gene mutations in vivo comes from a single dose in one experiment, the Committee member cautions about drawing a positive conclusion about a mutagenic mode of action from the Gi *et al.,* (2018) study alone. The member recommended that at this time it would be more scientific to state that there is insufficient evidence to conclude that 1,4-Dioxane is	To better support weight of evidence conclusions related to mutagenicity and genotoxicity, EPA performed data quality review for all studies considered in this section. EPA revised the narrative and associated appendix table of all genotoxicity studies to reflect this change. EPA also made minor edits to improve clarity of the narrative in Section 4.2.3.2. For 1,4-dioxane, EPA concluded that there is insufficient evidence to determine whether 1,4-dioxane or its metabolites act through a mutagenic or otherwise genotoxic mode of action. EPA also reviewed evidence for several plausible MOAs and concluded that there is insufficient evidence to determine the mechanism of action for carcinogenicity of 1,4-dioxane for any of the tumor locations. While some evidence for the proposed MOA of metabolic saturation followed by cytotoxicity and regenerative proliferation is available for liver tumors, the available evidence is also consistent with alternate plausible MOAs (as outlined in

	mutagenic or induces cancer through a mutagenic mode of action. **General Public Comment:** • The analysis is performed in a narrative format that is difficult to follow and, in many places, appears contradictory. **Public Comments in support of a non-genotoxic MOA** • In the draft risk evaluation, EPA agreed with the IRIS assessment conclusion that 1,4-dioxane is not genotoxic in the absence of cytotoxicity but then incorrectly interpreted additional data as a positive indication of genotoxicity. • Data from Goldsworthy *et al.*, (1991) indicates that the observed stimulation of DNA synthesis at elevated exposure levels did not represent a genotoxic event, but rather is a key event for regenerative cell proliferation and/or tumor promotion. • Studies by Itoh and Hattori (2019), Gi *et al.*, (2018), and Morita and Hayashi (1998) should be re-evaluated as the study authors argue the observed effects were due to non-genotoxic mechanisms. • Observations of some genotoxicity at cytotoxic extremely high levels is not relevant to a genotoxic MOA at lower doses. **Public Comments in support of a genotoxic MOA:** EPA dismisses key data relevant to genotoxicity and independent scientific conclusions in support of genotoxic mechanisms. • Gi *et al.*, (2018) concludes that "1,4-dioxane is a	Appendix I). Applying a threshold approach to evaluate cancer risk for 1,4-dioxane would not be adequately supported by available mechanistic evidence. Consistent with EPA guidance, EPA performed BMD analysis on tumor data and applied the best fit models for the data In response to SACC and public comment, EPA has slightly modified the weight of evidence conclusions of the genotoxicity narrative to be more precise. The final risk evaluation now concludes the section on genotoxicity as follows: "Based on the weight of scientific evidence, EPA concluded that there is some evidence for genotoxicity in vivo at high doses, but there is insufficient evidence to conclude that 1,4-dioxane is mutagenic or induces cancer through a mutagenic mode of action." EPA arrived at this conclusion based on the weight of scientific evidence with an awareness of the potential for differences in genotoxicity across endpoints and tissue types.

	genotoxic hepatocarcinogen and induces hepatocarcinogenesis through a mutagenic MOA." However, EPA states "the weight of scientific evidence supports that 1,4-dioxane is not mutagenic" (p. 96). The "weight of evidence" approach that EPA utilized to reach this conclusion should be clearly outlined.	
24	**Genotoxicity- Historical controls** **Public Comment**: Itoh and Hattori (2019) discounted the statistically significant increase in micronucleated immature erythrocytes (MNIE) because these changes were within the historical control range. EPA cancer guidelines state that statistically significant increases in tumors should not be discounted simply because incidence rates in the treated groups are within the range of historical controls	The equivocal findings for MNIE in rats reported by Itoh and Hattori were consistent with the mix of both positive and negative studies for this endpoint reported in other studies. The weight of evidence for this endpoint supports EPA's overall conclusion that there is some evidence for genotoxicity in vivo at high doses. The EPA cancer guidelines refer specifically to tumor incidence and are not directly applicable to micronucleus assays.
58	**Genotoxicity- Studies to consider** **Public Comment:** The following list of studies are in a support of a genotoxic MOA: meiotic nondisjunction (Munoz and Barnett, 2002); micronucleus formation (*i.e.* clastogenic activity) (Mirkova, 1994; Morita and Hayashi, 1998; Roy *et al.*, 2005; Itoh and Hattori, 2019); point mutations (Gi *et al.*, 2018); single-strand breaks (Sina *et al.*, 1983; Kitchin and Brown, 1990); and replicative DNA synthesis (Miyagawa *et al.*, 1999).	All of these studies were considered and contributed to the weight of evidence for genotoxicity. EPA evaluated data quality for each of these studies.
22	**Genotoxicity- ToxCast Screening Assay Evidence** **Public Comment:** Regarding ToxCast results, EPA incorrectly states that 1,4-dioxane was observed to	Data for the assay EPA describes can be found on the EPA Chemistry Dashboard by searching for 1,4-dioxane and clicking on the ToxCast summary. The relevant assay names are TOX21_p53_BLA_p4_ch2 and

	increase the transcriptional activity of the p53 tumor suppressor protein in human colon cancer cells (HCT116) 24 hours after 1,4-dioxane exposure, and that this is indicative of an active DNA damage and repair response. However, the ToxCast results for 113 assays on 1,4-dioxane were all negative and do not support a conclusion that there is any activity associated with DNA damage and repair. It is unclear how EPA weighed the evidence from these ToxCast studies and integrated the disparate results (compared to IRIS) to arrive at a conclusion.	TOX21_p53_BLA_p4_ratio
Mode of Action Comments		
SACC	**MOA – Apply the MOA Framework** **SACC Recommendation:** The EPA needs to explain and follow its guidelines for evaluating the MOA Framework. **SACC Recommendation:** Clarify and expand on environmental exposure and MOA.	EPA has substantially modified the discussion of plausible MOAs for 1,4-dioxane carcinogenicity. EPA now more explicitly describes and follows the MOA framework to evaluate evidence for a specific proposed MOA in the new Appendix I.
SACC, 59	**MOA- Role of Metabolic Saturation** **SACC Recommendation:** The section discussing the importance of 1,4-Dioxane metabolism in its MOA needs to be edited. It should be made clear that high systemic concentrations of 1,4-Dioxane does not necessarily indicate metabolic saturation but could result from decreasing hepatic blood flow. And, if there is extensive first pass clearance in the liver, then overall hepatic metabolic clearance may be perfusion limited. **Public Comment:** The draft risk evaluation concludes that the data from Kasai *et al.,* (2009) do not support saturation from inhalation exposures since the blood levels of 1,4-dioxane increased linearly with doses above	EPA has included a new appendix applying the MOA framework to evaluate the hypothesis that the MOA of 1,4-dioxane carcinogenicity is related to metabolic saturation. In general, EPA concluded that there is insufficient evidence to conclude that metabolic saturation is a necessary key event in liver carcinogenesis. EPA considered the alternate hypothesis presented by the SACC member that reduced rates of metabolism may be due to reduced liver perfusion at high doses. EPA concluded that it is unlikely for liver toxicity from the single dose administered in the toxicokinetic study to lead so rapidly to reduced metabolism due to reduced liver function. Kasai *et al.,* 2008 report that plasma levels of 1,4-dioxane

	400 ppm (~400 mg/kg/day). However, the information presented by Kasai *et al.,* is not sufficient to identify a transition from the low dose, first-order metabolism and the higher-dose, zero order threshold since the doses exceed the reported threshold of 30-100 mg/kg/day in rats. Although Kasai *et al.,* does not provide information for the lower doses used in the study (100 and 200 ppm), the omission of this information suggests that 1,4-dioxane blood levels were below the limit of detection – suggesting that saturation occurred somewhere between 100 and 400 ppm.	were detected in the concentrations of exposure to 400 ppm and above, and increased linearly with the increase in the exposure concentration. These observations are consistent with linear first order kinetics. Had saturation occurred between 100 and 400, we would expect plasma concentrations at higher levels of exposure to increase in a non-linear fashion consistent with Michaelis-Menten kinetics. The threshold for metabolic saturation proposed based on evidence in oral exposure studies cannot be assumed to apply to inhalation exposures because of differences in kinetics across exposure routes (*e.g.* first-pass metabolism).
48, 22,	**MOA- Proposed MOA for Liver Tumors** **Public Comments:** • The non-mutagenic, alternative threshold, high-dose-induced cytoproliferative MOA was not carried through the entire analysis and was not included in the risk characterization. • The EPA is encouraged to further/more closely consider the following studies which support the threshold MOA: Dourson *et al.,* 2014; Dourson *et al.,* 2017; Julien *et al.,* 2009; Boobis *et al.,* 2009; Young *et al.,* 1978; Nannelli *et al.,* 2005; Young *et al.,* 1977; Sweeney *et al.,* 2008; Woo *et al.,* 1977; and US Army Public Health Command, Studies on metabolism of 1,4-dioxane, Toxicology Report No. 87-XE-08WR-09, Aberdeen Proving Ground, MD (March 2010); and Toxicology and Environmental Research and Consulting (TERC), Investigating the mode of action for 1,4-dioxane-induced liver tumors in B6D2F1/Crl mice, Midland, MI. (2019), Report to be submitted to EPA.	In a new Appendix I, EPA methodically applies the MOA framework outlined in the Guidelines for Carcinogen Risk Assessment to evaluate evidence for the MOA for liver tumors proposed by Dourson *et al.,* (2014, 2017). In the proposed MOA, metabolic saturation leads to accumulation of the parent compound followed by cytotoxicity and regenerative proliferation. This expanded analysis incorporates more complete data summaries from Kociba (1974) and the reanalyzed data from NCI (1971) reported in McConnell (2013). The specific issues raised in these public comments are addressed in that appendix. In the risk evaluation, EPA has reviewed and discussed Dourson *et al.,* 2014, Dourson *et al.,* 2017, Nannelli *et al.,* 2005, Young *et al.,* 1998, Young *et al.,* 1977; Sweeney *et al.,* 2008; Woo *et al.,* 1977 and many other studies related to metabolism and MOA. While some of these studies provide evidence that is consistent with the proposed hypothesis, evidence in these studies cannot rule out alternate hypotheses. Furthermore, evidence in several studies indicates that key events in the MOA proposed by Dourson *et al.*, are not necessary precursors to tumor formation, lending

		to support to alternate hypotheses. Ultimately EPA concluded that there is insufficient evidence to support a specific MOA for liver carcinogenicity.
22	**MOA- Specific evidence to consider in support of a proliferative regenerative repair MOA** **Public Comment:** The EPA should re-evaluate and consider the following data as support of a proliferative-regenerative repair MOA: • The increase in hepatocellular foci in mid and high dose males, and in high dose females in the study by Kano *et al.*, (2008). These occur at doses that exceed the limit of metabolic saturation. • Kociba *et al.*, (1974) reported hepatic degeneration and regenerative hyperplasia at or below dose levels that produced liver tumors, but incidence for these effects was not reported. • EPA reported that nuclear enlargement in the respiratory and olfactory epithelium in a chronic exposure assay was not adverse; however, these could also be key event changes observed with tumor promotion.	As described above, EPA has added a new Appendix I that methodically applies the MOA framework outlined in the Guidelines for Carcinogen Risk Assessment to evaluate evidence for the MOA for liver tumors proposed by Dourson *et al.*, (2014, 2017). In the proposed MOA, metabolic saturation leads to accumulation of the parent compound followed by cytotoxicity and regenerative proliferation. EPA considered all of the specific evidence outlined in these comments, including evidence of hepatocellular foci reported in Kano (2008) and evidence of hyperplasia reported in Kociba (1974). EPA weighed the available evidence, including each of the arguments articulated in these comments, and concluded that there is insufficient evidence to support the proposed MOA. While the evidence highlighted in these comments is consistent with the proposed hypothesis, alternate hypotheses cannot be ruled out. Other evidence suggests that not all of the proposed key events are necessary precursors to tumor formation. For example, evidence from Kano 2009 indicates increased incidence of liver tumors at doses below those associated with hepatocellular toxicity. This suggests that cytotoxicity may not be a necessary key event in 1,4-dioxane exposure leading to liver carcinogenesis. In addition, there are several datagaps that prevent EPA from identifying causal relationships between key events. For example, there is no clear evidence demonstrating that cytotoxicity is a necessary precursor to observed cell proliferation and there is not clear evidence that 1,4-dioxane rather than a metabolite is the toxic moiety. 1,4-dioxane or a metabolite may lead to cell

		proliferation through an alternate mechanism.
59	**MOA- Use of new ACC data** **Public Comment:** The ACC has sponsored a new 90-day repeated dose study that was submitted along with comments. This study demonstrates a clear threshold for any effect in the liver at a genomic level. Results of this study are consistent with those in the 13-week drinking water study reported by Kano *et al.,* (2008) in which BDF1 mice were exposed to up to 25,000 ppm of 1,4-dioxane in drinking water. Results are consistent with changing metabolic competency of the female mice as a critical key event in 1,4-dioxane toxicity. The available evidence points to the parent 1,4-dioxane as the toxic species. A direct mitogenic response is triggered in the liver of female mice. This mitogenic response occurs relatively early and likely adds to the regenerative repair that is suggested with the slight increase in single cell necrosis (apoptosis) seen in this study as well as in the chronic 2-year findings where more regenerative repair has been reported. There is a clear threshold for all of these effects, supporting a threshold for the eventual induction of liver cancer. The ACC study also provides toxicokinetic data indicating the metabolism of 1,4-dioxane shifts from linear, first-order metabolism to a zero-order kinetics with increasing dose indicating metabolic saturation. Once saturated, increased exposures result in a disproportional increase in circulating levels of 1,4-dioxane. This supports a threshold response.	EPA considered the additional unpublished evidence submitted by ACC but did not include this evidence in the MOA analysis. The evidence in this unpublished report is not sufficiently specific to provide support for a specific MOA. While the study may identify thresholds for specific effects evaluated in the study, a 90-day study that does not include tumor endpoints is not able to demonstrate that the key events in question are necessary precursors of liver tumor formation.
14, 58	**MOA- General critiques of the MOA for liver carcinogenicity proposed by Dourson *et al.*** **Public Comments:**	As described above, EPA has added a new Appendix I that methodically applies the MOA framework outlined in the

	• Dourson *et al.,* (2017) adjusted doses from sub-chronic studies by dividing them by a factor of 3 in an apparent attempt to compare them to values from chronic studies. It is not appropriate to compare data from different studies for the purpose of attempting to define a quantitative relationship across studies by adjusting doses for effects in sub-chronic studies. • Dourson *et al.,* (2017)'s claim of a chronology of the appearance of endpoints leading to liver tumors is based on the appearance of liver pathology at different doses, not over time. One cannot infer chronology from dose-response data only. • The doses of 1,4-dioxane at which cytotoxicity and cell proliferation were observed were greater than the doses for tumor induction. • Dourson *et al.,* (2017) relied on seven studies to argue that their chronology of events resulted in tumor formation. However, only three of the seven studies provided tumor data.	Guidelines for Carcinogen Risk Assessment to evaluate evidence for the MOA for liver tumors proposed by Dourson *et al.,* (2014, 2017). EPA considered each of these critiques of the MOA proposed by Dourson *et al.,* in development of the MOA analysis in Appendix I. EPA weighed the available evidence, including each of the arguments articulated in these comments, and concluded that there is insufficient evidence to support the MOA proposed by Dourson *et. al.*. While some of the available evidence is consistent with the proposed hypothesis, alternate hypotheses cannot be ruled out. As discussed in Appendix I, much of the evidence articulated in these comments suggests that not all of the proposed key events are necessary precursors to tumor formation. In addition, there are several datagaps that prevent EPA from identifying causal relationships between key events. For example, as noted by commenters, there is no clear evidence demonstrating that cytotoxicity is a necessary precursor to observed cell proliferation.
58	**MOA- Specific evidence for cytotoxicity and necrosis as a key event leading to liver carcinogenesis** **Public Comments:** • Dourson *et al.,* (2017) notes that tumors were found in the low-dose group in the mouse study (Kano *et al.,* 2009), below the dose postulated to reflect saturation kinetics. This is evidence that tumor formation and non-tumor toxicity are decoupled. In the Kano *et al.,* (2009) study, hyperplasia but not the postulated intermediate step of necrosis/inflammation was seen at 1,000 ppm. • Dourson *et al.,* (2014) suggests that 1,4-dioxane	As described above, EPA has added a new Appendix I that methodically applies the MOA framework outlined in the Guidelines for Carcinogen Risk Assessment to evaluate evidence for the MOA for liver tumors proposed by Dourson *et al.,* (2014, 2017). EPA considered the available evidence for each key event in the MOA for liver carcinogenicity proposed by Dourson *et al.,* including cytotoxicity.

	causes liver tumors in rats and mice through a pathway involving cytotoxicity (as indicated by hypertrophy and necrosis) followed by regenerative hyperplasia. This conclusion is not supported by the data in female mice. • Liver tumors identified from rodent liver bioassays occurred in the absence of reported lesions related to cytotoxicity (Kano *et al.*, 2008; JBRC, 1998; NCI, 1978), suggesting that cytotoxicity may not be a key event after 1,4-dioxane exposure leading to liver carcinogenesis.	Based on the available evidence (including the evidence outlined in these comments), EPA concluded that the available evidence from Kano (2009) indicates increased incidence of liver tumors at doses below those associated with hepatocellular toxicity. This suggests that cytotoxicity may not be a necessary key event in 1,4-dioxane exposure leading to liver carcinogenesis. EPA's conclusion is consistent with conclusions of these comments.
58	**MOA- Evidence for hyperplasia as a key event in liver carcinogenesis** **Public Comment:** • In the two-year drinking water study (Kociba *et al.*, 1971, 1974), hyperplasia/abnormal tumor foci were not observed at a dose that did produce tumors. "[C]ritical intermediate steps (effects) in this causal chain are missing even when subsequent steps are observed, including at doses identified by Dourson *et al.*, (2017) as resulting in saturation kinetics." • In the NCI (1978) study, hyperplasia showed a dose-response that significantly differed from that for adenoma tumors. Relative to controls, the incidence of hyperplasia dropped while adenoma incidence increased. These data strongly suggest no significant linkage between hyperplasia and adenomas.	As described above, EPA has added a new Appendix I that methodically applies the MOA framework outlined in the Guidelines for Carcinogen Risk Assessment to evaluate evidence for the MOA for liver tumors proposed by Dourson *et al.*, (2014, 2017). EPA considered the available evidence for each key event in the MOA for liver carcinogenicity proposed by Dourson *et al.*, including hyperplasia. Based on the available evidence (including the evidence outlined in these comments) EPA concluded that the available evidence suggests there may be a dose-response relationship between 1,4-dioxane and bile duct epithelial hyperplasia in Kociba (1974), but did not show a dose-response relationship between 1,4-dioxane and hepatocellular hyperplasia or demonstrate that hyperplasia precedes tumor formation.

22, 58	**MOA- Evidence from nasal tumors** **Public Comment:** • The key events for rat nasal tumor formation (Kasai *et al.,* 2009) show tissue injury with regenerative repair (metaplasia) occurring in both respiratory and olfactory mucosa. • The observed incidence of rare nasal tumor types following 1,4-dioxane exposure is likely the result of a genotoxic or mutagenic MOA and unlikely to be attributed to a cytotoxic MOA (as evidenced by other nasal carcinogens). Evidence for a genotoxic or mutagenic MOA in one organ (*i.e.,* the olfactory system) should create a strong presumption that the same MOA is operating in other organs (*i.e.,* the liver), absent compelling counterevidence.	EPA considered evidence for MOAs in each tumor type independently. There is insufficient evidence to support a specific MOA or perform an in-depth MOA analysis for tumor types reported in tissues other than liver. For tumor types in the respiratory and olfactory mucosa, EPA summarized possible MOAs proposed by Kasai 2009 and Kano 2009. As noted by SACC peer reviewers, the rare nature of the nasal tumor types associated with 1,4-dioxane exposure in rats indicates that the MOA for nasal tumors is unlikely to be a generic cytotoxic/regenerative repair response.
SACC	**Toxicokinetics- Clarity of Discussion** **SACC Recommendation:** Improve the discussion of toxicokinetics (Section 4.2.2) which the Committee found confusing and vaguely worded.	EPA has substantially revised Section 4.2.2 on toxicokinetics to use more precise language, incorporate specific examples from experimental data, and provide more quantitative information.
SACC	**Toxicokinetics- Quantification** **SACC Recommendation:** Given there seem to be some populations/situations involving chronic (repeated) exposures, metabolism and elimination must be treated quantitatively to determine temporal (spikes and troughs) patterns in blood levels as part of the toxicokinetic evaluation.	This would be possible if there was an adequate PBPK model. EPA concluded an adequate PBPK model was not available and could not be developed from available data. EPA acknowledges that there is uncertainty around the magnitude of variation in toxicokinetic factors across individuals. EPA applied an uncertainty factor of 10 to account for interindividual variability associated with differences in toxicokinetic and toxicodynamics, though there is uncertainty around whether the factor of 10 is sufficient to protect potentially susceptible subpopulations.
SACC, 58	**Acute Non-Cancer – Endpoint and Study Selection**	EPA identified Mattie *et al.,* 2012 as the best available information to support an acute POD. Acute exposure

	SACC Recommendation: Justify the use of Mattie *et al.,* (2012) given its lack of critical detail (no histological slides) and unclear quality control. **SACC Recommendation:** Clarify how the relative weight given the neurotoxicity studies of Mattie and Goldberg was determined. An additional study by Kanada (1994), which was apparently not considered in the Evaluation, may need to be included in the neurotoxicity systematic review and subsequent discussion. **Public Comment:** The use of Mattie *et al.,* (2012) for derivation of an acute/short term inhalation point of departure (POD) human equivalent concentration (HEC) instead of the human study by Ernstgard *et al.,* (2006) which does not require interspecies extrapolation, is not clearly justified. No assessment of data quality for this study was presented to support its dismissal. It is suggested that EPA use Ernstgard *et al.,* (2006) as the basis for its acute/short term inhalation modeling.	studies evaluating irritation and inflammation responses in small numbers of human volunteers also contribute to the overall weight of scientific evidence. The NOAEL for acute irritation identified in short-term human studies indicates that the acute POD (and corresponding benchmark MOE) derived from the Mattie 2012 study is protective of acute irritation in humans. The Kanada 1994 study would have been filtered out in the systematic review because it evaluates acute effects from a single exposure and does not provide dose-response information. While it identifies significant effects on dopamine and serotonin following a relatively high dose and provides qualitative evidence for neurotoxicity, it does not provide information to support quantitative dose-response analysis at lower levels of exposure. The Goldberg study provided dose-response information on behavioral outcomes, but the lowest dose evaluated in the study was only half of the LD50. The Mattie study was selected as the basis for the acute POD in part because it provides quantitative dose-response information on effects at a lower level of exposure. The Ernstgard *et al.,* 2006 paper was considered in the overall weight of scientific evidence for acute hazard for 1,4-dioxane. EPA did not select it as the basis for the POD because it is narrowly focused on evaluating acute irritation and inflammatory response following just 2-3 hours of exposure in a small sample of volunteers. Furthermore, it did not identify any acute effects and therefore did not provide quantitative information about dose-response beyond identification of a NOAEL for a limited range of acute outcomes. The Mattie study evaluates a panel of liver,

		kidney, and respiratory effects following a longer duration of exposure in rats. The results of the Ernstgard study (which identified a NOAEL of 72mg/m3) indicate that the POD derived from the Mattie study (a POD of 284 mg/m3 with a benchmark MOE of 300 to account for uncertainty) is protective of acute irritation or inflammatory effects in humans
24	**Developmental toxicity- discussing data gaps** **Public Comment:** EPA acknowledges that the database for potential reproductive and developmental toxicity of 1,4-dioxane is deficient (p. 108), but later states it "did not include women of reproductive age or pregnant women who may work with 1,4-dioxane or children ages 16-21 because the acute effects on liver enzymes and CNS effects are not expected to preferentially affect women or developing children." EPA should not assume that a lack of data is equivalent to a lack of risk.	EPA has rephrased the statement cited by the commenter to be more clear that this decision is based on a lack of information: "EPA does not have information to indicate that the acute effects on liver enzymes and CNS effects would preferentially affect women or developing children."
58	**Developmental toxicity- filling data gaps** **Public Comment:** EPA should use its information authorities to fill data gaps identified in the risk evaluation, including dermal toxicity data and reproductive/developmental/ neurodevelopmental toxicity data.	As described in previous responses (see Section 1), EPA had sufficient information to complete the 1,4-dioxane risk evaluation using a weight of scientific evidence approach. EPA selected the first 10 chemicals for risk evaluation based in part on its assessment that these chemicals could be assessed without the need for regulatory information collection or development. When preparing this risk evaluation, EPA obtained and considered reasonably available information, defined as information that EPA possesses, or can reasonably obtain and synthesize for use in risk evaluations, considering the deadlines for completing the evaluation. In some cases, when information available to EPA was limited, the Agency relied on models; the use of modeled data is in line with EPA's final Risk Evaluation Rule and EPA's risk assessment guidelines.

		EPA will continue to improve on its method and data collection for the next round of chemicals to be assessed under TSCA.
SACC	**Nasal Effects- Evidence for systemic delivery** **SACC Recommendation:** Add a justification for excluding all nasal effects in the extrapolation to dermal routes from inhalation exposures. Delivery of 1,4-Dioxane (or metabolite) in the blood stream may well have contributed to the observed nasal effects. This is documented by the widespread olfactory mucosal distribution of lesions (which is typical of systemic agents, not inhaled agent delivery). Also, nasal injury was seen after oral exposures. Although aspiration of drinking fluid might have occurred it can't be excluded as a cause. More justification is needed.	EPA has reviewed the evidence of respiratory lesions and concluded that these effects are consistent with systemic delivery as opposed to exposure via portal of entry. EPA has revised the dermal PODs extrapolated from inhalation exposure for cancer and chronic noncancer endpoints to incorporate nasal effects believed to be a result of systemic delivery. EPA has also modified the discussion around these PODs to reflect that conclusion. The revised chronic dermal non-cancer POD is now based on nasal effects in inhalation studies and is highly consistent (less than 2-fold difference) with PODs derived from systemic effects following oral exposures.
SACC	**Nasal Effects- Characterization of Nasal Toxicology** **SACC Recommendation:** There were several issues with the nasal toxicology that need to be addressed. For example, the term "nasal" is too vague. More specific language should be used to distinguish respiratory and olfactory effects. The description of the nasal tumors should include information on their distribution; this could help define MOA. The document would be strengthened by inclusion of a nasal toxicologist on the writing team, and inclusion of a cogent discussion of the nasal lesions relative to the current state of the art.	The original studies do not consistently provide the level of specificity that would be required for detailed nasal mapping. Where possible, EPA has revised language around nasal lesions to be more specific. EPA has also revised several PODs based on evidence for widespread distribution of nasal lesions. As noted by SACC reviewers, the uniform distribution of lesions (ie the lack of airflow gradient), in combination with evidence of systemic circulation of 1,4-dioxane following inhalation exposures, indicates that lesions in the olfactory and respiratory epithelium can be attributed to systemic delivery rather than portal of entry effects.
Point of Departure Comments		
SACC, 58, 59	**PODs- BMD Modeling for Respiratory Metaplasia**	EPA applied BMD modeling for all endpoints that were amenable to modeling. Specific reasons that specific

	SACC Recommendation: The benchmark modeling of the respiratory metaplasia would benefit from additional explanation and clarity. This includes explaining why a high confidence benchmark dose (BMD) can be derived from only two dose groups plus controls. **Public Comment:** All endpoints within a study judged to be relevant to the exposure should be considered when modeling. This will help ensure that no endpoints with the potential of having the most sensitive effect for risk assessment applications, usually having the lowest BMDL, are excluded from the analysis. **Public Comment:** EPA needs to clarify its decisions to use BMD modeling for some data sets, but not others (*e.g.*, modeling respiratory metaplasia but not atrophy of the olfactory epithelium reported by Kasai *et al.*, 2009). BMD guidance suggests that neither data set meets the minimum criteria for modeling since all of the non-control exposures show a similar response level -- limiting any modelling of a dose-response relationship. The response rate for both lesions at the lowest dose (68 and 80 percent) significantly exceeds the specified benchmark response (BMR) of 10%. The large disparity in the BMR and incidence rate at the lowest dose is a strong indicator of lack of fit in the BMD modeling and subsequent inappropriate BMD estimates. The draft evaluation rejects a BMD approach for a mouse data set with a very similar dose response. It is not clear why this same logic was not applied to the evaluation of nasal lesions from the rat studies. Given the uncertainty introduced in applying the BMD modeling of the respiratory metaplasia data, the Agency	endpoints were determined not to be amenable to BMD modeling are stated in footnotes to each table. Additional endpoint-specific explanations are provided in the BMD modeling appendix (Appendix J). The LOAEC/NOAEC was used for endpoints that were not amenable to benchmark dose modeling. As described in Appendix J, EPA modeled respiratory metaplasia using only two doses because the highest dose group was excluded to achieve better model fit. EPA does not automatically consider data based on only 2 doses to be concerning. Graphs and other results are evaluated on a case-by-case basis for each endpoint, in particular for an idea of how the results may be affected by choice of doses. In this case it is seen that the fitted curve is superlinear in the range of doses evaluated. Had there been additional testing at lower doses, such testing might have revealed a comparatively flat portion of the curve at low doses, which it seems would have raised the BMDL. Thus, the BMDL reported is probably below the true BMD. The BMDL is a bound, not a point estimate. From a purely statistical viewpoint, what it means to have confidence in the BMDL is, we are reasonably comfortable assuming that the BMDL is no larger than the population BMD. Additionally, in this particular case, the BMDL of 4.7 ppm obtained from modeling the respiratory metaplasia data with the high dose dropped is virtually the same as what one would get using the "fall back" LOAEC approach in which an additional uncertainty factor of 10 is applied to the benchmark MOE to account for LOAEC to NOAEC extrapolation (LOAEL POD of 50 ppm/10 = 5 ppm). Female mouse liver tumor data that was initially determined

	should instead use the LOAEC to derive the HEC for metaplasia. Since the LOAEC is the same as for atrophy, the HEC for either lesion should be 17.6 mg/m3. Although the dose response for the two endpoints is very similar, there is a ten-fold difference in the HEC, therefore (if modeling is going to be done), then both endpoints should be modeled.	not to be amenable to modeling has since been incorporated into the final draft using an alternate modeling approach.
58	**PODs- LOAEC vs. BMD Approach** **Public Comment:** EPA states that the "LOAEC was used with an uncertainty factor for LOAEC to NOAEC extrapolation." However, where and how it did so is not explained clearly in earlier sections of the document (*e.g.*, Section 4.2.6.2.3, pp. 111-114), where text and tabular calculations are provided for this outcome. It is unclear why EPA included this text about the LOAEC to NOAEC extrapolation within the discussion of Risk Characterization Assumptions and Uncertainties (p. 150), given that benchmark dose modeling (BMD) was used in these calculations.	In the case of the chronic noncancer inhalation POD, there were several endpoints that could not be modeled. In the interest of transparency, EPA shows its quantitative dose-response analysis for all relevant endpoints. The sensitive endpoint that was ultimately selected as the basis for the chronic POD used in quantitative risk calculations was evaluated using BMD modeling. The discussion of uncertainty related to the LOAEC and NOAEC in the Risk Characterization Assumptions and Uncertainties (noted by the commenter) was not relevant to the chronic endpoints used in risk characterization and has been revised for clarity.
SACC, 58	**PODs- Methodology for Calculating PODs for Portal of Entry Effects** **SACC Recommendation:** Clarify why a flawed Reference Concentration (RfC) methodology for portal of entry effects is used in this Evaluation. The approach and calculations for the inhalation POD appear to follow standard EPA procedure and are calculated correctly according to that procedure. However, it needs to be recognized that the RfC procedure for portal of entry effects itself is fundamentally flawed. It is based on faulty assumptions and the RfC procedures provide dosimetry estimates that are widely variant from actual experimental	In response to other SACC feedback, EPA reviewed evidence in support of portal of entry vs. systemic effects. Based on the location of lesions relative to airflow, and the detection of 1,4-dioxane in blood following inhalation exposure, EPA is now considering respiratory lesions described in the literature to be primarily the result of systemic delivery. EPA is therefore no longer calculating any PODs for portal of entry effects in the revised RE. EPA instead calculated PODs for chronic inhalation risk based on assumptions about systemic effects. To extrapolate dermal PODs from inhalation PODs, EPA calculated human equivalent doses based on an inhalation

	measurements. The EPA recognized this problem; a subsequent review of the 1994 EPA RfC procedure clearly described the inadequacy of the RfC protocol [U.S.EPA (2009). Advances in inhalation dosimetry of gases and vapors with portal of entry effects in the upper respiratory tract (Vol. EPA/600/R-09/072). Washington, DC]. **Public Comment:** EPA appears to use inappropriate model inputs for the chronic non-cancer assessment for dermal exposures extrapolated from chronic inhalation studies (p. 117): The agency uses an inhalation rate of 1.25 m^3/hr for their inhalation to dermal conversion. This does not match with the number in the EPA Exposure Factors Handbook for average adult moderate activity level (Table 6-28 suggests 2.1 m^3/hr). EPA should explain the rationale for this deviation.	rate of 1.25m^3/hr. as recommended in EPA's Engineering Manual (Chemical Engineering Branch Manual For The Preparation Of Engineering Assessments, 1991) That value is based on a standard estimate that the typical worker inhales 10m^3 over the course of an 8 hour workday (see REACH guidance on information requirements and chemical safety assessment {ECHA, 2010, 6322478}). This is the same breathing rate assumption that is used for occupational exposure limits. This estimate of average inhalation rate over the course of a workday reflects the fact that work intensity varies substantially across the workday. The hourly rates reported in the EPA Exposure Factors Handbook do not easily translate to an 8 hr workday because of these variations in work intensity over the course of a shift. The daily average value of 1.25m^3/hr is slightly above NIOSH's estimated inhalation rate for light work (1.18m^3/hr) and below the NIOSH estimated inhalation rate for moderate work (1.75m^3/hr). Note also that assuming a higher inhalation rate based on moderate intensity work for the purposes of route-to-route POD extrapolation would result in a higher POD that may not be appropriate or adequately health protective for all exposure scenarios.
SACC	**PODs- Kasai *et al.*, LOAEC** **SACC Recommendation:** Provide more justification for the selection of 50 ppm as a LOAEC rather than as a frank effect given the finding in the Kasai *et al.*, (2009) paper.	EPA does not make a distinction between a LOAEC and frank effect in this risk evaluation. There is no functional difference in how a LOAEC or a frank effect are used as the basis for risk characterization.
SACC	**PODs- 1,4-Dioxane Gas Category** **SACC Recommendation:** Given that this document is	Rather than apply default assumptions for a general gas category, EPA has applied chemical-specific information that informs the extent to which 1,4-dioxane toxicity is the

	relying upon the RfC methodology, it is important that the document explicitly state whether 1,4-Dioxane is viewed as a category 1, 2 or 3 gas.	result of systemic delivery. EPA has substantially expanded the discussion of the properties of 1,4-dioxane and experimental observations (including its detection in blood, systemic toxicity, and the uniform distribution of lesions in olfactory and respiratory epithelium following inhalation exposures) that provide insight into the role of systemic delivery in its respiratory effects following inhalation exposure (see Section 4.2.6.2.3). Based on these observations, EPA treated 1,4-dioxane as a systemic acting gas.
SACC, 24	**Uncertainty Factors- Toxicokinetics** **SACC Recommendation:** Include the rationale for not including a toxicokinetic uncertainty factor given the toxicokinetic uncertainties associated with route to route extrapolation. **Public Comment:** EPA relied on oral-to-dermal extrapolation (p. 90) for sub-chronic/chronic non-cancer outcomes, with little acknowledgment of the substantial uncertainties associated with route-to-route extrapolation. The guidance cited for its extrapolation protocol explicitly indicates the need for a thorough evaluation of uncertainty, including "a qualitative evaluation of key exposure variables and models, and their impact on the outcome." Yet only a single statement of uncertainty -- "oral to dermal route-to-route extrapolation assumes that the oral route of exposure is most relevant to dermal exposures" is provided, which is far from sufficient. Additional discussion of the uncertainty associated with this extrapolation is needed. Prior research suggests the inclusion of additional uncertainty factors for route-to-route extrapolation may be appropriate. EPA should apply	A toxicokinetic uncertainty factor could be applied to address uncertainty associated with route-to-route extrapolation. A primary source of uncertainty related to route-to-route extrapolation from inhalation exposures is the relative efficiency of absorption through the lungs vs. absorption through the skin. Absorption through lungs is generally expected to be more efficient for solvents. The dermal PODs derived under the assumption of 100% absorption may therefore be artificially low but are unlikely to be artificially high. Another source of uncertainty in extrapolation from inhalation exposures is that some of the key inhalation studies used whole body exposures which could have resulted in simultaneous exposure through other pathways (eg oral exposure via grooming and vapor-through-skin). These additional routes of exposure could result in an underestimate of the amount of 1,4-dioxane require to produce an effect in inhalation studies. If such alternate pathways do contribute to total exposure in the inhalation studies, the PODs derived from these studies (which assume that all effects are due to inhalation exposure alone) could be artificially low.

	an additional uncertainty factor of 10 to account for these uncertainties.	The primary source of uncertainty related to oral-to-dermal extrapolation is the difference in kinetics related to first pass metabolism. It is unknown whether 1,4-dioxane or its metabolites are the primary source of toxicity, or whether metabolism in the skin and other tissues produce unique metabolites with higher or lower toxicity. While these are important source of uncertainty for most tissues, In this risk evaluation, EPA performed oral-to-dermal extrapolation for liver endpoints (an HED based on hepatocellular toxicity and a CSF based on liver tumors in female mice). Given first pass metabolism, it is unlikely that dermal exposure would result in greater exposure to the liver than oral exposures would. Because the sources of uncertainty related to route-to-route extrapolation in this risk evaluation all contribute to a potential underestimate of the POD, extrapolation from inhalation or oral to dermal exposure is expected to be a relatively conservative approach. EPA concluded that it is not necessary to apply an additional uncertainty factor.
24, 58	**Uncertainty Factors- Database Uncertainty** **Public Comments:** • EPA fails to include necessary uncertainty factors in its calculations of benchmark margins of exposure (BMOE) for risks to workers of non-cancer effects from inhalation and dermal exposure. The BMOE that EPA derives is 30, resulting from the multiplication of two uncertainty factors—3 for interspecies variation (UFA) and 10 for intraspecies variation (UFH). EPA should include an additional uncertainty factor for "the	There is no universal list of hazard data required when evaluating chemical risks under TSCA. Furthermore, for 1,4-dioxane, EPA has sufficient, reasonably available hazard information to conduct a risk evaluation and support the use of the chosen hazard endpoints. Therefore, EPA did not use a database uncertainty factor for hazard in the 1,4-dioxane risk evaluation.

	uncertainty associated with extrapolation from animal data when the database is incomplete." • With regard to the database uncertainty factor, the EPA Risk Assessment Forum notes in its 2002 report, A Review of the Reference Dose and Reference Concentration Processes: The database UF is intended to account for the potential for deriving an under-protective RfD/RfC as a result of an incomplete characterization of the chemical's toxicity. • The 1,4-dioxane database is clearly incomplete. There is no dermal toxicity data at all and only a single short-term developmental toxicity study; hence, the Agency lacks any sub-chronic or chronic reproductive, developmental or neurotoxicity data. Thus, it is imperative that EPA apply an additional uncertainty factor of 10 to account for these data gaps.	
59	**Cancer- Selection of relevant endpoints** **Public Comment:** Evidence suggests that peritoneal mesothelioma and mammary gland adenomas presented in drinking water studies were spontaneous tumors and likely not appropriate for inclusion in the risk evaluation.	EPA included these tumor types in the MS-combo cancer models because dose-response data indicate an association between exposure to 1,4-dioxane and increased incidence of these tumor types. This is consistent with EPA cancer guidelines, which state that, "The default option is that positive effects in animal cancer studies indicate that the agent under study can have carcinogenic potential in humans".
14, 24, 53	**Cancer- Kano (2009) data on liver tumors in female mice** **Public Comment:** EPA should reconsider evidence for tumors in mice and re-evaluate the threshold for cancer in workers to align with prior agency practice. Specifically, the female hepatocellular carcinoma data from Kano *et*	In response to these comments, EPA revised the dermal cancer slope factor (extrapolated from effects observed in oral exposure studies) to incorporate the sensitive liver cancer endpoints observed in female mice in Kano 2009. EPA revised associated risk calculations and tables to reflect this change. While the data were initially excluded because they are not well suited to modeling, EPA was able to collect

	al., (2009), which was chosen as the basis for the USEPA IRIS oral cancer slope factor, was disregarded. The EPA rationale is not scientifically supportable, and it is recommended that the IRIS oral cancer slope factor be used as the oral cancer slope factor in the risk evaluation; the IRIS CSF is more stringent than the chosen value. Exclusion of this data results in an oral CSF of 0.021 (mg/kg/day) that is approximately 5-fold less protective than the CSF identified the 2013 IRIS assessment. Table 4-12 (pg. 126) must include hepatocellular tumors observed in female mice in the Kano *et al.,* (2009) study.	additional individual animal data from the study authors to support a time-to-tumor analysis that provides a stronger basis for modeling. The new approach to modeling the female liver tumor data resulted in a revised oral (and dermal) CSF of 0.1 (mg/kg/day)-^{1}.
24, 56, 48	**Cancer- Apply Cancer Guidelines to selection of linear vs. threshold approach** **Public Comments in Support of the Linear Approach** • According to agency cancer guidelines, the agency shall use the default linear approach in the absence of an alternative known MOA. Only when "alternative approaches have significant biological support" should an "assessment...present results using alternative approaches". • There is a scientific consensus that there is insufficient evidence to support a threshold approach and therefore, the EPA should follow agency guidelines and not entertain the development of a threshold model. • Human variability with respect to the individual thresholds for a nongenotoxic cancer mechanism can still result in linear dose-response relationships in the population. **Public Comments in Support of a Threshold Approach** • EPA's cancer guidelines state: If critical analysis of	EPA's cancer guidelines state that "When the weight of evidence evaluation of all available data are insufficient to establish the mode of action for a tumor site and when scientifically plausible based on the available data, linear extrapolation is used as a default approach, because linear extrapolation generally is considered to be a health-protective approach. Nonlinear approaches generally should not be used in cases where the mode of action has not been ascertained. Where alternative approaches with significant biological support are available for the same tumor response and no scientific consensus favors a single approach, an assessment may present results based on more than one approach" (p.3-21 of the guidelines). For 1,4-dioxane, EPA concluded that there is insufficient evidence to determine whether 1,4-dioxane or its metabolites act through a mutagenic or otherwise genotoxic mode of action. EPA also reviewed evidence for several plausible MOAs and concluded that there is insufficient evidence to determine the mechanism of action for carcinogenicity of 1,4-dioxane for any of the tumor locations. While some

	agent-specific information is consistent with one or more biologically based models as well as with the default option, the alternative models and the default option are both carried through the assessment and characterized for the risk manager.	evidence for the proposed MOA of metabolic saturation followed by cytotoxicity and regenerative proliferation is available for liver tumors, the available evidence is also consistent with alternate plausible MOAs (as outlined in Appendix I). Applying a threshold approach to evaluate cancer risk for 1,4-dioxane would not be adequately supported by available mechanistic evidence. Consistent with EPA guidance, EPA performed BMD analysis on tumor data and applied the best fit models for the data.
48, 56	**Cancer- Use MOA evidence to inform selection of a linear vs. threshold approach** **Public Comment in Support of a threshold approach based on MOA evidence:** • EPA failed to fully consider all of the available evidence for key events supporting a threshold for carcinogenic response in exposed animals • The conclusion that evidence for a threshold mode of action was not sufficiently robust is incorrect. • The weight of evidence clearly supports that the mode of action for rodent tumors associated with high doses of 1,4-dioxane does not include the potential for mutagenicity, and the science clearly supports a threshold for both noncancer and cancer effects. Therefore, linear extrapolation was inappropriate. **Public Comment in Support of a linear approach based on MOA evidence:** • The practice of assigning "nonlinear" MOAs does not account for mechanistic factors that can create linearity at a low dose, such as when an exposure contributes to an existing disease process.	As described above, EPA has added a new Appendix I that methodically applies the MOA framework outlined in the Guidelines for Carcinogen Risk Assessment to consider all of the available evidence for the MOA for liver tumors proposed by Dourson *et al.*, (2014, 2017). EPA concluded that there is insufficient evidence to determine whether 1,4-dioxane or its metabolites act through a mutagenic or otherwise genotoxic mode of action. EPA also reviewed evidence for several plausible MOAs and concluded that there is insufficient evidence to determine the mechanism of action for carcinogenicity of 1,4-dioxane for any of the tumor locations. While some evidence for the proposed MOA of metabolic saturation followed by cytotoxicity and regenerative proliferation is available for liver tumors, the available evidence is also consistent with alternate plausible MOAs (as outlined in Appendix I). Applying a threshold approach to evaluate cancer risk for 1,4-dioxane would not be adequately supported by available mechanistic evidence. Consistent with EPA guidance, EPA performed BMD analysis on tumor data and applied the best fit models for the data.

48, 59,	**Cancer- Specific Comments in Support of a Non-Linear Threshold Approach** **Public Comments:** • EPA should consider the Health Canada approach for the assessment of 1,4-dioxane in drinking water. This approach, which has been informed by Meek *et al.,* (2014) ultimately considers the cancer and non-cancer effects of 1,4-dioxane together using a threshold approach. • Evidence for a threshold effect caused by accumulation of the parent compound is strongest for liver tumors. • Nasal squamous cell carcinoma, peritoneal mesothelioma, subcutis fibroma, and hepatocellular adenoma or carcinoma tumor incidence data from Kano *et al.,* (2009) and Kociba *et al.,* (1974) were reported to be "clearly associated with a threshold" (also supported by Torkelson *et al.,* 1974), and should not have been applied to a linear model.	As stated above, EPA concluded that there is insufficient evidence to determine whether 1,4-dioxane or its metabolites act through a mutagenic or otherwise genotoxic mode of action. Consistent with EPA guidance, EPA performed BMD analysis on tumor data and applied the best fit models for the data. • Rather than follow the Health Canada approach, EPA applied an approach consistent with its own guidelines for carcinogen risk assessment. • While the mechanistic evidence is strongest for liver tumors, EPA concluded there is not sufficient evidence to support a specific MOA for liver carcinogenicity. • While there is some indication of an apparent threshold for tumor incidence in animal studies, EPA considered all of the available evidence, including dose-response information across all studies and tumor locations and mechanistic information to inform model selection. EPA performed a sensitivity analysis to quantify the impact of applying a linear vs. threshold model for liver tumors on overall cancer risk estimates.
58, 24, 56	**Cancer- Specific Comments in Support of a Linear Approach** **Public Comments:** • The most compelling argument for retaining the U.S. EPA default assumption of linearity for 1,4-dioxane is the presence of multiple tumor types in rodent models, all of which are relevant to humans. • Although the linear non-threshold model for carcinogenicity is the correct choice, language in the Risk Evaluation sows doubt on its by stating that there was a high degree of uncertainty in all of the MOA	• EPA agrees that assuming linearity is appropriate given the lack of information about MOA for several of the tumor sites. EPA also used the MS-combo model to perform a sensitivity analysis to determine the impact of applying a linear vs. threshold approach for liver tumors on overall cancer risk. • In the revised risk evaluation, EPA performed an in depth MOA analysis (Appendix I) to demonstrate that all evidence had been considered in reaching the decision to

	hypotheses considered in the evaluation (*e.g.*, mutagenic mode of action or threshold response to cytotoxicity and regenerative hyperplasia for liver tumors). • With regard to a potential threshold based on enzyme saturation, it is well documented that enzymatic metabolic activity varies across the population. Therefore, it is inappropriate to assume that a possible threshold found in limited in vivo studies in laboratory animals or in vitro studies apply across the entire distribution of the human population. Even if there were a threshold seen in such studies based on metabolic saturation, EPA would need to consider variation in the human population and protect the most sensitive individuals, who may experience this purported "threshold" at lower doses. • In animal tests, a specific chemical may cause cancer through a nonlinear dose-response process, but for the human population, the dose-response relationship for the same chemical is likely a low-dose linear one, given the high prevalence of pre-existing disease and background processes that can interact with a chemical exposure, and given the multitude of chemical exposures and high variability in human susceptibility.	apply a linear model and to ensure transparency in the process. EPA concluded that there is uncertainty in all of the MOA hypotheses because there is in fact insufficient information to decisively identify a particular MOA of carcinogenesis for any tumor location. • EPA concluded that there was insufficient evidence to conclude that metabolic saturation is a key event in liver carcinogenesis for 1,4-dioxane. The final cancer risk calculations for 1,4-dioxane do not rely on a threshold approach and therefore do not require adjustments for sensitive individuals for whom the threshold may be lower. • EPA has considered the potential for pre-existing disease and other factors that aren't reflected in animal studies and may make some people more susceptible to both the cancer and non-cancer effects of 1,4-dioxane (see discussion on potentially exposed and susceptible subpopulations in Section 4.4). The final cancer risk calculations do not a rely on a threshold approach.
23, 59	**Cancer- BMD Modeling** **Public Comment:** EPA needs to clarify why MS-Combo was applied twice to tumor data to evaluate uncertainties related to model choice and mechanisms. • Rationale for the decision to choose default linear low-dose extrapolation to develop a unit risk estimate and	EPA ran MS-Combo with and without liver tumors included. This was performed as a sensitivity analysis to determine the impact of including liver tumors on overall cancer risk. For inhalation, EPA found that excluding liver tumors had little impact on overall model results. This means that applying a threshold model based on alternate MOA conclusions for liver tumors would not substantially alter overall inhalation

	cancer slope factor based on benchmark dose modeling for multiple tumor sites is inadequately described. • Use of MS-Combo requires that data sets exhibit a statistically or biologically significant dose-related trend. Neither is true for the following tumor types– Zymbal gland adenoma, renal cell carcinoma, and subcutis fibroma. While the increase in peritoneum mesothelioma and mammary gland adenoma is statistically significant, the biological significance of these tumors to humans is questionable. • Given the failure of many of the tumor types to meet the criteria for benchmark dose modeling, significant uncertainty in interpreting multi-tumor analysis, and since almost all of the target organs have an increased tumor incidence only at the highest dose, the use of the MS-Combo model for assessing the cancer risk of 1,4-dioxane is inappropriate. • The importance of access to individual animal data versus aggregated tumor dose-response data should be investigated. Without access to individual animal data, it is not known whether the same or different rats have developed tumors in the various target organs. If the same subset of rats has developed multiple tumors, one might draw a different conclusion than if they were observed in different rats and MS-Combo should not be applied. • No justification is provided for choosing an alternative threshold ($\alpha = 0.05$) for the cancer model.	cancer risk conclusions. This has been clarified in the dose-response section. EPA assumed that different tumor types are independent and used the MS-Combo model to characterize total cancer risk in studies where 1,4-dioxane increased incidence of multiple tumor types. This approach is consistent with NRC conclusions that an approach based on counts of animals with one or more endpoints would tend to underestimate risk when tumors occur independently across sites (NRC, 1994). Individual animal data showing that multiple tumors occur in the same animal would not provide clear, sufficient information to determine whether or not the tumors arose independently.
59	**Cancer- MS-Combo Model**	The MS-Combo model was peer reviewed in 2011. As noted on EPA's website, "The peer reviewers were specifically

	Public Comment: Peer review of the application of the MS-Combo model is needed before this model is used in chemical-specific risk assessments. The EPA draft indicates that the MS-Combo module has been peer-reviewed. In fact, however, the first sentence of the 2011 report emphasizes that documentation provided to users is clear enough to be adequate to allow users to run the program and obtain program output, but is not adequate to inform users concerning details about the context in which applying the model is appropriate or intended.	asked to evaluate MS-Combo with respect to clarity of the documentation and model output, and the adequacy of testing methods and test results. The reviewers generally agreed that the model produced statistically valid results but made several recommendations regarding enhancements that could facilitate or expand its practical application, and how the documentation and outputs could be improved with respect to clarity. EPA revised the MS-Combo software and documentation in response to these comments, incorporating most of the suggested revisions." While the model itself may not provide instructions about the context in which applying the model is appropriate or intended, EPA modelers can evaluate this on a case-by-case basis. EPA also relies on the SACC to provide peer review of its methods. SACC peer reviewers did not raise concerns about the validity of EPA's application of the MS-combo model for 1,4-dioxane.
56	**Uncertainty- Interindividual Variability** **Public Comment:** The NAS has recommended that human variability in response to carcinogens be accounted for. A factor of 25- to 50- may account for the variability between the median individual and those with more extreme responses, and 25 was recommended as a reasonable default value.	EPA evaluated cancer risk from 1,4-dioxane using an approach consistent with the EPA Guidelines for Carcinogen Risk Assessment.
24	**Uncertainty- BMD Modeling** **Public Comment:** A discussion of assumptions and uncertainties relevant to BMD should be provided	In response to this comment, EPA has inserted additional discussion of strengths and limitations of BMD modeling approaches for each endpoint into a new section describing "overall confidence" in PODs (Section 4.2.7) as well as in the "assumptions and uncertainties" section of the Risk Characterization (Section 5.3). There is also detailed discussion of BMD modeling assumptions for each endpoint

		in Appendix J.
56	**Uncertainties- Susceptible Populations/Human Variability in Cancer Risk** **Public Comment:** California EPA reviewed the evidence on differential susceptibility to carcinogens based on age and life stage and derived age adjustment values for carcinogens which include the prenatal period, proposing a default Age-Sensitivity Factor of 10 for the third trimester until age 2 years, and a factor of 3 for ages 2 through 15 years to account for potential increased sensitivity to carcinogens during childhood. At a minimum, EPA should incorporate factors to account for human variability in response to carcinogens, as well as Cal EPA's age adjustment values to address these known susceptibilities. Uncertainty factors should be applied to account for susceptibility of certain subpopulations based on pre-existing health conditions.	Current EPA guidance recommends application of age-dependent adjustment factors (ADAFs) only for carcinogens shown to act through a mutagenic mode of action. For 1,4-dioxane, EPA concluded that there is insufficient information to determine whether a mutagenic mode of action contributes to carcinogenicity.
SACC	**General- Clarification Regarding NIOSH Criteria** **SACC Recommendation:** Clarify the text on page 153 regarding the entry for NIOSH (2017). As written this entry could be interpreted to suggest NIOSH developed its criteria document and the Recommended Exposure Limit (REL) for 1,4-Dioxane using a linear 10-4 theoretical excess cancer risk level—the REL was derived in 1977, which is 5 years before publication of the Howe and Crump (1982) GLOBAL82 method report to OSHA.	EPA has modified this text to make clear that it is referring to general NIOSH guidance: "For 1,4-dioxane, EPA used 1 x 10^{-4} as the benchmark for the purposes of this unreasonable risk determination for individuals in industrial and commercial work environments subject to Occupational Safety and Health Act (OSHA) requirements. This cancer benchmark is consistent with guidance outlined in the 2017 NIOSH chemical carcinogen policy." EPA has also modified the accompanying footnote to add the following "Note that the NIOSH REL for 1,4-dioxane was established prior to this guidance."
SACC	**General- Defining Qualifying terms** **SACC Recommendation:** Explicitly define qualifying	Where possible, EPA has replaced vague words with more precise language and/or supported them with specific quantitative information. For example, EPA substantially

	terms used throughout the text (*e.g.,* "acceptable," "high," "extensive," "appreciable accumulation," and "rapid").	revised the section on toxicokinetics to include more specific experimental observations on the "extent" of absorption and metabolism. The term "acceptable" is used in reference to study quality. As described in the human health hazards "approach and methodology" section of the risk evaluation, EPA uses a quantitative scoring system to rate studies as high, medium, low, or unacceptable. "Acceptable" study quality means that the study met minimum inclusion criteria (ie it was not "unacceptable") when EPA applied the systematic review protocol.

6. Risk Characterization

Charge Question 6.1: Please comment on the objectivity of the underlying data used to support the risk characterization and the sensitivity of the agency's conclusions to analytic assumptions made.

Charge Question 6.2: Please comment on the characterization of uncertainties and assumptions including whether EPA has presented a clear explanation of underlying assumptions, accurate contextualization of uncertainties and, as appropriate, the probabilities associated with both optimistic and pessimistic projections, including best-case and worst-case scenarios. Please provide information on additional uncertainties and assumptions that EPA has not adequately presented.

Charge Question 6.3: Please comment on whether the information presented supports the findings outlined in the draft risk characterization section. If not, please suggest alternative approaches or information that could be used to develop a risk finding in the context of the requirements of the EPA's Final Rule, Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act (82 FR 33726).

#	Summary of Comments for Specific Issues Related to Charge Question 6	EPA/OPPT Response
SACC, 46, 55, 58	**Data Gaps and Scope** **SACC Recommendation:** Clarify portions of text as indicated **Specific examples in need of clarification identified by committee members:** • limited data sets from the EU risk assessment • monitoring data lacked descriptions of worker tasks, exposure sources, and possible engineering controls, assumed as personal breathing zone (PBZ) measurements, sampling rate missing for some 2016 data • the Agency recognizing some data sources may be biased • uncertainty on the underlying exposure distribution • take home exposure from workers to family	Where possible EPA has clarified language related to these issues. Several of the examples of topics requiring clarification identify data gaps. EPA is charged with performing risk evaluations based on the best available science. EPA believes it has sufficient information to make a reasoned analysis regarding 1,4-dioxane in the limited time available for completing the risk evaluation. EPA recognizes that limited data for some exposure scenarios, hazard endpoints and mechanisms introduces additional uncertainty around final risk conclusions. These uncertainties are acknowledged in the uncertainties sections (Section 5.3). • The limitations of the EU Risk Assessment data sets are discussed in the *Key Uncertainties* section of the risk evaluation.

	members was not considered
	• There are what appear to be inconsistencies or flawed assumptions in the discussion of the estimates of number of workers exposed (page 146):
	  ○ "Furthermore, market penetration data was unavailable, therefore, EPA was unable to estimate the number of establishments within each NAICS code that used 1,4-Dioxane instead of other chemicals. This would result in a systematic overestimation of the count of exposed workers." The assumption of overestimation in the count of exposed workers is not self-evident. It could be more establishments actually use the chemical and thus more workers are actually exposed.
	  ○ "Second, EPA's judgments about which industries" (represented by North American Industrial Classification System (NAICS) codes) and occupations (represented by Standard Occupational Classification (SOC) codes) "are associated with the uses assessed in this report are based on EPA's understanding of how 1,4-Dioxane is used in each industry. Designations of some industries/occupations with few exposures might erroneously be included, or some industries/occupations with exposures might erroneously be excluded. This would result in inaccuracy but would be unlikely to systematically either overestimate or underestimate the count of exposed workers." There does not appear to be enough evidence to make the case that number of workers would
		• EPA assumes this comment is in relation to the BASF manufacturing data based on context. The limitations and uncertainties of this monitoring data and the monitoring data for all other occupational exposure scenarios are discussed in the *Key Uncertainties* sections of the risk evaluation.
		• EPA acknowledges the potential for increased bias in some of the monitoring data, especially that which was promulgated from employee complaints. Discussion of bias is included in the *Key Uncertainties* sections of the risk evaluation.
		• EPA recognizes the uncertainty attached to the data it uses in the *Key Uncertainties* sections of the risk evaluation.
		• Take home exposure was not addressed as it was defined out-of-scope for the risk evaluation.
		• In the absence of market penetration data for a given condition of use, EPA assumed 1,4-dioxane may be used at up to all sites and by up to all workers calculated in the method described in Appendix F.5 of the RE. In cases where this approach is used, the number of workers estimated is considered a bounding estimate with the actual number of workers exposed being less than this estimate.
		• EPA has reworded the final phrase to better reflect the confidence of the cited statement. Revision reads: "... This would result in inaccuracy but **is not expected** to systematically either overestimate or underestimate the count of exposed workers." This revision, though minor, removes the word "unlikely," which could be interpreted as a qualitative representation of statistical odds, which EPA does not know.
		  ○ EPA acknowledges that in some cases, ONU exposures may be higher than worker exposures because of unusual facility layout but expects this to be the

	not be systematically influenced. ○ "Exposure data for ONUs were not available for most scenarios. EPA assumes that these exposures are expected to be lower than worker exposures, since ONUs do not typically directly handle the 1,4-Dioxane nor are in the immediate proximity of 1,4-Dioxane. Only inhalation exposures to vapors are expected, which will likely be less than worker exposures." However, given that inhalation is the primary route of exposure, such an assumption requires knowing something about the layout of the facilities and how close ONUs may actually be to where 1,4-Dioxane is being used by workers. Given that this is a vapor, it is likely not to be contained to direct use areas. • The Evaluation shows bias in its discussion of potential bias: "Some data sources may be inherently biased. For example, NIOSH HHEs for the open system functional fluids and film cement uses were conducted to address concerns regarding adverse human health effects reported following exposures during use. Both HHEs were requested by relevant workers' unions (United Paperworkers International Union and Film Technicians Union, respectively)." Industry monitoring data are possibly biased towards lower values, via, *e.g.*, repeated measurements or representativeness, as also cited in the limitations. • There are serious limitations regarding the exposure data, as cited in the section on limitations: "The 95th and 50th percentile exposure concentrations were calculated using reasonably available data.	exception. In most cases ONU exposure will be less than a worker because ONU work tasks are more distant to the inhalation source compared to those directly working with 1,4-dioxane. • EPA recognizes the potential for bias in industry data. The cited NIOSH HHE was used as an example to show bias but is not presented as the only incidence of bias in the risk evaluation. EPA has reviewed and added a more balanced discussion on bias to underscore the potential for bias in all areas, not just with HHEs and reported issues. • EPA understands the limitations of the data and the resulting limitations of the risk evaluation. The limitations are discussed in many places within the risk evaluation. During systematic review, EPA determined that there were nine (9) acceptable studies that characterized the aquatic toxicity of 1,4-dioxane. These happen to be the same studies that were used in previous risk assessments for 1,4-dioxane. As a result of EPA's systematic review process, these studies were rated "acceptable," "high," or "medium" quality. EPA only evaluated studies that were "acceptable" and rated as "high," "medium," or "low" quality. EPA evaluated two acceptable studies that reported chronic toxicity to fish. Other studies that addressed chronic ecotoxicity were not acceptable for this assessment. In addition, EPA applied assessment factors to derive the environmental concern levels in the environment. These assessment factors provided a lower bound effect level that would likely encompass more sensitive species that are not specifically represented by the reasonably available experimental data. Assessment factors account for differences in inter- and intra-species variability, as well as laboratory-to-field variability. Additional data for chronic ecotoxicity would only reiterate the conclusion the hazard

	The 95th percentile exposure concentration is intended to represent a high-end exposure level, while the 50th percentile exposure concentration represents typical exposure level. The underlying distribution of the data, and the representativeness of the available data, are not known." Recognizing the limitations, this nonetheless raises serious questions about the risk characterizations for the inhalation exposures overall. • limited chronic toxicity studies available for assessing the long-term effects to aquatic species • only one developmental study available • high degree of uncertainty in the MOA evaluations in general • skin sensitization and respiratory sensitization were not considered • Uncertainties include the provision of unmeasured exposure concentrations in the Bringman and Kuhn (1977) study. It is also uncertain how "intoxication" is defined for that study. While the fathead minnow study provided data regarding hatch and development which were used in the chronic threshold, no fish reproduction study could be found. The lack of reproduction assessment suggests significant uncertainty and may require implementation of an additional safety factor. **Public Comment** • EPA's risk determinations for 1,4-dioxane are weakened by numerous data gaps that should have been identified and addressed before initiating the evaluation. • EPA's occupational exposure assessment is not	of 1,4-dioxane is low. Therefore, EPA is confident that 1,4-dioxane does not pose any hazard resulting from chronic exposures. • EPA has acknowledged the limited developmental toxicity data as a source of uncertainty • EPA has substantially expanded the discussion of the MOA in a new appendix and acknowledges the lack of clear MOA as a source of uncertainty. EPA also includes a sensitivity analysis showing that exclusion of liver tumors that may occur through an alternate MOA does not substantially change the cancer risk estimates for inhalation exposures • EPA considered reasonably available hazard data and acknowledged the uncertainties associated with data gaps. • EPA did not find where "intoxication" was reported for any studies that were evaluated by Bringman and Kuhn (1977). For Daphnia magna, behavior, equilibrium and immobilization were reported as effect to acute exposure to 1,4-dioxane. For algae, population growth was used to summarize the effects.

	supported by sufficient inhalation or dermal exposure data. • EPA's reliance on summaries of foreign exposures does not provide substantial evidence for EPA's determinations of no reasonable risk or satisfy EPA's TSCA obligation to consider all reasonably available information. ○ Courts have previously held that foreign studies of occupational exposure and risk "do not constitute substantial evidence for OSHA's finding of a significant risk," due to the differences in working conditions between the countries where the studies were conducted and the United States.	
SACC, 24, 46, 50, 54, 58	**Data Gaps- Use authority to obtain additional data** **SACC Recommendation:** The Agency should use its authority to obtain additional data to fill data gaps and/or perform a quantitative sensitivity analysis. This could further direct the Agency to areas where additional important data are to be obtained, clarified, and/or to apply a quantitative uncertainty analysis. • due to the lack of rigorous uncertainty and sensitivity analysis, it is difficult to know whether filling certain data gaps would make a material difference to the Agency's conclusions. **Public Comment:** • Qualitative and screening-level environmental assessments were conducted where data are lacking (*e.g.,* sediment, land-applied biosolids). TSCA requires EPA to conduct risk evaluations of	As described in previous responses (see Section 1), EPA had sufficient information to complete the 1,4-dioxane risk evaluation using a weight of scientific evidence approach. EPA selected the first 10 chemicals for risk evaluation based in part on its assessment that these chemicals could be assessed without the need for regulatory information collection or development. When preparing this risk evaluation, EPA obtained and considered reasonably available information, defined as information that EPA possesses, or can reasonably obtain and synthesize for use in risk evaluations, considering the deadlines for completing the evaluation. 40 CFR 702.33. In some cases, when information available to EPA was limited, the Agency relied on models; the use of modeled data is in line with EPA's final Risk Evaluation Rule and EPA's risk assessment guidelines. EPA will continue to improve on its method and data collection for the next round of chemicals to be assessed under TSCA.

	chemicals that are based on the "best available science" (TSCA section 26(h)) and all "reasonably available information" on hazards and exposures (TSCA section 26(k)). EPA did not use its authority to reasonably generate, obtain, or synthesize data for use in risk evaluations."	
SACC, 22, 58	**Assumptions and Uncertainties- General/Overall Risk** **SACC Recommendation:** Make it more transparent where uncertainties are quantified and provide justification where they are not **SACC Recommendation:** Provide more explanation where requested. • Committee members wanted more uncertainty and sensitivity analysis to ascertain whether the underlying data are sufficient for the risk characterization; One Committee member provided references on quantifying uncertainties to inform decision making (NAS 2014, Simon *et al.*, 2016) • What information does EPA consider to be "reasonably available?" That phrase is used throughout the document without adequate explanation. • Some of the assumptions and the resultant uncertainty factors require more detailed explanation. Examples include dermal absorption fractions and interspecies uncertainty factors (UFA). Considering statements about the lack of data in some of the human studies, despite some	• To the extent possible, EPA has tried to quantify uncertainty where possible and to identify sources of uncertainty where quantification is not possible. • As described above, reasonably available information is defined as information that EPA possesses, or can reasonably obtain and synthesize for use in risk evaluations, considering the deadlines for completing the evaluation. 40 CFR 702.33. • EPA has inserted additional discussion of the uncertainty factors that were applied in the risk characterization • EPA has modified the discussion of uncertainties related to dermal risk characterization to remove misleading language and reflect changes in our approach. The discussion of uncertainty related to the LOAEC and NOAEC in Section 5.2.4 on Risk Characterization Assumptions and Uncertainties (noted by the SACC) was not relevant to the endpoints used in risk characterization and has been revised for clarity. • EPA has rephrased the statement about risks to pregnant women and children (ages 16-21) to clarify that there is a lack of data on specific effects in these groups: "Workers were identified as relevant potentially exposed or susceptible subpopulations, but EPA did not specifically identify women of reproductive age or pregnant women

	degree of correspondence between effects observed in humans and experimental animals, the UFA of 3 seems unjustified; a full value of 10 seems more appropriate. • The third paragraph on page150 is confusing. Evaporation from skin is assumed to not occur for some of the dermal extrapolations, but it was assumed to occur for others. Much more clarity is needed. The last sentence of this paragraph makes no sense. "Metabolism occurs in both oral and dermal routes and inhalation is not as relevant to dermal as absorption is more rapid by inhalation." Also, many of the dermal extrapolations are determined from inhalation data, which apparently this sentence is saying is inappropriate. • In Section 5.2.4 Risk Characterizations the second paragraph on page 150 is confusing. Is the critical effect (respiratory metaplasia) evaluated by a BMDL (lower confidence limit for BMD)? If so, what is the point of raising concerns about using LOAECs? • On what did EPA base the cutoff age of 16 for adult that is used in several places? The Department of Human Health Services (DHHS) standard cutoff is age 18. **Public Comments:** • The present draft evaluation confounds parameter uncertainty and variability, when variability (inherent natural variation) and uncertainty (lack of knowledge) are distinct considerations in a	who may work with 1,4-dioxane or children ages 16 to 21 because EPA does not have information to indicate that 1,4-dioxane would preferentially affect women or developing children." • In Section 2.4.1 and Table 4-3, EPA stated that for the purpose of this assessment. EPA considered exposure of the occupational users and non-users, which include but are not limited to male and female workers of reproductive age who are >16 years of age. Female workers of reproductive age are >16 to less than 50 years old. Adolescents (>16 to <21 years old) are a small part of this total workforce. The occupational exposure assessment is applicable to and covers the entire workforce who are exposed to 1,4-dioxane. • EPA did not assess the toxicity of 1,4-dioxane for the sediment environment. Because1,4-dioxane is not expected to sorb to sediment and will instead remain in pore water, *Daphnia magna* and *Gammarus pseudolimnaeus* are two species that feed through the entire water column and in sediment were deemed to be an acceptable surrogate species for sediment invertebrates. Therefore, EPA did not view this as a data need. It has been well documented that D. magna has been used to study the effects of hazardous chemical to pore water and sediment contaminates such as metals and organic compounds (Giesy *et al.*, 1998; Othoudt *et al.*, 1991; Ristola *et al.*, 1995; Coen and Janssen, 1998; Suedel and Rodgers 1996; CPA, 2004; Parkak *et al.*, 2010). The results from these studies, procedures and protocols have been used for establishing benchmark dose levels for sediment toxicity.

	probabilistic assessment. EPA needs to further clarify parameter uncertainty and variability. • EPA did not integrate information about uncertainty and variability into an overall characterization of the impact of uncertainty and variability on estimated risks.	
SACC, 24, 48, 58	**Assumptions and Uncertainties - Exposure** **SACC Recommendation:** Provide more explanation where requested. • In some scenarios where exposure is described as a "reasonable worst case," the Evaluation does not provide sufficient details on how exposure estimates are determined to guess the percentile represented by the exposure (*e.g.*, is it an upper 10%, 5% or 1% scenario). **Public Comments:** • With respect to its use of exposure models in occupational settings, EPA should include sensitivity analyses for models where assumptions and uncertainty are prevalent**.** • Inaccurate assumptions used in dermal exposure modeling may underestimate exposure. Issues include: reliance on Bronaugh (1982); EPA's extrapolation from inhalation to dermal risks without considering flux dynamics that are uniquely applicable to dermal absorption; EPA's assumption that time equals infinity in its dermal modeling (which overestimates evaporation and	• EPA recognizes that some occupational exposure scenarios rely on models or small datasets due to limited available data but acknowledges that every available effort was made to collect data. In preparation for the risk evaluation EPA collected monitoring and exposure data directly from industry, NIOSH, OSHA, KCNSC and other sources in addition to an exhaustive search of published data. • As indicated earlier in this response to comment document, the dermal exposure calculations have been updated and validated by using sensitivity analysis and by comparing test results reported by the researchers at the Kansas State University, Manhattan, Kansas; and at the University Erlangen-Nuremberg, Erlangen, Germany. The above-mentioned references are cited in the revised risk evaluation document (see Section 2.4.1.14 - Dermal Exposure Assessment). • The revised risk evaluation document has been updated by deleting Bronaugh (1982) and the relevant paragraph as the Bronaugh (1982) cited data are not used in the dermal exposure assessment. The dermal calculations have been updated in the revised risk evaluation by including a conceptual diagram (Figure 2-1), tiered analysis using: a) updated calculations; b) sensitivity analysis to evaluate chemical fluxes at various fractional absorption varying from negligible (~0) to complete absorption (1.0) (see

	underestimates absorption); mistakes in the dermal dose equation calculations; and EPA's use of fixed glove PFs of 5x, 10x, and 20x	Figure 2-2); c) overall comparison of modeled chemical fluxes with in-vitro and ex-vivo test data reported in the literature. Regarding the considerations of glove PF, the EPA included a thorough analysis on incorporation of glove protection, limitations and protections of glove use, potential for occlusion in Appendices E (E5 and E6), and G. Additional information are also included in Supplemental document (Engineering Assessment of Occupational Exposure for 1,4-Dioxane).
SACC, 24, 58,	**Assumptions and Uncertainties - Hazard** **SACC Recommendation:** Provide more explanation where requested. • On page 149, there is brief discussion of metabolism. There is a seeming presumption that metabolism is not required, but it is unclear what the plausible mechanism would be for the parent compound as opposed to a reactive intermediate. • In 5.3.3, the first full paragraph on page 149 states that the main uncertainty for the human health hazard is the unknown mode of action (MOA). What is the basis for this assertion? Is this greater than the potential for species difference or other factors? The statement that there is no information on the MOA for tissues other than the liver is not strictly correct. The comprehensive evaluation of the totality of the nasal toxicity/cancer data could indeed provide insights into modes of action at this site. Such an evaluation was not done. • In 5.3.3, on page 149 in the second paragraph it states metabolic saturation is a proposed event in the MOA. As highlighted above in this review, the evidence for metabolic saturation is weak at best.	EPA has revised the discussion under the heading Human Health Hazard Assumptions and Uncertainties in response to these comments. • EPA agrees that there is uncertainty around whether toxicity is caused by 1,4-dioxane itself or by metabolites and describes this as a source of uncertainty. • EPA has modified the language on uncertainty related to the MOA to state that it is "one source of uncertainty for cancer risk estimates" rather than the main uncertainty. EPA also deleted the statement that there is no information about MOA for tissues other than liver. Instead, the final language states that EPA concluded there was insufficient information to support a specific MOA for any tumor type. • EPA considered the alternate explanation that the reduced rate of metabolism is the result of perfusion limited metabolism rather than metabolic saturation. Perfusion limited metabolism would require liver toxicity that results in reduced liver function to occur very rapidly in toxicokinetic studies where metabolic saturation is observed. In the MOA analysis, EPA notes that evidence in support of metabolic saturation as a necessary key event for liver tumor carcinogenesis is very limited. • EPA has inserted additional discussion of uncertainties related to route-to-route extrapolation.

	Indeed if 1,4-Dioxane is a high extraction compound (in the liver) then perfusion limitation or capacity limitation are potential events, not metabolic saturation. Moreover, while hepatic metabolic saturation may reduce active metabolite formed in the liver it would also serve to diminish hepatic clearance and increase delivery of 1,4-Dioxane to other tissues. **Public Comments:** • EPA should discuss the uncertainties that route-to-route extrapolations introduce. The source EPA cites for its approach to extrapolation (p. 150, citing USEPA 2004) recommends that, at a minimum, a thorough discussion of associated uncertainties be included when such extrapolation is used. EPA relied on oral-to-dermal extrapolation (p. 90) for sub-chronic/chronic non-cancer outcomes, with little acknowledgment of the uncertainties associated with route-to-route extrapolation. The inclusion of additional UF for route-to-route extrapolation may be appropriate. As is recommended for route-to-route extrapolation generally and oral-to-dermal extrapolation specifically, EPA should apply an additional uncertainty factor of 10 to account for these uncertainties. • EPA states in the Risk Determination section that the agency's approach to estimating dermal exposures "could overestimate risk, as EPA used 3.2%, the higher dermal absorption factor value from Bronaugh (1982) in the risk evaluation. Inclusion of an additional UF would affect the conclusion that risk is overestimated.	• The format of the Unreasonable Risk Determination section has been revised and no longer includes discussion on these types of uncertainties. Uncertainties are now discussed in Section 4.

SACC	**Study Quality** **SACC Recommendation:** Each time Mattie *et al.,* 2012 is cited that EPA add "after Kasai *et al.,* (2008)." • Several Committee members were not comfortable with the reliance on a single government report that was not published in a peer-reviewed journal, Mattie *et al.,* (2012). It was also noted that Mattie *et al.,* (2012) is a limited repeat of the study reported in Kasai *et al.,* (2008) and that each time Mattie *et al.,* (2012) is cited Kasai *et al.,* (2008) should be included	Kasai *et al.,* (2008) is a high-quality inhalation study, but it only reports effects of a 13-week exposure. It did not evaluate acute and short-term effects of 6-hour and two-week exposure periods and cannot be used to inform dose-response for short-term exposures. While some of the endpoints evaluated are similar, the acute and short-term studies in Mattie *et al.,* 2012 are not replications of the sub-chronic study reported in Kasai *et al.,* (2008). A previous two-week drinking water exposure study performed by JBRC was not published and only limited results of that study are available (See limited data available from JBRC, 1998 at HERO ID: 196242). In addition, the inhalation exposures evaluated in Mattie *et al.,* are more directly relevant for evaluating acute inhalation risk than results from the drinking water study. While EPA recognizes the weakness of the Mattie *et al.,* (2012) report, it is a high-quality study that provides some of the best available information for acute effects of 1,4-dioxane. The original draft risk evaluation misstated the results of the data quality evaluation for the 2-week exposure study as medium quality when the study in fact received a high data quality rating (details of the scoring can be found in the supplemental file). EPA has corrected this error. The POD derived from Mattie *et al.,* 2012 is supported by the broader weight of evidence, including results of another two-week study on neurological effects and by no effect levels reported in acute human exposures.
59	**Risk Calculations- Approach** **Public Comment:** Methods used in this risk evaluation differ from existing evaluations of 1,4-dioxane, mainly the occupational risk assessments conducted by other US bodies (OSHA, ACGIH) and international agencies (ECHA). EPA is encouraged to	EPA applied risk assessment methods tailored to the needs of TSCA implementation. TSCA compels EPA to conduct risk evaluations to determine whether a chemical substance presents unreasonable risk, without consideration of cost or other non-risk factors, under the conditions of use. Occupational risk assessments and conclusions are performed for a different purpose using a different set of assumptions and

	re-examine the methodologies employed in those occupational risk assessments and the conclusions.	considerations.
SACC	**Risk Calculations- Error in Dermal Risk Estimates** **SACC Recommendation:** Correct the substantial error in the dermal risk estimates that makes the risk characterization invalid.	EPA made an error in dermal risk calculations presented in the draft RE. By incorporating a dermal adjustment factor in both the hazard and exposure portions of the risk calculations, EPA had effectively compared PODs in terms of applied dermal dose to predicted exposures in terms of absorbed dermal dose. In the final RE, EPA has revised all dermal PODs to reflect absorbed dermal dose rather than the applied dermal dose calculated in the draft RE. This eliminates the error by putting the exposure and hazard parts of the risk equation in common terms that are more directly comparable. The revised risk calculations predicted higher levels of risk from dermal exposure than previously calculated.
SACC	**Risk Calculations- Presentation and Clarity** **SACC Recommendation:** Provide more clarity where requested. Specifically, add the suggested table to clarify where EPA has and has not determined there to be risk and unreasonable risk • One Committee member presented an idea for a different table to clarify presentation of risk estimates for a different audience. • Explain or give an example how values of column 1 (PF=1) in tables 5-9, 5-10, and 5-11 are calculated. In table 5-10 the risk estimates for import/packaging are given by ratios (*e.g.,* 30/16 for PF=1). Why are they different from the other bin 1 values? • Move 2nd paragraph page 143 to Section 3.4.1.14 where dermal exposure assessment is discussed.	EPA made the following changes in response to these recommendations • EPA has included a new summary table showing risk estimates for all COUs (with links back to corresponding occupational exposure scenarios) • The risk estimates in all tables are calculated according to the MOE and cancer risk equation described in Section 5.2.1. Exposure and hazard values used as the basis for all risk calculations are available in the Risk Calculator supplemental excel file. The risk estimates for import/packaging in Table 5-10 in the draft RE were indicating different risks for bottle vs. drum repackaging. The bottle and drum repackaging scenarios have been split into separate rows in the final risk evaluation to make this clearer (in what is now Table 5-11) • The paragraph on dermal absorption (on p.143 summarizes information that is now included in Section 3.4.1.14 on dermal exposure assessment and has been substantially

		condensed.
19, 24, 47, 50, 51, 54, 55, 56, 58	**Potentially Exposed or Susceptible Subpopulations** **Public Comments:** • Failing to consider risks to vulnerable subpopulations, such as children, the elderly, pregnant women, and people who live near 1,4-dioxane contaminated sites. • Risks to people living near disposal sites, including (but not limited to) those living near so-called "legacy" disposal sites were ignored. • There is specific concern for populations living in Pleasantville, where underground tanks storing 1,4-dioxane leaked, contaminating groundwater and soil in adjacent areas. • Failing to consider exposures linked to disposal, legacy uses, associated disposal, and legacy disposal underestimates the background level of exposures. • Environmental justice communities are often disproportionately exposed and were not considered. • The assumption that exposure to the general public, including children, the elderly, and pregnant women is adequately assessed, and that risks are effectively managed by other statutes is not supported. • No effort was made to identify all vulnerable populations. • Communities where hydraulic fracturing is common may be considered a sensitive subpopulation.	EPA has determined that general population exposures due to drinking water contamination, groundwater contamination, and air emissions are under the jurisdiction of other statutes and are outside the scope of this risk evaluation. Therefore, subpopulations who may be exposed through these pathways are outside the scope of the risk evaluation. However, the final risk evaluation includes an evaluation of general population exposures through recreational activities (*i.e.*, swimming) in ambient water bodies. See Section 1.4.2 of the final risk evaluation. EPA has added a footnote to the Executive Summary to clarify that EPA did not identify any legacy uses of 1,4-dioxane. EPA did not evaluate "legacy disposal" (*i.e.*, disposals that have already occurred) in the risk evaluation, because legacy disposal is not a "condition of use" under Safer Chemicals, 943 F.3d 397. Regarding body care and cosmetic products, they are excluded from the definition of "chemical substance" per TSCA section 3(2) and are outside the scope of this risk evaluation. EPA's review of the FracFocus reports on 1,4-dioxane indicates that the 1,4-dioxane is likely present as an impurity in the ethoxylated alcohols that are also named in the same reports. EPA initially excluded production of 1,4-dioxane as a by-product from certain other chemicals and presence as a contaminant in industrial, commercial and consumer products from the scope of the risk evaluation using EPA's discretion under TSCA section 6(b)(4)(D). While EPA has addressed some conditions of use related to 1,4-dioxane as a byproduct in

	• Consumers and adult women who use multiple cosmetics and cleaning products may be considered a susceptible subpopulation. • Adolescent girls use more body care and cosmetic products than adult women and may be considered a sensitive subpopulation for carcinogenic effects.	this risk evaluation, EPA expects that 1,4-dioxane exposures associated with the use of ethoxylated alcohols used in hydraulic fracturing fluids would be considered in the scope of a risk evaluation for ethoxylated alcohols. In cases like this, EPA believes its regulatory tools under TSCA section 6(a) are better suited to addressing any unreasonable risks that might arise from these activities through regulation of the activities that generate 1,4-dioxane as an impurity or cause it to be present as a contaminant than they are to addressing them through direct regulation of 1,4-dioxane. This case-by-case approach for byproducts exposures is consistent with the various scenarios explained in the Risk Evaluation Rule, 82 FR at 33730. As discussed in Section 4.5 of the final risk evaluation, EPA did not aggregate exposure across exposure routes (dermal, inhalation or oral) for occupational, consumer, or general population exposures. EPA chose not to employ simple additivity of exposure pathways within a condition of use because of the uncertainties present in the current exposure estimation procedures. There is currently no PBPK model available to facilitate evaluation of aggregate exposure from simultaneous exposure through inhalation, dermal, and oral contact with 1,4-dioxane. Without a PBPK model containing a dermal compartment to account for toxicokinetic processes the true internal dose for any given exposure cannot be determined, and aggregating exposures by simply adding exposures from multiple routes could inappropriately overestimate total exposure. Conversely, not aggregating exposures in any manner may potentially underestimate total exposure for a given individual. EPA acknowledges in Section 4.3.2 that the decision not to aggregate risk could result in an underestimate of risk. This approach is consistent with the approach taken and peer

		reviewed for the other solvent chemicals recently evaluated and finalized.
SACC, 24, 56, 58	**Potentially Susceptible Subpopulations** **SACC Recommendation:** EPA should more fully address susceptible populations including pregnant women or women who may become pregnant. Modeling and sensitivity analysis may help address these data gaps. **SACC Recommendation:** Provide more clarity where requested. • How can the following conclusion be determined given the absence of any separation of effects by gender in these studies? "In developing the risk evaluation, the EPA analyzed the reasonably available information to ascertain whether some human receptor groups may have greater exposure than the general population to the hazard posed by a chemical. The results of the available human health data for all routes of exposure evaluated (*i.e.*, dermal and inhalation) indicate that there is no evidence of increased susceptibility for any single group relative to the general population. Exposures of 1,4-Dioxane would be expected to be higher amongst workers and ONUs using 1,4-Dioxane as compared to the general population." (page 151); In fact, prior statements in the document contradict this, stating: "Information on induction of liver enzymes, genetic polymorphisms and gender differences was inadequate to quantitatively assess toxicokinetic or toxicodynamic differences in 1,4-	EPA has modified the language related to potentially exposed or susceptible subpopulations in the risk characterization section to be more transparent about uncertainties and data gaps. The revised language acknowledges that some subpopulations may be more susceptible due to lifestage, genetic differences, pre-existing diseases, or other factors that impair metabolism or increase susceptibility of the target organs of 1,4-dioxane: "…it's possible that some subpopulations are more biologically susceptible to the effects of 1,4-dioxane due to genetic variability, pre-existing health conditions, lifestage, pregnancy, or other factors that alter metabolism or increase target organ susceptibility. For example, people with liver disease may by more susceptible due to reduced metabolism of 1,4-dioxane and increased susceptibility of a target organ. EPA does not have sufficient information about these potential sources of susceptibility to quantitatively incorporate them into the risk assessment."

	Dioxane hazard between animals and humans and the potential variability in human susceptibility." • Page 151, last paragraph, does this describe an approach that EPA will take in the future to differentiate the risk for subpopulations with varying exposure or severity of the health effects? An alternative way to describe this is to discuss the limitation of the current approach. **Public Comments:** • General population and worker subpopulations that have pre-existing conditions that affect the liver may be considered a sensitive subpopulation. • There is significant evidence that the prenatal life stage is more susceptible to carcinogens. Pregnant women should be evaluated as a sensitive subpopulation • The agency assumes that all workers are "healthy" in its risk characterization (p. 132) but indicates elsewhere that there may be numerous worker subpopulations with pre-existing conditions that affect the liver or other targets of 1,4-dioxane.	With regard to the comment on the last paragraph on page 151 of the draft risk evaluation, EPA has adjusted its approach to unreasonable risk determinations for workers in the final risk evaluation. While EPA has evaluated worker risk with and without PPE, as a matter of policy, EPA does not believe it should assume that workers are unprotected by PPE where such PPE might be necessary to meet federal regulations, unless it has evidence that workers are unprotected. In consideration of these uncertainties and variabilities in PPE usage, EPA uses the high-end exposure value when making its unreasonable risk determination in order to address those uncertainties.
SACC	**Scope- Calculate risk for general population and PESS** **SACC Recommendation:** Include estimates of risk to general population and susceptible populations, especially in other pathways of exposure such as drinking water.	General population exposures via drinking water, ambient air, and other pathways are not in the scope of this risk evaluation (see Section 1.4.2). For example, EPA determined that exposures to 1,4-dioxane through drinking water are under the jurisdiction of the Safe Drinking Water Act. However, the final risk evaluation includes an evaluation of general population exposures through recreational activities (*i.e.*, swimming) in ambient water bodies. See Section 2.4.2 of the final risk evaluation.
43, 46,	**Scope- Regulatory Nexus**	EPA found that exposures to the general population may occur

48, 58	**Public Comments:** • EPA explains the exclusion of consideration of numerous exposure pathways, hazards, and conditions of use based on the assumption that the exposures evaluated in this risk evaluation are "likely to represent the greatest areas of concern to EPA" (p. 156). No support for this assertion is provided. a. Reduced EPA enforcement provides less assurance that exposures through the excluded pathways are being effectively managed. b. This whole-substance focus begins during prioritization. The definitions of high- and low-priority substances make clear it is the "substance" that receives the designation, not selected conditions of use, exposures, or hazards. • When a pathway is excluded from further analysis, EPA must have developed and applied a sound basis for assessing the exposure level. EPA then must consider how exposure from an individual pathway combines with other sources of exposure. • EPA assumes that other environmental statutes have or will sometime in the future address potential risks of 1,4-dioxane that were not covered in the current risk evaluation (*e.g.*, general population, consumer exposure, and PESS). EPA cannot assume that other regulatory authorities (*e.g.*, OSHA, the Safe Drinking Water Act, the Clean Water Act, DOT, and the Resource Conservation Recovery Act) will adequately assess	from the conditions of use due to releases to air, water or land. The exposures to the general population via drinking water, ambient air and sediment pathways falls under the jurisdiction of other environmental statutes administered by EPA, *i.e.*, CAA, SDWA, and RCRA. As explained in more detail in section 1.4.2, EPA believes it is both reasonable and prudent to tailor TSCA risk evaluations when other EPA offices have expertise and experience to address specific environmental media, rather than attempt to evaluate and regulate potential exposures and risks from those media under TSCA. EPA has therefore tailored the scope of the risk evaluations for 1,4-dioxane using authorities in TSCA sections 6(b) and 9(b)(1). EPA did not evaluate hazards or exposures to the general population via certain pathways in the risk evaluation, and as such the unreasonable risk determinations for relevant conditions of use do not account for exposures to the general population for certain pathways. However, the final risk evaluation includes an evaluation of general population exposures through recreational activities (*i.e.*, swimming) in ambient water bodies. See Section 2.4.2 of the final risk evaluation.

	and manage risks from 1,4-dioxane. OSHA standards do not protect public sector workers or construction workers who are classified as independent contractors and are therefore not covered by OSHA. EPA's risk evaluations indicate that such contractors would be exposed to 1,4-dioxane, yet EPA does not discuss how their status as workers affects EPA's PPE analyses and assumptions.	
SACC, 47, 55, 56	**Aggregate Exposures** **SACC Recommendation:** EPA should evaluate combined exposures through several pathways, including pathways that were not evaluated such as drinking water. • Page 152, line 16, states: "As a result of the limited nature of all routes of exposure to individuals resulting from the conditions of use of 1, 4-Dioxane, a consideration of aggregate exposures of 1, 4-Dioxane was deemed not to be applicable for this risk evaluation": This does not seem a strong justification for not considering aggregated exposure. If all routes of exposure are of limited nature, then would not a single route be of even more limited nature? From a practical standard point, there are technical challenges to combining cancer and non-cancer risk when different approaches are taken to quantify non-cancer risk (MOE) and cancer risk (slope factor). While it is in principle possible to combine different health outcomes or risk metrics into a joint estimate of risk associated with aggregated exposure from	TSCA section 6(b)(4)(F)(ii) directs EPA to "describe whether aggregate or sentinel exposures to a chemical substance under the conditions of use were considered and the basis for that consideration" in risk evaluations. EPA defines aggregate exposures as the combined exposures to an individual from a single chemical substance across multiple routes (*i.e.*, dermal, inhalation, or oral) and across multiple pathways (*i.e.*, exposure from different sources). 40 CFR 702.33. EPA has determined that using the high-end risk estimate for inhalation and dermal risks separately as the basis for the unreasonable risk determination is a best available science approach. There is low confidence in the result of aggregating the dermal and inhalation exposures and risks for this chemical if EPA uses an additive approach, due to the uncertainty in the data. EPA does not have data that could be reliably modeled into the aggregate exposure, such as would occur with a PBPK model. Using an additive approach to aggregate exposure and risk in this case would result in an overestimate of risk. Given all the limitations that exist with the data, EPA's approach is the best available science. As explained in the scope document, 1,4-dioxane may be found as a contaminant in consumer products that are readily available for public purchase. In the final risk evaluation, eight consumer

	multiple route, this is an area that requires more research. EPA can be more transparent with these limitations. **Public Comments:** • Overall, there is concern that cancer risk was underestimated because a) the totality of exposures (*e.g.*, consumer uses and drinking water) were not considered and b) risks from different routes of exposure (*e.g.*, dermal and inhalation) were not combined and, therefore, potential additive effects were not assessed. This is of particular concern since the IRIS database lists 1,4-dioxane as a probable human carcinogen.	conditions of use are evaluated based on the uses identified in EPA's 2015 TSCA Work Plan Chemical Problem Formulation and Initial Assessment of 1,4-Dioxane (U.S. EPA, 2015). See Section 2.4.3 of the final risk evaluation.
SACC, 21, 22, 46,	**PPE Assumptions** **SACC Recommendation:** Further explain PPE use and its relation to risk assessment and risk evaluation. • In many incidences EPA shows the use of protective devices with a certain level of Assigned Protection Factor (APF) would bring the risk level (MOE or cancer slope factor) to a reasonable level (in reference to benchmark). If the intention is to demonstrate the effectiveness of use of a protective device, EPA should report the results associated with the smallest Protection Factor (PF) that achieves the desired level of risk reduction when such a device is available. The Evaluation's presentation, in the current version, is inconsistent in that in some cases the "risk level" (MOE or cancer slope) is below and in other cases remained	The OSHA regulations at 29 CFR 1910.132 require employers to assess a workplace to determine if hazards are present or likely to be present which necessitate the use of personal protective equipment (PPE). If the employer determines hazards are present or likely to be present, the employer must select the types of PPE that will protect against the identified hazards, require employees to use that PPE, communicate the selection decisions to each affected employee, and select PPE that properly fits each affected employee. OSHA has established a permissible exposure limit (PEL) of 100 ppm (8-hour TWA) for 1,4-dioxane. However, as noted on OSHA's website, "*OSHA recognizes that many of its permissible exposure limits (PELs) are outdated and inadequate for ensuring protection of worker health. Most of OSHA's PELs were issued shortly after adoption of the Occupational Safety and Health (OSH) Act in 1970, and have not been updated since that time*." OSHA provides an annotated list of PELs on its website, including alternate exposure levels. For 1,4-

	above the benchmark level. **Public Comments:** • In the risk evaluation, EPA determines that occupational inhalation of 1,4-dioxane causes risks up to 48 times greater than levels EPA deems acceptable; however, EPA concludes that few risks associated with 1,4-dioxane are unreasonable. EPA assumes that exposed workers would be provided with, would consistently use, and would be adequately protected by personal protective equipment ("PPE"). EPA should not assume use of PPE in the risk evaluation to avoid concluding "unreasonable risk". • It is not clear how EPA has considered compliance with OSHA's worker protection standards in the 1,4 dioxane risk evaluation. This should be clarified in the document. • EPA cites no evidence that workers exposed to 1,4-dioxane are provided with, or consistently use, PPE. The studies that EPA relies on to determine occupational exposure levels do not mention PPE use. • EPA discounts the reported exposure levels based on the assumption that all workers are provided with, and use, appropriate PPE. • EPA's risk evaluation assumes the use of PPE and also the specific types and protectiveness of such equipment. For 1,4-dioxane, EPA assumes that workers will wear respirators with an average assigned protection factor ("APF") of at least 50 and impervious gloves with a protectiveness factor ("PF") of at least 20. The Safety Data Sheets ("SDS") referenced by EPA—described below, are	dioxane, the alternates provided are the California OSHA PEL of 0.28 ppm and the ACGIH TLV of 20 ppm. (https://www.osha.gov/dsg/annotated-pels/tablez-1.html) EPA's approach for developing exposure assessments for workers is to use the reasonably available information and expert judgment. When appropriate, in the risk evaluation, EPA will use exposure scenarios both with and without engineering controls and/or personal protective equipment (PPE) that may be applicable to particular worker tasks on a case-specific basis for a given chemical. Again, while EPA has evaluated worker risk with and without PPE, as a matter of policy, EPA does not believe it should assume that workers are unprotected by PPE where such PPE might be necessary to meet federal regulations, unless it has evidence that workers are unprotected. For the purpose of determining whether or not a condition of use presents unreasonable risks, EPA incorporates assumptions regarding PPE use based on information and judgment underlying the exposure scenarios. These assumptions are described in the unreasonable risk determination for each condition of use, in section 5.2 of the risk evaluation. Additionally, in consideration of the uncertainties and variabilities in PPE usage, EPA uses the high-end exposure value when making its unreasonable risk determination in order to address those uncertainties. EPA has also outlined its PPE assumptions in section 5.1 of the risk evaluation. Further, in the final risk evaluation for 1,4-dioxane, EPA has determined that most conditions of use pose an unreasonable risk to workers even with the assumed PPE.

	not binding on employers. According to EPA, "a specific glove material or protection factor rating was not provided" in the 1,4-dioxane SDSs. An SDS for a chemical reagent which is 50-60% 1,4-dioxane by weight states that "the use of this product should not require respiratory protection." Other SDSs referenced in the draft risk evaluation recommend unspecified respirators only "if workplace exposure limit(s) of product or any component is exceeded."	
SACC, 56	**Non-cancer Benchmark MOEs** **SACC Recommendation:** Provide more clarity where requested: • Define Benchmark MOE formally, preferably using an equation, giving adequate references and interpretation. **Public Comments:** • EPA should use a unified linear approach for dose-response analysis and risk calculations for all carcinogens and non-carcinogens as recommended by the National Academy of Sciences (NAS); EPA should not use the margin of exposure (MOE) approach. • Use of MOEs is a restrictive approach. MOEs do not provide a risk estimate, but a single number similar to a reference dose. Similar to cancer, a non-MOE approach should be applied to risk calculations for all other health endpoints.	The MOE is a standard risk assessment approach. EPA applies an MOE approach because it allows for the presentation of a range of risk estimates and does not create a "bright line" for regulation. EPA has inserted a definition of the benchmark MOE in the "human health risk estimation approach".
SACC, 24, 50, 54, 58	**Cancer Benchmarks** **SACC Recommendation:** Provide more clarity where requested:	ONUs work in the industrial and commercial environment. As such, consistent with 2017 NIOSH guidance, EPA used $1x10^{-4}$ as the benchmark for the purposes of the unreasonable risk

	• Explain why 10-4 is appropriate for ONUs given that 10-6 is usually used for the general population. • Give reference for the cancer benchmark level of 10-4 (*e.g.*, Table 5-3). Referencing the key findings in the result tables would improve the presentation. **Public Comments:** • EPA relied on NIOSH guidance in order to establish 1 x 10-4 as the cancer risk benchmark for workers, although acknowledging that other laws have standards that differ from TSCA's (p. 153). • It is unclear why a cancer risk benchmark of one-in-10,000 was used as the threshold for unreasonable risk to workers who inhale but "do not typically directly handle" 1,4-dioxane in the scope of their jobs. • EPA guidelines state that the appropriate cancer risk threshold can be anywhere from one-in-10,000 to one-in-one million. Why was the less protective one-in-10,000 threshold chosen? • In this risk evaluation, EPA has set a risk level for the entire worker population that is the same as the level EPA elsewhere set for the most exposed individual in a population. EPA then invokes this level repeatedly to find the majority of conditions of use of 1,4-dioxane to pose no risk to any workers, thereby subjecting many tens of thousands of workers to cancer risks that are as much as two orders of magnitude higher than warranted. This approach must be rejected on scientific as well as legal grounds.	determination for individuals in industrial and commercial work environments who are exposed to 1,4-dioxane. As noted in the draft risk evaluation (Section 5.1.1), EPA relied on NIOSH guidance (Whittaker *et al.*, 2016) when choosing the 10^{-4} cancer risk benchmark to evaluate risks to workers from 1,4-dioxane exposure. NIOSH's mandate, on pg iii of Whittaker *et al.*, (2016), is to: "… describe exposure levels that are safe for various periods of employment, including but not limited to exposure levels at which no employee will suffer impaired health or functional capacities or diminished life expectancy as a result of his work experience." Although NIOSH guidance, p. 20, states that: "exposures should be kept *below* a risk level of 1 in 10,000, *if practical* [emphasis added]" EPA adheres to the 1 in 10,000 benchmark during the risk evaluation stage for TSCA chemicals. Other precedents (*e.g.*, Office of Water; Office of Air) are the basis for cancer benchmarks to be used for risks to the general population. Consistent with these precedents, EPA applied a cancer risk benchmark of 10^{-6} to evaluate cancer risks for consumers. Standard cancer benchmarks used by EPA and other regulatory agencies are an increased cancer risk above benchmarks ranging from 1 in 1,000,000 to 1 in 10,000 (*i.e.*, $1x10^{-6}$ to $1x10^{-4}$) depending on the subpopulation exposed. EPA, consistent with 2017 NIOSH guidance, used $1x10^{-4}$ as the benchmark for the purposes of this unreasonable risk determination for individuals in industrial and commercial work environments. It is important to note that cancer risk thresholds ($1x10^{-4}$ or $1x10^{-6}$) are not a bright line and EPA has discretion to make unreasonable risk determinations based on other

	• For all 10 COUs, inhalation cancer risk levels for workers are above 1 in 100,000 – even with respirator use – for both central tendency and high-end exposures. For 7 of the 10 COUs, high-end cancer risk levels for workers are above 1 in 10,000. For 1 of these, even an APF=50 respirator is not sufficient to get the high-end cancer risk below this risk level. For the other 6 COUs, respirators are necessary to get the high-end cancer risk levels below 1 in 10,000 (APF=50 for 2 COUs; APF=25 for 3 COUs; APF=10 for 1 COU). For 5 of 10 COUs, central tendency cancer risk levels are also above 1 in 10,000. For these, respirators are necessary to get the central tendency cancer risks risk levels below 1 in 10,000 (APF=25 for 1 COU; APF=10 for 4 COUs). • For Dermal cancers, For 9 of 11 COUs, dermal cancer risk levels for workers are above 1 in 100,000 – even with PF=20 glove use. For 9 of 11 COUs, dermal cancer risk levels for workers are above 1 in 10,000 – even with PF=5 glove use. For 8 of these, PF=10 gloves still leave risk above 1 in 10,000, and For 6 of these, even PF=20 gloves are not sufficient to get risk below 1 in 10,000. • Studies with statistically significant data, in regard to human health, were dismissed, which also contradicts EPA cancer guidelines	benchmarks as appropriate. See section 5.1.1.2 of the risk evaluation for additional information. For the purposes of determining whether or not an occupational condition of use presents unreasonable risks, EPA incorporates assumptions regarding PPE use based on information and judgement underlying the exposure scenarios. These assumptions are described in the unreasonable risk determination for each condition of use, in section 5.2. Additionally, in consideration of the uncertainties and variabilities in PPE usage, EPA uses the high-end exposure value when making its unreasonable risk determination in order to address those uncertainties. EPA has also outlined its PPE assumptions in section 5.1. Further, in the final risk evaluation for 1,4-dioxane, EPA has determined that most conditions of use pose an unreasonable risk to workers even with the expected PPE.
SACC	**Risk Determination- Clarity** **SACC Recommendation:** Provide more clarity where	The format of the unreasonable risk determination section has been revised, which should address the comments in bullets 1, 2, and 4.

	requested: • Under Risk Considerations, EPA acknowledges that some models and/or assumptions could lead to overestimation of risk (conservative assumptions) and then the text proceeds to give examples of where these uncertainties might exist. However, the text proceeds to read "For this pathway, EPA expects that the risks are not underestimated." Shouldn't this read: "As a result, EPA expects that the risks are not underestimated for this pathway." given this seems a likely conclusion if models and assumptions increase the likelihood of overestimation? • In Section 6, related to the risk characterization assumptions, the text of the table (first on page 158 and then repeated) indicates that whole body inhalation studies overestimate the risk for portal of entry effects because of uncertainty with respect to the actual doses received. The justification for why an overexposure would be expected from consideration of only whole-body inhalation exposures is not clear. The risk evaluation should discuss more the pathways (indirect via blood concentration or direct via direct deposition via dust inhalation and/or preening) expected for nasal tissue exposures and whole-body inhalation study data would lead to overestimation of risk. • On page 173, for disposal, workers are inappropriately included in both assessment statements. There is either an unreasonable risk of injury or not, it can't be both: "Presents an	For bullet 3, EPA thanks the SACC and has corrected the error. Workers should not appear in both places.

	unreasonable risk of injury to health (workers)"; "Does not present an unreasonable risk of injury to health (workers and occupational non-users) or to aquatic vertebrates, aquatic invertebrates, and aquatic plants from exposures to 1,4-Dioxane in surface waters. • In the summary table (Table 6-1) that provides EPA's risk determinations, each "Risk Considerations" section should discuss factors that may over- or under-estimate the risk.	
SACC, 19, 24, 46, 48, 58	**Risk Determination- Unreasonable Risk Conclusions** **SACC Recommendation**: Modify statements of no unreasonable risk with appropriate qualifiers such as "if appropriate personal protective equipment is used" or if "engineering controls are used." **SACC Recommendation:** Provide more clarity where requested: • One member noted that in Table 6-1 there are instances where the MOE is less than 30 with PPE, but no unreasonable risk is noted and suggested this is an error. This points to the difficulty interpreting these tables as other Committee members noted the determination of unreasonable risk came from a different table. **Public Comments:** • EPA finds no unreasonable risk for some conditions of use despite having estimated MOEs	In response to the comments received, the format of the unreasonable risk determination section has been revised and there is increased clarification regarding when assumptions were made regarding use of PPE. The revised format of the unreasonable risk determination section also reduces the challenges identified with table interpretations comment. The format of the unreasonable risk determination section has been revised, which should address this comment. With respect to the risk determinations discussed by the public commenters, many of the risk estimates have been revised for the final risk evaluation and the unreasonable risk determinations have changed for some conditions of use. In the final risk evaluation, all but three of the conditions of use

	only slightly above the benchmark MOE. o Table 5-5, rightmost column for Film Cement: calculated MOE of 31 vs benchmark MOE of 30 is deemed not to represent unreasonable risk. o Table 5-4, rightmost column for Industrial Use: calculated MOE of 338 vs benchmark MOE of 300 is deemed not to represent unreasonable risk. • EPA has not explained how the MOEs being in "proximity" to the benchmark negates the finding of unreasonable risk. While EPA emphasizes that some uncertainties might overestimate the risk presented by these conditions of use, EPA fails to account for how these or other uncertainties might underestimate the risk. • EPA finds no unreasonable risk even when the high-end risk exceeds relevant benchmarks, an approach that is not adequately protective. • EPA calculates central tendency and high-end exposure scenarios for all occupational uses. • Where the high-end scenario does not result in findings of unreasonable risk (assuming the use of PPE), EPA relies on that scenario for its risk determinations. • In at least two instances, however, EPA discounts high-end scenarios where the calculating margin of exposure fell outside EPA's acceptable range and relied on central tendency assumptions in order to avoid finding unreasonable risk. EPA offers no rationale for this approach. • The central tendency scenario is not protective of	present unreasonable risks to workers, ONUs, or both, including Film Cement and Industrial Use. For the purposes of determining whether or not a condition of use presents unreasonable risks, EPA incorporates assumptions regarding PPE use based on information and judgement underlying the exposure scenarios. These assumptions are described in the unreasonable risk determination for each condition of use, in section 5.2. Additionally, in consideration of the uncertainties and variabilities in PPE usage, EPA uses the high-end exposure value when making its unreasonable risk determination in order to address those uncertainties. EPA has also outlined its PPE assumptions in section 5.1. While EPA believes that discussions of the rationale for the determination of unreasonable risk is outside the scope of the SACC, EPA is committed to providing the public with sufficient information on the basis for that determination. TSCA requires EPA to determine whether chemicals in the marketplace present unreasonable risks to health or the environment. While the law does not specifically define this term, during the risk evaluation process EPA weighs a variety of factors including the health effects of the chemical on humans or the environment, who are exposed (including any sensitive subpopulations), the severity of the hazard, and uncertainties. This approach is outlined in EPA's 2017 *Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act* rule (risk evaluation rule) preamble on how risk evaluations will be conducted. [82 FR 33726, at 33735 (July 20, 2017)] EPA has provided more information on uncertainties in Section 4.3.

	workers. EPA assumes a 31-year career (nine fewer than the OSHA default level). In its risk evaluation, EPA must also evaluate and account for the risks posed by intermittent peak exposures. • In this risk evaluation, EPA is more likely to determine unreasonable risk exists for workers where risks greater than the acceptable benchmarks are identified for both central tendency and high-end exposures under the conditions of use. However, worker exposure to contaminants in drinking water or other "regulated pathways" under central tendency or high-end conditions is not evaluated, so worker exposures are being underestimated under both scenarios. • The SACC should evaluate whether EPA has sufficiently established the scientific basis upon which to determine that EPA's risk determinations are supported by the risk characterization. If the SACC determines that EPA has not established that scientific basis, the SACC should provide suggestions as to how EPA can improve those components of the risk evaluation. • EPA's failure to address uncertainty in its quantitative risk characterizations and determinations means that it cannot conclude that 1,4-dioxane does not present unreasonable risks under its conditions of use. • EPA states that the degree of confidence or uncertainty in the data it has will be a factor in making its risk determinations (pp. 152, 154), but never explains how this will factor in.	

7. Editorial Comments

Editorial Comments		

22, 24, 58	• The draft risk evaluation is missing citations, sources, and tables, and cites sources that are not publicly available, contain no HERO entries, lack hyperlinks, and/or cannot be located through internet searches. These include:
	  • Bronaugh (1982), which EPA cites as the basis for its skin absorption estimates, is a chapter in a book that cannot be located.
	  • USEPA (2018a), which EPA used to estimate exposures to 1,4-dioxane in spray foam applications in the absence of monitoring data (p. 68).
	  • McConnell (2013), a technical report which EPA uses to describe cytotoxicity as a potential MOA of liver toxicity and cancer.
	  • BASF (2016) and BASF (2018). The former includes no link in HERO. The latter includes a link, which is routed to an "error" in regulations.gov.
	  • JBRC (1998), a 2-year animal study conducted in Japan.
	  • Dennerlein, K. *et al.,* Studies on percutaneous penetration of chemicals – Impact of storage conditions for excised human skin, Toxicology in Vitro, Volume 27, Issue 2, 2013, pp. 708-713.
	  • Communications with the racing authorities banning the use of 1,4-dioxane as fuel or fuel additive do not appear to be publicly available for consideration by the public.
	• A table explaining the calculations for section 4.2.6.2.5: Chronic Non-Cancer POD for Dermal Exposures extrapolated from Chronic Inhalation Studies (p. 117) should be included to ensure transparency.
	• Tables presenting dermal data need revision for accuracy and clarification:
	  • Table 5-9:
		• EPA included missing citation sources and tables, and corrected errors in the final risk evaluation as noted below:
		• The Bronaugh (1982) book-chapter is available at several libraries in the Washington DC area, including the Library of Congress.
		• EPA has added a link to the USEPA (2018a) HERO entry (HERO ID: 5080424) to provide public access to the referenced Generic Scenario for the Application of Spray Polyurethane Foam Insulation.
		• McConnell (2013) and JBRC (1998) are unpublished reports that are not publicly available. EPA has therefore posted them to the docket to ensure public access.
		• The Dennerlein *et al.*, study is a published study that is publicly available online. EPA cannot post this copyrighted material.
		• (Part 1): BASF (2016), with HERO ID: 5079874, has been fixed in HERO and now links to the correct document.

	i. Columns showing the results for central tendency scenarios need to be added. ii. The values in the PF=5 column that are <3400 need to be boldfaced. • Tables 5-10 and 5-11 i. Columns showing the results for central tendency as well as high-end scenarios need to be added. • EPA's calculated acute COC is inconsistently reported. In the text, it is listed as 59,800 ppb (p. 35), while in Appendix C it is listed as 20,000 ppb (p. 70). • Table 6-1 (starting on page 157) requires more detailed information and editing. • Other than the "risk estimate" statements, (which include the types of PPE used and the Tables in the document that support these), there are no specific citations to the pages or tables in the risk evaluation that support EPA's conclusions about "unreasonable risk driver," "driver benchmarks," the "systematic review" findings or the "risk considerations." These citations should be added. • EPA should consider including a modified table that represents the relevant endpoints and drivers, potentially color-coded with regard to those that exceed benchmarks. • The subheadings in the table for each of the conditions of use are not identical throughout the table. Does this imply differences? • The consideration of PPE in this table is confusing; in the conditions of use section, the reader is left to assume workers are not being protected with PPE, which then contradicts statements made in the "risk considerations" section. • Section 6.2 of the draft requires more attention if it is going to serve as a solid risk communication tool to the public. For example, Section 6.2 summarizes the risk determination in 1.5 pages but does not include a sub-header for "workers," even though workers are a primary focus of the draft risk determination.	• (Part 2): (BASF, 2018a), with HERO ID: 5079871 provides a URL to a file in the 1,4-dioxane docket, but the link had a typo. EPA corrected the link in HERO and resolves this comment. • EPA updated dermal tables 5-9, 5-10, and 5-11 to include central tendency and resolved various boldfaced formatting errors for PF=5. Note, EPA reads the comment that "values in the PF=5 column that are <3400 need to be boldfaced" as a typo that should read <300, the Benchmark MOE. • EPA inadvertently calculated the short term (acute) concentrations of concerns (COCs) for fish rather than for the algal endpoint. EPA has since updated the COC for the correct endpoint. In addition, EPA has updated the calculations used for determining the assessment factor for the acute endpoint. • EPA appreciates the feedback that the unreasonable risk determination section and table should include additional detail and have greater consistency across chemicals. EPA has revised the formatting and clarity of the unreasonable risk determination section. In addition, upon issuance of the risk evaluation (a scientific and policy document), EPA intends to provide risk

	• EPA's HERO entries for references in the draft risk evaluation that cite the REACH dossier for 1,4-dioxane erroneously state that the author of the study summaries and underlying studies is ECHA itself, when in fact it is the registrant. Examples of such erroneous entries include:
	  • https://hero.epa.gov/hero/index.cfm/reference/details/reference_id/3809089 (linked to on p. 211 of the draft risk evaluation as "ECHA, 1996")
	  • https://hero.epa.gov/hero/index.cfm/reference/details/reference_id/3809095 (linked to on p. 223 of the draft risk evaluation as "ECHA, 2014").
	• There is a discrepancy in the "disposal" condition of use (p. 173), which both declares: "Presents an unreasonable risk of injury to health (workers)" – and in the next paragraph reads "Does not present an unreasonable risk of injury to health (workers and occupational non-users).
		communication materials applicable to a broad range of stakeholders.
		• This is an error. The final unreasonable risk determination correctly reflects that the disposal condition of use presents an unreasonable risk to workers and ONUs.

8. Supplemental Analysis

Public Comments		
#	**Summary of Comments for Specific Issues Related to the Supplemental Analysis**	**EPA/OPPT Response**
Peer Review & Public Comment Extension Requests		
77, 82, 83, 85, 88, 89	• EPA has not provided sufficient time for the public to review and comment on the Supplemental Analysis, which contains new and highly technical analyses of risks that were not addressed in EPA's prior risk evaluation for 1,4-dioxane. EPA provided only 20 days to comment on its new evaluation of 1,4-dioxane (one of which was Thanksgiving), despite EPA regulations mandating a 60-day comment period on TSCA risk evaluations. • EPA granted a 30-day extension of the public comment period for the Pigment Violet 29 supplemental draft, 10 days longer than the period it	• As EPA explained in the Draft Supplemental Analysis to the Draft Risk Evaluation, the draft supplemental analysis was not peer reviewed for the sake of expediency to finalize the first ten risk evaluations.TSCA section 6(b)(4)(H) requires a 30-day notice and comment period on the draft risk

	has now afforded for 1,4-dioxane. PV-29 has narrower uses and impacts a far smaller population than 1,4-dioxane. • This truncated process is without precedent. It has curtailed the public's ability to provide informed feedback on the supplement.	evaluation prior to publication of the final risk evaluation. Additionally, 40 CFR 702.49(a) provides for a 60-day public comment period. EPA complied with these statutory and regulatory requirements by providing a 60-day comment period from July 1, 2019 to August 30, 2019 on the draft risk evaluation.
77, 82, 83, 85, 88, 89	• EPA's decision to dispense with peer review for the supplemental evaluation is in contrast to PV-29, irresponsible, and compromises the credibility of the Agency. Now that EPA has broadened the scope of the evaluation to include exposures affecting a broad segment of the US population, further peer review is essential to assure protection of public health. • The supplement provides entirely new analyses related to two topics that EPA excluded from its prior evaluation: (1) the risks associated with the presence of 1,4-dioxane in consumer products and (2) the risks associated with exposure to 1,4-dioxane from swimming and fishing in contaminated water. The "Supplemental Analysis" is the first and only evaluation of those risks prepared by EPA, and it must be treated as a risk evaluation for the purpose of public comment. • Neither TSCA nor EPA's Risk Evaluation Rule provides an exception from peer review of risk evaluations based on "expediency." EPA made clear that issuance of a partial risk evaluation – as it has done in the Supplement – still requires that the document be subject to peer review – which it has not done. It also makes clear that a risk determination cannot be made on a condition of use without peer review. • EPA must integrate its new analysis into an integrated risk evaluation and subject that full document to peer review before finalizing the risk evaluation and risk determinations. In addition, the public must be afforded the opportunity to review and comment on that integrated document. in-depth review of the supplement by the public and independent scientists is essential to assure that the final evaluation is credible and compliant with TSCA.	• • TSCA section 6(b)(4)(H) requires a 30-day notice and comment period on the draft risk evaluation prior to publication of the final risk evaluation. Additionally, 40 CFR 702.49(a) provides for a 60-day public comment period. EPA complied with these statutory and regulatory requirements by providing a 60-day comment period from July 1, 2019 to August 30, 2019 on the draft risk evaluation. • EPA is working diligently to publish the final risk evaluation on 1,4-dioxane as soon as possible. Given the relatively small number of conditions of use addressed by the supplemental analysis, EPA believes that 20 days, while expedited, was sufficient to allow for public comment. This will enable EPA to quickly consider the public

		comments, revise the document as appropriate, and publish the final risk evaluation without further delay.
Systematic Review/Literature Search and Screening Comments		
83	• Because EPA is ignoring contaminated drinking water and exposure via ingestion, EPA's literature search excludes key sources of exposure information relevant and necessary to comprehensively characterize actual risks to relevant receptors from the presence of 1,4-dioxane as a byproduct in consumer and commercial products. For example, Figure 1-3 indicates that 13,296 of 21,373 references were excluded as non-consumer references. While some of these may not be relevant to fully assessing risk from 1,4-dioxane as a byproduct, others may well be relevant to characterizing aspects of risk EPA has ignored. • EPA's supplemental literature selection process commenced with a search for references specific to assessing 1,4-dioxane exposure to consumers, yielding 8,077 filtered references. EPA then applied a machine learning model to rank "how similar the filtered references were to a pre-determined set of consumer references (positive seeds), and how unsimilar [sic] the filtered references were to a pre-determined set of non-consumer references (negative seeds)." (p.13) EPA does not appear to have provided the list of the positive and negative seeds in the risk evaluation, the Supplement, or the supporting documents; it needs to do so. Additionally, EPA should explain the basis for its choice of relevancy cut-offs (0.1 for references with just titles and 0.4 for references with abstracts) and the decision to use different relevancy cut-offs dependent on the presence or absence of an abstract; the latter seems especially arbitrary and potentially biased against sources of information that are not structured in the conventional peer-reviewed literature format. EPA's reliance on the machine learning model is clearly consequential as it reduced the number of supplemental information sources from 8,077 to 239. Additional explanation of key filtering/cut-off decisions by EPA is necessary if there is to be any	• The systematic review effort was tailored to the scope of the risk evaluation. Therefore, during screening steps, literature that is not relevant to the evaluated pathways were not included for further evaluation, extraction, and integration. • EPA has updated its supplemental file [*Consumer References, Data Screening*] to include a list of the positive and negative seeds utilized in the referenced machine learning process. The relevancy cut-off language has been updates to reflect the process accurately. EPA utilized a 0.1 relevancy cut-off for all sources. • The supplemental search was initiated on a chemical name basis. Therefore, the pool of literature was very large relative to sources that contained useful information on consumer exposures, consumer products, emission rates from consumer products, etc. The process is described and shown in Section 1.5.1 of the final risk evaluation.

	confidence in the decisions that excluded so many sources from full consideration. • Of the 545 references screened (239 supplemental references plus 272 initial references from the risk evaluation), only 37 were subject to formal data evaluation, in addition to 17 sources that were qualitatively evaluated. EPA does not but needs to provide some explanation for why the vast majority of studies it screened were not subject to evaluation.	
General Population Exposure Comments		
78	• EPA should also evaluate the risks of consuming contaminated fish because the supplemental analysis documents a bioconcentration factor (BCF) of 0.9, resulting in tissue levels nearly equivalent to the water concentration. Even though 1,4-dioxane is not bioaccumulative, fish tissue concentrations may still pose a risk to consumers.	• EPA has determined that fish consumption does not present an unreasonable risk to the general population. As described in Section 2.4.2 of the risk evaluation, 1,4-dioxane's bioaccumulation factor (BAF) indicates that concentrations in fish tissues are expected to be lower than aqueous concentrations and supports the expectation that fish ingestion is not a primary pathway of human exposure for 1,4-dioxane. Given its hydrophilic properties and short half-life, 1,4-dioxane is not expected to accumulate in tissue.
78, 89	• EPA states that risks of surface water contaminated with 1,4-dioxane on swimmers were evaluated owing to the lack of human health water quality criteria and thus regulation under the Clean Water Act. EPA inaccurately indicates that human health criteria are designed to protect swimmers and fish consumers; they are designed to protect drinking water consumers and fish consumers. EPA publishes separate recreational water quality criteria to protect swimmers. The human health water quality criteria methodology is based on the source water protection principle that the polluter should pay for pollution control rather than the downstream drinking water customer. EPA should have	• TSCA Section 6(b)(4)(D) requires EPA, in developing the scope of a risk evaluation, to identify the hazards, exposures, conditions of use, and potentially exposed or susceptible subpopulations the Agency "expects to consider" in a risk evaluation. This language suggests that EPA is not required to consider all conditions of use,

	evaluated the impact of 1,4-dioxane wastewater discharges on the quality of source water for public water supply systems and been prepared to find an unreasonable risk if predicted concentrations exceeded EPA's recommended lifetime drinking water health advisory. EPA's evaluation of the impact of these discharges on swimming and fish consumption are appropriate analyses but do not substitute for analysis of the much higher risk pathway of drinking water. • Focusing on occasional recreational exposure, the analysis of surface water fails to satisfy the source water protection goals of water quality criteria for human health under CWA.	hazards, or exposure pathways in risk evaluations. EPA has therefore tailored the scope of the risk evaluations for 1,4-dioxane using authorities in TSCA sections 6(b) and 9(b) and focused this fit-for-purpose evaluation on general population exposures to ambient water via recreational activities such as swimming.
78	• It is well known that 1,4-dioxane is an impurity in a broad range of personal care and cleaning products used by millions of consumers. These "down the drain" products contribute 1,4-dioxane to wastewater and surface water and, together with other sources of this chemical, account for the widespread presence of 1,4-dioxane in drinking water throughout the country. Given that 1,4-dioxane is a likely human carcinogen, is highly soluble in water, and does not readily biodegrade in the environment, it is critical that the TSCA risk evaluation of this chemical focus on the impact of wastewater discharges on drinking water in the U.S. Regulation of pollutant discharges under the Clean Water Act is based on the need to protect source water for drinking water utilities so that the costs of pollution are borne by the polluter, not by the utility. It is very difficult to remove 1,4-dioxane from source water, and few utilities in the country employ the expensive, energy-intensive advanced oxidation or other processes needed to remove or otherwise treat this chemical. It is imperative that the parties responsible for 1,4-dioxane releases to the environment posing unacceptable risks to public health be responsible for eliminating those risks, and it is imperative that the TSCA risk evaluation ensures this happens.	• In its evaluation of the ambient water, general population pathway, EPA focused its analysis using releases from the scoped industrial and/or commercial conditions of use shown in Table 2-2 of the final risk evaluation. These were based on reasonably available 1,40-dioxane release data. It also incorporated monitoring data that were submitted during the public comment period and SACC review of the draft risk evaluation. • Section 1.4.2 of the risk evaluation describes exposure pathways and risks that fall under the jurisdiction of other EPA-administered statutes. As described in Section 1.4.2 of the risk evaluation, EPA believes it is both reasonable and prudent to tailor TSCA risk evaluations when other EPA offices have expertise and experience to address specific
82, 85	• In the Supplemental Analysis, US EPA expressly recognizes that "1,4-Dioxane exposures to the general population may occur from the conditions of use due to releases to air, water or land." Nonetheless, it admits that it "did not evaluate unreasonable risk to the general	

	population from ambient air, drinking water, and sediment pathways for any conditions of use in this risk evaluation, and the draft unreasonable risk determinations do not account for exposures to the general population from ambient air, drinking water, and sediment pathways." • EPA wrongfully asserts that it need not evaluate general population and other exposures because such exposures might be covered under other environmental statutes administered by EPA. • The supplemental Analysis does not identify any authority that would allow US EPA to disregard its TSCA obligations merely because they may overlap with obligations under other environmental laws. Reading TSCA in this light would have the effect of rewriting the requirement that US EPA conduct risk evaluations "without consideration of costs or other nonrisk factors."	environmental media, rather than attempt to evaluate and regulate potential exposures and risks from those media under TSCA. EPA has therefore tailored the scope of the risk evaluation for 1,4-dioxane using authorities in TSCA Sections 6(b) and 9(b)(1).
83	• EPA ignored much of its own data obtained through the Toxics Release Inventory (TRI) in its ambient water exposure analysis. EPA's Enforcement and Compliance History Online (ECHO) Water Pollution Search database provides significant data ignored in EPA's analysis. EPA arbitrarily chose to limit its analysis to facilities fitting select Occupational Exposure Scenarios it developed for the risk evaluation (EPA Table 2-4), leading it to omit many emitting facilities as well as contaminated watersheds and resulting in an underestimation of both the extent and magnitude of 1,4-dioxane discharged to ambient water. The ECHO database demonstrates that in 2018, numerous U.S. watersheds received discharges of 1,4-dioxane that EPA did not include in its analysis. These include three watersheds receiving more 1,4-dioxane than those that EPA used for its analysis of ambient water exposures. These watersheds and their associated facilities are: Spring Creek-Mud Creek in Alabama (Indorama Ventures), Kendrick Creek-South Fork Holston River in Tennessee (Eastman Chemical Co Tennessee operations), and Back Creek in North Carolina (Starpet Inc.). APG Polytech LLC also had a greater discharge, although its associated watershed is not reported in the public database. The watershed receiving the greatest discharges in 2018, Spring Creed-Mud Creek in	• The modeled releases are based on the evaluated occupational exposure scenarios (*i.e.,* industrial and/or commercial conditions of use, see Table 2-2 in the final risk evaluation) and are not intended to reflect or capture contributions from other industrial, commercial, or consumer sources. • EPA thanks the commenter for flagging this potential transcription error. However, EPA utilized the entirety of the mass discharged to publicly owned treatment works (POTWs), which sums to 37,304 lbs/yr, for the purposes of assessing releases for the referenced site (Suez WTS Solutions USA Inc.).

	Alabama, had indirect discharges more than six times higher than the watershed EPA relied on as its upper bound (Ninemile Creek polluted by Suez WTS Solutions USA Inc.) based on the 2018 data. EPA also ignored 1,4-dioxane discharges into three other watersheds: Back River-Cooper River in South Carolina (Dak Americas LLC Cooper River Plant), Singleton Swamp in South Carolina (Nan Ya Plastics Corp America), and Brushy Creek-Enoree River in South Carolina (Mitsubishi Polyester Film Inc.). • There appears to be a major transcription error in Table 2-4 for the releases into Ninemile Creek from Suez WTS Solutions USA Inc. EPA's error led it to use a higher discharge than actually reported in the 2018 TRI (see footnote 44). However, this should not reduce the upper bound of EPA's predicted surface water concentrations; rather, EPA should use the significantly higher level discharged by Indorama Ventures into Spring Creek-Mud Creek, Alabama.	
83	• EPA has not provided sufficient analysis or explanation to support its selection of concentrations to represent 1,4-dioxane in ambient water. EPA included monitoring data from Minnesota (MN) and North Carolina (NC) state agencies because the data were submitted during the 2019 comment period. Although data from NC, specifically Haw River and Cape Fear River, and MN were the only data submitted during the comment period, they are not the only states with available data on 1,4-dioxane concentrations in surface water. While EPA appears to have used the concentrations at the upper end of the range of the MN and NC monitoring data, there is a lack of transparency regarding why only these data were used. The agency stated (on p. 28) that its predicted values (modeled using E-FAST) for surface water concentrations taken as a whole cover a range that encompasses the ranges reported by NC and MN; however, EPA did not explain why it excluded other available data. • EPA inappropriately excluded data points from its STORET database. Our review of the STORET and NWIS data between the years 2009-	• In its evaluation of the ambient water, general population pathway, EPA focused its analysis using releases from the scoped industrial and/or commercial conditions of use shown in Table 2-2 of the final risk evaluation. These were based on reasonably available 1,40-dioxane release data. It also incorporated monitoring data that were submitted during the public comment period and SACC review of the draft risk evaluation. • EPA thanks the commenter for pointing out this consideration of the STORET data cited in the draft risk evaluation. While EPA did consider the referenced range from STORET

	2019 revealed that there were 59 samples with method detection limits (MDLs) greater than 100 ug/L. Of these, 34 were from surface water samples, some of which had MDLs as high as 28,000 ug/L–nearly six times higher than the upper end of the range of values in the Supplement that EPA derived using E-FAST (p. 28). EPA discarded all of these values –even though the "true" concentration of these surface water samples may be well above its E-FAST derived values EPA uses to estimate risk. In such cases, researchers would typically either use the MDL or a value that is one-half of the MDL. EPA simply eliminated the data from consideration without basis. • 1,4-Dioxane was measured in various water systems from 2013-2015 as part of the Third Unregulated Contaminant Monitoring Rule (UCMR3). The UCMR3 provide relevant 1,4-dioxane water concentration data from multiple states (US EPA, 2016).	for years 2007 through 2017 in its draft risk evaluation, the RQs presented in Table 5-2 are dependent on results of the screening-level modeling analysis. Additionally, though some of the sampling MDLs were higher than the chronic COC, EPA did not use unreported/unknown levels below such MDLs as the basis for an RQ or unreasonable risk determination. In response, EPA has augmented its discussion of uncertainty in Section 4.3.2 with a discussion of this point. • Data from UCMR3, which provides nationally representative data on the occurrence of contaminants in drinking water, were not utilized in the aquatic exposure assessment due to a focus on ambient surface water levels since general population drinking water exposures were not included in the scope of the risk evaluation (see Section 1.4.2).
90	• The draft supplemental analysis includes an evaluation of general population exposures to 1,4-dioxane from recreational activities (*i.e.,* swimming) in ambient surface water, using modeled surface water concentrations based on E-FAST modeling and measured surface water concentrations. The modeled concentrations are based on incidental exposure to 1,4-dioxane in surface waters (swimming) downstream of industrial discharges (Table 2-6). The measured concentrations are from three reports: Sun et al. (2016), North Carolina DEQ, and Minnesota DEQ. Based on the concentrations observed, Sun et al. (2016) suggests	• The modeled releases are based on occupational exposure scenarios (*i.e.,* industrial and/or commercial conditions of use) and are not intended to reflect contributions from the use and/or disposal of consumer products. The modeling captures reported releases from industrial facilities or WWTPs that directly

	that one or more industrial sources overshadowed the contribution from 1,4-dioxane that can be expected from the use of consumer products. However, EPA neglected to cite and use Simonich et al. (2013), which calculates surface-water concentrations based on measured concentration from municipal WWTP.	release or transfer 1,4-dioxane. Similarly, the monitoring data that were submitted during the draft's public comment period and SACC review were utilized but relative contributions from specific industrial and/or consumer sources of 1,4-dioxane are unknown.
83	• The uncertainties (in general population and consumer exposure estimates) arise in large measure from EPA's failure to have used its TSCA information authorities to require the development and submission of the information EPA needed to inform its exposure assessments. This failure has been raised repeatedly to EPA by stakeholders over the past several years.	• EPA had sufficient information to complete the 1,4-dioxane risk evaluation using a weight of scientific evidence approach. EPA selected the first 10 chemicals for risk evaluation based in part on its assessment that these chemicals could be assessed without the need for regulatory information collection or development. When preparing this risk evaluation, EPA obtained and considered reasonably available information, defined as information that EPA possesses, or can reasonably obtain and synthesize for use in risk evaluations, considering the deadlines for completing the evaluation.
Byproducts Comments		
90	• ACC recognizes that this draft supplemental analysis was developed in response to public and peer review comments on the draft risk evaluation for 1,4-dioxane. However, including trace levels of byproducts and impurities in TSCA risk evaluations should not be routine, given that byproducts and impurities are by definition not intentionally added or present for commercial purposes, and are often	• TSCA defines "condition of use" under section 3(4) as "the circumstances, as determined by the Administrator, under which a chemical substance is intended, known, or reasonably foreseen to be

	not present at significant levels. The risk evaluation process must continue to allow EPA to focus its resources on the conditions of use that present the greatest potential for risk.	manufactured, processed, distributed in commerce, used, or disposed of." Further, EPA explained in the Risk Evaluation Rule that: "In exercising its discretion under section 6(b)(4)(D), EPA believes it is important for the Agency to have the discretion to make reasonable, technically sound scoping decisions in light of the overall objective of determining whether chemical substances in commerce present an unreasonable risk. For example, EPA intends to exercise discretion in addressing circumstances where the chemical substance subject to scoping is unintentionally present as an impurity in another chemical substance that is not the subject of the pertinent scoping. In some instances, it may be most appropriate from a technical and policy perspective to evaluate the potential risks arising from a chemical impurity within the scope of the risk evaluations for the impurity itself. In other cases, it may be more appropriate to evaluate such risks within the scope of the risk evaluation for the separate chemical substances that bear the impurity. (EPA has previously taken an analogous approach, in requiring chemical testing of certain chemical

		substances under 40 CFR part 766, based on the potential for the chemical substance to be manufactured in such a manner as to be contaminated with dioxins). In still other cases, EPA may choose not to include a particular impurity within the Scope of any risk evaluation, where EPA has a basis to foresee that the risk from the presence of the impurity would be *'de minimis'* or otherwise insignificant." 82 FR at 33730.
Consumer Exposure Comments		
89, 83, 86	• Findings reported by IRIS and ATSDR demonstrate the prevalence of background concentrations of 1,4-dioxane in the indoor environment – in some cases at levels that exceed EPA's cancer risk benchmark. As with other volatile substances like TCE and PCE, 1,4-dioxane's widespread presence in indoor air is evidence of chronic exposure by consumers and adds to the dermal and inhalation exposures resulting from consumer product use. • EPA fails to account for background exposure from personal care and cosmetic products despite SACC reporting that "[t]he decision not to further analyze background levels of 1,4-Dioxane in any matrix . . . cannot be supported by any risk assessment principle. Any current use scenarios increase exposures over those currently being experienced." • If EPA ignores the contribution of this background exposure and bases its risk determinations solely on exposure to TSCA-regulated products, it will underestimate the true cancer risk to consumers. In quantifying background exposure, EPA must factor in consumption levels for different subpopulations, particularly adult women, who are most highly exposed to 1,4-dioxane from personal care products and cosmetics. EPA must also factor in increased exposures by low wage workers and	• The approach of considering consumer exposures on a product-specific basis without the consideration of background or multiple sources of exposure is consistent with the approach taken and peer reviewed for the other solvent chemicals recently evaluated and finalized. This aspect of the evaluation is described in the uncertainties Section 4.3.2. • Regarding body care and cosmetic products, they are excluded from the definition of "chemical substance" per TSCA section 3(2) and are outside the scope of this risk evaluation. • As described in Section 1.4.2 of the risk evaluation, EPA believes it is

	communities of color, who are most highly exposed through the use of cleaning other consumer products and the disposal of wastes containing 1,4-dioxane in or near their neighborhoods. • EPA offers no rationale for its decision to ignore background and multi-source exposures. • Potentially exposed or susceptible subpopulations (PESS) have not been properly evaluated – disadvantaged communities can experience higher levels of dioxane in drinking water, higher incidences of legacy contamination, and higher concentrations in the products they use. • EPA explicitly calls out that it is ignoring relevant exposures "particularly for populations living near a facility emitting 1,4-dioxane." Yet TSCA requires EPA to evaluate a chemical across all of its conditions of use. • EPA must identify groups near sources of release of 1,4-dioxane as a potentially exposed subpopulation, given exposures to 1,4-dioxane at levels higher than the general population.	both reasonable and prudent to tailor TSCA risk evaluations when other EPA offices have expertise and experience to address specific environmental media, rather than attempt to evaluate and regulate potential exposures and risks from those media under TSCA. EPA has therefore tailored the scope of the risk evaluation for 1,4-dioxane using authorities in TSCA Sections 6(b) and 9(b)(1). • EPA did not consider aggregate or background exposure that workers, ONUs, consumers, or bystanders might be exposed to in addition to exposures from the conditions of use in the scope of the risk evaluation because there is insufficient information reasonably available as to the likelihood of this scenario or the relative distribution of exposures from each pathway. This may result in an underestimation of risk, and EPA acknowledges that risk is likely to be elevated for individuals who experience 1,4-dioxane exposure in multiple contexts. Additional discussion of this issue has been added to Sections 4.3.2 and 4.5. • EPA has added a footnote to the Executive Summary to clarify that EPA did not identify any legacy uses

		of 1,4-dioxane. EPA did not evaluate "legacy disposal" (*i.e.*, disposals that have already occurred) in the risk evaluation, because legacy disposal is not a "condition of use" under Safer Chemicals, 943 F.3d 397.
89, 83, 84, 90	• This document contains limited information on the unintentional presence of 1,4 dioxane in consumer products. Reported levels of 1,4-dioxane in consumer products are higher than the supplement assumes. The concentrations incorporated in the supplement span a broad range of values and are derived from an extremely limited number of samples, creating a high degree of uncertainty. • EPA provides little information with which to evaluate the few reported studies on which it relies and does not explain why it failed to include studies reporting higher levels that were cited in its 2015 problem formulation and the 2012 ATSDR ToxProfile. EPA did not consider all publicly available concentration data. The maximum levels reported for household detergents (160 ppm) are well above the maximum levels the supplement provides for dishwashing detergent (9.7 ppm) and laundry detergent (14 ppm). The higher levels would result in risks over 10 X greater than those calculated by EPA. Recent testing for New York DEC also reports higher levels for laundry detergent (21 ppm) and cleaning products (23.1 ppm), again resulting in higher estimates of exposure and risk. • The sources of the 1,4-dioxane concentrations in consumer products presented by EPA (see Table 2-11) are unclear. The Supplement indicates that the concentrations of 1,4-dioxane in these consumer products came primarily from the 2015 TSCA Workplan Assessment. But the 2015 document does not clearly present the sources EPA used to derive the concentrations, nor has EPA presented concentration data it derived from any additional sources it identified through its systematic review. While the Consumer References Data Screening file includes a list of articles that EPA presumably used to extract 1,4-dioxane	• Uncertainties associated with identifying concentration data for 1,4-dioxane present as a byproduct are acknowledged and described in Section 4.3.2. In the acute consumer exposure scenarios, EPA utilized the maximum identified weight fraction in its estimations. • EPA conducted a supplemental literature search per its TSCA systematic review approach in order to identify useful information on consumer exposures, consumer products, emission rates from consumer products, etc. The process is described and shown in Section 1.5.1 of the final risk evaluation. • The conditions of use evaluated were primarily based on those identified in the 2015 TSCA Workplan Assessment; however, sourcing of the product concentration data is shown in the Supplemental File [*Consumer Exposure Assessment Modeling Input Parameters*]. As described in Section 1.5.1 of the final risk evaluation, a supplemental systematic review

	concentrations in consumer products, the file does not present any concentration data. Furthermore, EPA does not describe the process it employed for choosing which concentrations to use in its analysis. • We would like clarification on the range of 1,4-dioxane concentrations in dish soap (0.7 – 204 ppm). The upper end of this range seems to be outside of the range with current data for this product category and it appears to be from a study that is no longer available and is not shown in supplemental file (Data Quality Evaluation for Data Sources on Consumer Exposure). • EPA used central tendency weight fractions for chronic exposure scenarios for high- and moderate-intensity users, rather than the highest measured concentration for the product class. Because of this approach, EPA's exposure and risk estimates would not capture products with the largest levels of 1,4-dioxane and thus would fail to estimate the use scenarios resulting in the highest risks to consumers, ignoring a potentially exposed or susceptible subpopulation (PESS) that EPA is required to consider. • For the supplemental literature search, EPA provides no evidence that it contacted manufacturers to identify household products containing 1,4-dioxane or analyzed products for its presence. EPA should require manufacturers to submit analyses of 1,4-dioxane levels in their products and, if such data are limited, direct them to conduct product testing under section 4 of TSCA. At a minimum EPA should compensate for the inadequate information in its possession by making conservative, high-end assumptions about the size of the relevant product universe and the levels of 1,4-dioxane present in these products.	process was carried out in support of this assessment. • The upper end of the referenced range (204 ppm) for dish soap was obtained from the source referenced in the full comment submission. This report is accessible through HERO at https://web.archive.org/web/20090320014254/http://www.organicconsumers.org/bodycare/DioxaneResults09.pdf • EPA used central tendency inputs, including weight fraction, when estimating lifetime exposures. As noted in Section 4.3.2, The models employed (CEM 2.1 and CEM) typically utilize central tendency inputs for weight fraction, duration, frequency, and mass when estimating lifetime exposures (U.S. EPA, 2019a; U.S. EPA, 2007). • EPA obtained relevant data consistent with the approaches taken and peer reviewed in the other recently finalized solvent risk evaluations. EPA utilized the maximum identified weight fraction in its estimation of acute exposures and considered and utilized a variety of sources including peer-reviewed journal articles, national assessments, public submissions, and NGO reports.

84	• The cleaning products industry is trending towards lower levels of 1,4-dioxane in ethoxylated ingredients and products that contain them. In California, concentrations of 1,4-dioxane in consumer and commercial products must be disclosed if greater than 10 ppm per the requirements of the Cleaning Product Right to Know Act of 2017. As of this writing, we are unaware of any product that discloses levels of 1,4-dioxane above the 10-ppm threshold; therefore, all of our member's products are reasonably assumed to be under 10 ppm, including concentrated products. Separately, New York has passed a law in 2019 banning the presence of 1,4-dioxane in cleaning products above 2 ppm in 2022 and 1 ppm in 2023. Manufacturers and suppliers have already initiated efforts to minimize 1,4-dioxane either by reformulation or via further reduction in raw materials. • ACI and member companies are working to demonstrate the minimum method principles that should be in place to detect 1,4-dioxane in cleaning products at levels appreciably lower than regulatory limits. To date, we have verified the analytical method principles on five cleaning product formulations representing hand dishwashing detergents and laundry detergents. The proposed test formulations (submitted into docket ad Attachment 1) are meant to be representative of the base technology used in many products currently on the consumer and I&I markets, without referencing any one single product or brand. The blend of materials in the test formulations was chosen to be a benchmark and represent typical levels of products on the market. The averaged measured 1,4-dioxane in the products was between 0.94 and 3.6 ppm (submitted to docket as Attachment 2). Anecdotal measurements from a company that undertook a cursory landscape scan of cleaning products found on store shelves found that all tested laundry products had < 10 ppm 1,4-dioxane (~70% being < 7 ppm) and top-selling hand dish products had levels of 1,4-dioxane < 4 ppm. • A recent (November 18, 2020) New York State Department of Environmental Conservation (NYS DEC) webinar on 1,4-dioxane limits for household cleaning, personal care, and cosmetic products presented	• EPA thanks ACI and HCPA for this additional context and information on levels of 1,4-dioxane in consumer products. The weight fractions utilized in the evaluation were higher than those supplied in the attachments submitted; however, no unreasonable risks were identified at the levels modeled. EPA augmented the uncertainties discussion in Section 4.3.2 to acknowledge uncertainty in the weight fractions applied in the modeling of the dish soap and laundry detergent consumer scenarios.

	data on a number of cleaning products with a median detection range from non-detectable to 2.5 ppm.	
84, 88, 86, 89	• EPA chose to only focus on consumer cleaning products without providing any explanation as to why industrial and institutional cleaning products were not included. We recommend that EPA evaluate corresponding industrial and institutional (I&I) and commercial product conditions of use that were considered for consumers. • ACI and HCPA would like further clarification and possible expansion of the "surface cleaner" scenario. The scenario includes inputs for a bathroom surface cleaner but does not address other surface cleaners such as all-purpose cleaners that may be used with some frequency on multiple surfaces. • EPA assumes that the use of surface cleaning products only involves the use of the inside of one hand, an assumption that understates risk to any consumer using a surface cleaning product with both hands.	• The surface cleaner scenario uses a bathroom as the selected room of use as a measure of conservatism for inhalation modeling. The bathroom has a smaller room volume than other options such as the kitchen or utility room. The scenario was not developed to reflect only bathroom cleaners – the weight fractions used reflect the range of identified concentrations for surface cleaners (not just bathroom cleaners). A clarification to this effect was added to Section 2.4.3.2.1. • The hand surface area chosen for the surface cleaning scenario is consistent with the surface area used in the evaluation of other cleaning/wiping consumer scenarios for other solvent chemicals recently evaluated and finalized.
83, 89, 86	• EPA inappropriately dismissed chronic inhalation and dermal exposure to consumer users from spray polyurethane foam, antifreeze, textile dye, and paint and floor lacquer. Products such as antifreeze, paints, and floor lacquer, may be used by "do-it-yourselfers" with more regularity. Textile dye and other arts-and-crafts products are used regularly by home hobbyists and artists. While chronic exposure may not be typical for most consumers, EPA failed to assess DIY users as a "potentially exposed or susceptible subpopulation." Furthermore, EPA has not considered exposures arising from gradual release of 1,4-dioxane following use of such products, for example, from surfaces to which	• The rationale for not estimating chronic, lifetime exposures to the referenced products per their expected intermittent use by household users is consistent with the approach taken and peer reviewed for the other solvent chemicals recently evaluated and finalized. The consumer exposure assessment did not evaluate off-gassing from stored

	they have been applied or during subsequent storage. • Adhesives are also not addressed in the supplement. Products with consumer applications included automotive refinishing coatings, paints, caulks, sealants, and adhesives. Although they fall within the general category of paints and coatings identified by EPA, the supplement does not discuss these specific products. • Users of these products likely overlap with users of four household cleaning products addressed by EPA and thus all products would contribute to chronic exposure by these consumers, resulting in a greater cumulative cancer risk. • EPA should include consumers who use multiple cosmetics and cleaning products as potentially exposed or susceptible subpopulations, given EPA's prior identification of those subpopulations as particularly likely to be exposed.	products as storage of a product cannot be linked to a condition of use evaluated and is not in and of itself identified as a consumer condition of use within the scope of the Risk Evaluation. Additionally, TSCA Section 6(b)(4)(F)(iv) instructs EPA to factor into TSCA risk evaluations "the likely duration, intensity, frequency, and number of exposures under the conditions of use." This suggests that activities for which duration, intensity, frequency, and number of exposures cannot be accurately predicted or calculated based on reasonably available information were not intended to be the focus of TSCA Risk Evaluation. • The conditions of use evaluated were primarily based on those identified in the 2015 TSCA Workplan Assessment; however, sourcing of the product concentration data is shown in the Supplemental File [*Consumer Exposure Assessment Modeling Input Parameters*]. As described in Section 1.5.1 of the final risk evaluation, a supplemental systematic review process was carried out in support of this assessment. • The approach of considering consumer exposures on a product-specific basis without the

		consideration of background or multiple sources of exposure is consistent with the approach taken and peer reviewed for the other solvent chemicals recently evaluated and finalized. This aspect of the evaluation is described in the uncertainties Section 4.3.2. • Regarding body care and cosmetic products, they are excluded from the definition of "chemical substance" per TSCA section 3(2) and are outside the scope of this risk evaluation.
88, 82, 83, 90	• EPA does not evaluate potential exposure risk to children under the age of 11 for acute exposure to 1,4-dioxane in consumer products via dermal pathways, despite the fact that children may come into contact with surfaces, dishes and clothing cleaned using products containing 1,4-dioxane, in addition to having access to the cleaning products themselves. EPA must expand its consumer analyses to include all age groups, including infants and children, to account for risks associated with acute or incidental exposures to household consumer products containing 1,4-dioxane. • In finalizing the Draft Risk Evaluation, US EPA should evaluate products marketed for infants and children to the extent those products fall under the jurisdiction of TSCA. It should also evaluate exposure scenarios specific to new parents and young children. • Children may be disproportionately exposed to 1,4-dioxane by virtue of relevant behavioral differences. Relative to adults, children particularly younger children, engage in significant hand-to-mouth activity and spend more time on the floor. As a result, children may be disproportionately exposed to residual 1,4-dioxane present, for example, from the use of surface and floor cleaners.	• Considering 1,4-dioxane's fate properties and concentrations of 1,4-dioxane present in such products (*e.g.*, laundry detergent and dishwasher detergent), EPA expects that any 1,4-dioxane present during washing will stay with the water and rinse down the drain rather than appreciably adhering to surfaces such as clothing or dishes in any appreciable amount. The focus on direct consumer exposures from the use of products is consistent with the approach taken and peer reviewed for the other solvent chemicals recently evaluated and finalized. Furthermore, the levels of 1,4-dioxane in the products is relatively low (up to 0.0009%).

	• EPA needs to identify children as a potentially exposed or susceptible subpopulation. • Evaluation of exposure to the 11 to 15 year-old receptor group from high-intensity use of antifreeze seems inappropriate.	• EPA's review of 1,4-dioxane concentration sources indicated that the products falling under the jurisdiction of TSCA are not those marketed for infants and children. Such products (*e.g.*, baby shampoos, lotions) are not under TSCA's purview and were not evaluated because the TSCA section 3(2) definition of chemical substance excludes cosmetics. • The estimation of children's dermal exposures during the consumer use of products is consistent with the approach taken and peer reviewed for the other solvent chemicals recently evaluated and finalized. Bystanders include men, women, and children of any age. • Included children ages 11 and up in the direct dermal contact scenarios is consistent with the approach taken and peer reviewed for the other solvent chemicals recently evaluated and finalized.
88, 83	• Bystanders, including children, may be present in the rooms where products containing 1,4-dioxane are used, they may also have dermal exposure to that chemical through their contact with the surfaces and dishes that those products are used on or clothes recently washed with a detergent contaminated with 1,4-dioxane as a byproduct. EPA must evaluate those known, intended and reasonably foreseen bystander exposures in its Supplemental Analysis. • EPA underestimated consumer bystander exposure by ignoring both	• Generally, individuals that have contact with liquid 1,4-dioxane would be users and not bystanders. Therefore, direct dermal exposures are not expected for bystanders and are only estimated for users. Bystanders include men, women, and children of any age. EPA's approach

	chronic inhalation exposures of this population as well as any dermal exposures. Bystanders, including young children, will be near sources (*e.g.*, recently cleaned surfaces, recently washed clothes) on a continual basis. While their exposure may be lower than the user, lower exposure is not equivalent to zero exposure, as EPA has effectively assumed. By ignoring the potential for chronic inhalation exposures to bystanders, EPA has underestimated risk to this population.	to evaluating bystander exposures is consistent with the approach taken and peer reviewed for the other solvent chemicals recently evaluated and finalized.
88	• EPA relies on outdated model to estimate home size. Home volume of 492 m^3 is outdated and EPA should have used the updated value of 446 m^3. Moreover, use of average building size leaves lower-income populations who often live in smaller homes at risk. The recommended low-end of housing volume is 154 m^3. • EPA relies on a Consumer Exposure Model that fails to account for the increases in breathing rates during and immediately following pregnancy. Instead, EPA's model relies on central tendency inhalation rate estimates for individuals across all age groups at light intensity activity levels. EPA's failure to consider for pregnancy- and postpartum-specific inhalation rates could significantly underestimate acute inhalation exposure to consumer products containing 1,4-dioxane in pregnant women and the developing fetus. To better evaluate exposure risks during vulnerable periods of development, EPA must consider pregnant women and the developing fetus as potentially exposed or susceptible subpopulations in this supplemental analysis.	• The home volume applied in the modeling of inhalation exposures is consistent with the approach taken and peer reviewed for the other solvent chemicals recently evaluated and finalized. However, EPA will consider the noted update in future evaluations. • EPA's models can account for age-specific breathing rate differences when estimating doses. However, in this evaluation, EPA utilized the 8-hour maximum time weighted average air concentrations for users and bystanders consistent with the approach taken and peer reviewed for the other solvent chemicals recently evaluated and finalized.
79	• The Draft Supplemental Analysis to the Draft Risk Evaluation for 1,4-Dioxane reviews potential consumer exposure to 1,4-Dioxane in SPF products. SFC agrees that the characterization of 1,4-Dioxane as a byproduct is correct. In the Draft Supplemental Analysis, EPA states that concentrations of 1,4-Dioxane in SPF formulations range between <0.5 to 500 ppm. While SFC's members that manufacture SPF believe EPA's estimated concentrations are high, due to the short comment period, SFC could not verify the exact potential concentrations.	• While application of SPF insulation products may primarily be occupational, a "do it yourself" or DIY installation of SPF is possible. There are consumer products available that may expose consumers (users and bystanders) to 1,4-dioxane

	• Moreover, EPA does not clearly define what types of SPF products are available for consumer application and, therefore, are included in the condition of use. There are 4 major types of SPF products. The products are generally distinguished by their packaging and application equipment. Figure 1 provides an overview of the four types of SPF products, their packaging, and their application equipment. High-pressure SPD are not available for consumer use, unlike low-pressure and one-component SPF products. Each SPF product has unique application equipment and exposure profiles. The types of SPF products available for consumer application are all bead applied, not sprayed. The supplemental analysis developed emission rates based on high-pressure SPF. The exposure profiles for one-component and low-pressure SPF are significantly lower than high-pressure SPF and the final risk evaluation should consider this distinction. SFC is not aware of any additional data to inform potential exposure to 1,4-dioxane from these consumer-type SPF products. • PPE and product safety recommendations protect consumer and occupational applicators. EPA should consider PPE and safety recommendations when evaluating this condition of use.	• EPA acknowledges in Section 4.3.2 that the emission rate used is derived from occupational-grade SPF products and that there is some uncertainty about the application of such data to consumer exposures. Additional language was added to further acknowledge the points made here. • EPA does not assume that consumer users or bystanders will use PPE. This approach for consumer conditions of use is consistent with the approach taken and peer reviewed for the other solvent chemicals recently evaluated and finalized.
82	• The Supplemental Analysis states that US EPA "did not identify any 'legacy uses' or 'associated disposal' But there are numerous scenarios under which consumers could be exposed to legacy uses. The Supplemental Analysis observes that 1,4-Dioxane is used in latex wall paints and in spray polyurethane foams. Consumers could be exposed to such paints and foams long after their initial application. • The Supplemental Analysis states that US EPA did not evaluate "legacy disposal" (i.e. disposals that have already occurred)" but does not explain whether US EPA identified such legacy disposals. The failure to address this point leaves open the possibility – particularly in light of the legacy exposure scenarios described above – that US EPA may have identified legacy uses but misclassified them as legacy disposals. US EPA should address this possibility by providing further explanation of the reasons it believes there would be no legacy uses of 1,4-Dioxane and	• EPA has added a footnote to the Executive Summary to clarify that EPA did not identify any legacy uses of 1,4-dioxane. EPA did not evaluate "legacy disposal" (*i.e.*, disposals that have already occurred) in the risk evaluation, because legacy disposal is not a "condition of use" under Safer Chemicals, 943 F.3d 397. EPA did not specifically identify any legacy disposals.

	by fully discussing which if any legacy disposals it identified but declined to consider.	
83	• EPA's acute inhalation risk estimates (MOEs) for both users and bystanders of spray polyurethane foam (SPF) in basements –317 and 384, respectively –are very close to its benchmark MOE of 300; see Table 4-3 on p. 63 and Table 4-8 on p. 68. EPA does not acknowledge this, however, or address how the sources of uncertainty it identifies (pp. 49-54) have been reflected in its decision not to regard this close margin as indicative of unreasonable risk. It should be noted that EPA's risk estimate assumes a given consumer has no other exposure to 1,4-dioxane whatsoever: no dermal exposure through SPF use; no exposure from the use of another consumer product; no exposure at work; no exposure through ambient water, no exposure through drinking water; no exposure from background sources. Otherwise what EPA asserts is not an unreasonable risk could quickly become one. These examples show just how narrow and arbitrary EPA's approach to addressing this chemical's risk is, and how hard it has had to work to avoid finding any unreasonable risk.	• EPA considers the uncertainties associated with each condition of use, and how the uncertainties may result in a risk estimate that overestimates or underestimates the risk. Based on such analysis, EPA determines whether or not the identified risks are unreasonable. Such consideration carries extra importance when the risk estimates are close to the benchmarks for acute, chronic non-cancer risks, and cancer risks. • EPA does not believe exposures need to be integrated for workers with the estimated general population exposures, as the exposures estimated to be experienced by workers are generally significantly higher than general population exposures
Occupational Exposure Comments		
85	• EPA discounts the risk to workers on the assumption that workers will use personal protective equipment ("PPE") and that the PPE will protect against 1,4-dioxane exposure. EPA states that it "expects there is compliance with federal and state laws, such as worker protection standards, unless case-specific facts indicate otherwise, and therefore existing [Occupational Safety and Health Administration (OSHA)] regulations for worker protection and hazard communication will result in use of appropriate PPE consistent with the applicable [safety data sheets] in a manner adequate to protect workers." However, EPA provides no evidence that PPE in the workplace is in fact used and effectively protects against 1,4-dioxane exposure. Indeed, OSHA itself	• OSHA provides an annotated list of PELs on its website, including alternate exposure levels. For 1,4-dioxane, the alternates provided are the California OSHA PEL of 0.28 ppm and the ACGIH TLV of 20 ppm. (https://www.osha.gov/dsg/annotated-pels/tablez-1.html). EPA's approach for developing exposure assessments for workers and ONUs is to use the reasonably available information and

	has recognized that many of its 1,4-dioxane standards are "outdated and inadequate for ensuring the protection of worker health." EPA must consider whether 1,4-dioxane presents an unreasonable risk to exposed workers without discounting that risk by assuming the use and effectiveness of PPE. • To the extent that EPA corrects its deficiencies in the Supplement to include workers exposed to products containing 1,4-dioxane as a byproduct (industrial laundries and dry cleaners, commercial vehicle washing, motor vehicle repair and maintenance, cleaning services, construction and painting), EPA must not distort OSHA standards or assume universal and effective use of personal protective equipment (PPE). Likewise, EPA should not assume adherence with recommendations included in safety data sheets (SDSs), which are not mandatory, often of insufficient quality to be useful and frequently not understood.	expert judgment. When appropriate, in the risk evaluation, EPA has used exposure scenarios both with and without engineering controls and/or PPE that may be applicable to particular worker tasks on a case-specific basis for a given chemical. Thus, while EPA has evaluated worker risk with and without PPE, as a matter of policy, EPA does not believe it should assume that workers are unprotected by PPE where such PPE might be necessary to meet federal regulations, unless it has evidence that workers are unprotected. For the purposes of determining whether or not a condition of use presents unreasonable risks, EPA incorporates assumptions regarding PPE use based on information and judgment underlying the exposure scenarios. These assumptions are described in the unreasonable risk determination for each condition of use, in section 5.2. Further, in the final risk evaluation for 1,4-dioxane, EPA has determined that most of the industrial and commercial conditions of use pose an unreasonable risk to workers even with the assumed PPE.
88, 83	• The Supplemental Analysis considers only consumer uses of the products, despite the fact that all of them have known, intended, or	• In response to peer review and public comments, EPA evaluated eight

	reasonably foreseen occupational uses as well. Workers use those products more frequently, for longer durations, and often in greater amounts than consumers do, and thus face greater exposures and risks than the average consumer. Those workers are thus a "potentially exposed or susceptible subpopulation," whose health EPA is required to take into account. • There are more than 2.3 million janitors and building cleaners in the United States, in addition to nearly 500,000 hotel housekeepers. These workers routinely work with cleaning products such as surface cleaners. However, EPA did not consider the risks to these cleaning workers in the Supplemental Analysis. Cleaning workers are exposed to, and harmed by, chemicals in cleaning products. Exposure to 1,4-dioxane has the potential to exacerbate those respiratory harms and subject workers to a range of other serious risks, including cancer, liver disease, and more. • In the Supplemental Analysis, EPA found even consumer use of surface cleaners containing 1,4-dioxane would result in risks equal to EPA's unreasonable risk threshold of one additional cancer for every 1,000,000 people. Had EPA considered workers' greater exposure to surface cleaners, it would have calculated cancer risks far beyond the unreasonable risk threshold, requiring EPA to regulate 1,4-dioxane "to the extent necessary" to eliminate those unreasonable risks. EPA's failure to consider occupational uses of cleaning products violates TSCA and leaves millions of workers potentially exposed to unsafe levels of a carcinogen. • There are also more than 2.2 million domestic workers nationwide, including more 343,000 paid house cleaners. More than ninety-five percent of those house cleaners are women, and nearly sixty percent are Latina. Twenty-five percent of house cleaners have household incomes below the poverty line, compared to five percent of non-domestic workers, and less than eight percent of house cleaners receive employer-provided health insurance, compared to forty-eight percent of non-domestic workers. These socioeconomic stressors render those workers	consumer uses of products that contain 1,4-dioxane as a byproduct. EPA made a policy decision in consideration of 1,4-dioxane as a byproduct, to limit consideration to consumers. TSCA Section 6(b)(4)(D) requires EPA, in developing the scope of a risk evaluation, to identify the hazards, exposures, conditions of use, and potentially exposed or susceptible subpopulations the Agency "expects to consider" in a risk evaluation. This language suggests that EPA is not required to consider all conditions of use, hazards, or exposure pathways in risk evaluations. EPA has therefore tailored the scope of the risk evaluations for 1,4-dioxane using authorities in TSCA sections 6(b) and focused this fit-for-purpose evaluation on consumer (and bystanders) exposures to household products containing 1,4-dioxane as a byproduct. • As described in Section 4.3.2 of the final risk evaluation, inhalation and dermal exposures were evaluated on a product-specific basis and are based on use of a single product type within a day, not multiple products. EPA does not believe exposures need to be integrated for workers with the

	more susceptible to the impacts of chemicals like 1,4-dioxane. Domestic workers' exposures to cleaning products containing 1,4-dioxane are far greater than the average consumer's. EPA's Supplemental Analysis does not attempt to measure those exposures, much less the corresponding risks. Moreover, domestic workers may work with, and be exposed to, multiple types of products containing 1,4-dioxane. In a single shift, a house cleaner or maid may use surface cleaners, dish soap, dishwasher detergent and laundry detergent. Because EPA evaluates the risks from all of those products separately, however, it fails to account for the combined risks to individuals who are exposed to all of them simultaneously. This omission further understates the risks to workers and violates EPA's statutory obligations. • 1,4-dioxane also has been detected in latex wall paint and floor lacquer. There are more than 379,000 house painters nationwide, and those workers "are potentially exposed to the chemicals found in paint products during their application and removal." In other risk evaluations, EPA evaluated painters' occupational exposures to methylene chloride, perchloroethylene, and pigment violet 29. However, EPA did not perform that analysis for 1,4-dioxane. EPA's exposure assumptions do not attempt to capture the known, occupational uses of paints and floor lacquer. EPA assumes that all exposures to those products are acute, as opposed to chronic, because of their allegedly "infrequent and intermittent use frequencies." For professional painters, however, the use of latex wall paint is neither infrequent nor intermittent; instead, they use paint every day on the job. In EPA's prior risk evaluations, it considered workers' chronic exposures to the chemicals contained in paints and coatings. EPA provides no explanation for its failure to consider those same exposures in the 1,4-dioxane Supplemental Analysis. • 1,4-dioxane is also present in aircraft de-icing fluids and antifreeze. In its Supplemental Analysis, EPA ignores aircraft de-icing and considers only consumer uses of antifreeze. EPA did not evaluate chronic exposure to antifreeze because of the product's allegedly "infrequent	estimated general population exposures, as the exposures estimated to be experienced by workers are generally significantly higher than general population exposures • The paint and lacquer uses are evaluated under consumer exposure. In addition, occupational exposure of lubricant and 1,4-dioxane mixture in sprayed applications, and functional fluids are discussed in the risk evaluation document and Appendix G. • EPA initially excluded production of 1,4-dioxane as a byproduct from certain other chemicals and presence as a contaminant in industrial, commercial and consumer products from the scope of the risk evaluation using EPA's discretion under TSCA section 6(b)(4)(D). While EPA has addressed some conditions of use related to 1,4-dioxane as a byproduct in this risk evaluation, EPA expects that the commercial use of aircraft de-icing fluid and similar products would be considered in the scope of a risk evaluation for ethylene glycol. In cases like this, EPA believes its regulatory tools under TSCA section 6(a) are better suited to addressing any unreasonable risks that might arise from these activities through

	and intermittent use frequencies." But that is not the case for mechanics, aircraft de-icers, and other workers who routinely use antifreeze and de-icing fluids. Increased levels of ethylene glycol, the active ingredient in antifreeze, have been detected in auto mechanics, the result of chronic usage and exposures. Those same workers and others face chronic exposure to 1,4-dioxane from antifreeze and de-icing fluids, and EPA must consider the risks from those exposures in its Supplemental Analysis. • Workers using surface cleaners, soaps, and detergents, those using paints, antifreeze, textile dyes, and SPF (*e.g.*, employees of painting service companies, automotive garages, textile businesses and home insulation installers) must certainly be considered chronically exposed to such products. They are clearly exposed more than once a day, for multiple days per week, and for longer periods of time per exposure event than EPA assumed for consumers.	regulation of the activities that generate 1,4-dioxane as an impurity or cause it to be present as a contaminant than they are to addressing them through direct regulation of 1,4-dioxane. This case-by-case approach for byproducts exposures is consistent with the various scenarios explained in the Risk Evaluation Rule, 82 FR at 33730. • With respect to commercial and industrial use of 1,4-dioxane-contaminated surface cleaners, soaps, detergents, paints, antifreeze, and textile dyes, EPA made a policy decision in consideration of 1,4-dioxane as a byproduct, to limit consideration to consumers. TSCA Section 6(b)(4)(D) requires EPA, in developing the scope of a risk evaluation, to identify the hazards, exposures, conditions of use, and potentially exposed or susceptible subpopulations the Agency "expects to consider" in a risk evaluation. This language suggests that EPA is not required to consider all conditions of use, hazards, or exposure pathways in risk evaluations. EPA has therefore tailored the scope of the risk evaluations for 1,4-dioxane using

		authorities in TSCA sections 6(b) and focused this fit-for-purpose evaluation on consumer (and bystanders) exposures to household products containing 1,4-dioxane as a byproduct.
88	• The exclusion of drinking water exposures impacts workers as well as the general public. UAW represents members at a facility in Florida where 1,4-dioxane was detected in the water used on site. In addition to drinking water exposures, this water supply is used in eye wash stations and for various work-related activities, contributing to employee exposures. Under TSCA, EPA must evaluate all known, intended, and reasonably foreseen exposures associated with 1,4-dioxane's conditions of use, including exposures from drinking and process water.	• As described in Section 1.4.2 of the risk evaluation, EPA believes it is both reasonable and prudent to tailor TSCA risk evaluations when other EPA offices have expertise and experience to address specific environmental media, rather than attempt to evaluate and regulate potential exposures and risks from those media under TSCA. EPA has therefore tailored the scope of the risk evaluation for 1,4-dioxane using authorities in TSCA Sections 6(b) and 9(b)(1). Currently, EPA is evaluating 1,4 Dioxane through the SDWA statutory processes for developing a National Primary Drinking Water regulation. However, EPA has not developed CWA section 304(a) recommended water quality criteria for the protection of aquatic life or human health for 1,4-dioxane and therefore evaluated exposures to aquatic species and the general

		population from ambient water in the 1,4-dioxane risk evaluation.
86, 88	• The expanded scope fails to consider exposure of occupational receptors (*e.g.*, housecleaners, janitors, dishwashers, commercial launders, professional painters). The chronic exposure scenarios still assume one exposure event per day and therefore may not capture users that continuously use products throughout the day. Occupational exposures for agricultural workers and workers at wastewater treatment plants that may inhale 1,4-dioxane are also omitted. • EPA estimates that surface cleaners will be used only once per day, for 15–30 minutes. Regardless of whether that assumption is accurate for consumers (and EPA has not shown that it is), it clearly underestimates exposures for janitors, hospitality workers, and others who use cleaning products repeatedly over the course of their work shifts. In the absence of information to the contrary, EPA must assume at least eight hours of daily exposures for those workers over the course of a working lifetime, as it has for other workers who use 1,4-dioxane for commercial and industrial purposes.	• TSCA Section 6(b)(4)(D) requires EPA, in developing the scope of a risk evaluation, to identify the hazards, exposures, conditions of use, and potentially exposed or susceptible subpopulations the Agency "expects to consider" in a risk evaluation. This language suggests that EPA is not required to consider all conditions of use, hazards, or exposure pathways in risk evaluations. EPA has therefore tailored the scope of the risk evaluations for 1,4-dioxane using authorities in TSCA sections 6(b) and 9(b)(1) and focused this fit-for-purpose evaluation on consumer exposures to products containing 1,4-dioxane as a byproduct. • The expanded scope, including use patterns and other modeling inputs, is relevant to household consumers and bystanders and is not intended to reflect exposures or risks to occupational or commercial users.
88, 89	• EPA also fails to evaluate the risks to workers who manufacture and process the foregoing products. Even if 1,4-dioxane is not intentionally added to those products, it is still present as a byproduct, and workers who manufacture cleaning products, paints, and other products containing 1,4-dioxane may still inhale and come into contact with that	• EPA made a policy decision in consideration of dioxane as a byproduct, to limit consideration to consumers. TSCA Section 6(b)(4)(D) requires EPA, in developing the

	chemical. Their risks were not considered in either the draft risk evaluation or the Supplemental Analysis. • Although the supplement partially addresses consumer exposure to 1,4-dioxane-containing products, it continues to exclude workplace risks relating to these conditions of use. This is unjustified under TSCA. EPA cannot address some phases of chemical's life-cycle and ignore others. Having designated consumer use of these products as TSCA conditions of use, it cannot fail to evaluate other "circumstances" of their manufacture, processing and use, including worker exposure that occurs during these activities. • EPA's final risk evaluation must include risks to workers from exposure that occurs during manufacture, processing and commercial use of products containing 1,4 dioxane as a byproduct. It is particularly critical for EPA to examine risks to the large population of workers who use cleaning products in industrial and commercial facilities, such as stores, offices, schools, public buildings, warehouses and factories.	scope of a risk evaluation, to identify the hazards, exposures, conditions of use, and potentially exposed or susceptible subpopulations the Agency "expects to consider" in a risk evaluation. This language suggests that EPA is not required to consider all conditions of use, hazards, or exposure pathways in risk evaluations. EPA has therefore tailored the scope of the risk evaluations for 1,4-dioxane using authorities in TSCA sections 6(b) and 9(b)(1) focused this fit-for-purpose evaluation on consumer exposures to products containing 1,4-dioxane as a byproduct.
Drinking Water Exposure Comments		
76	• EPA has the authority under TSCA to control the introduction into the environment of contaminants such as 1,4-dioxane that degrade water quality and increase the cost of water treatment. EPA should be leveraging all the potential regulatory programs available to reduce exposure and ergo risk across the environmental spectrum.	• As described in Section 1.4.2 of the risk evaluation, EPA believes it is both reasonable and prudent to tailor TSCA risk evaluations when other EPA offices have expertise and experience to address specific environmental media, rather than attempt to evaluate and regulate potential exposures and risks from those media under TSCA. EPA has therefore tailored the scope of the risk evaluation for 1,4-dioxane using authorities in TSCA Sections 6(b)
76, 81	• Exclusion of drinking water risks is inconsistent with the Frank R. Lautenberg Chemical Safety for the 21st Century Act, which specifically highlights the potential to contaminate drinking water as a criterion for prioritization, establishing the need to consider potential drinking water risks. A reliance on other environmental statutes to address these risks may result in gaps in protection. The fact that controls may be implemented under other statutes does not obviate the Agency's responsibility to limit the introduction or a problematic chemical into the environment (including public water supplies and groundwater used by individual household wells).	

76, 87	• Exposures from 1,4-dioxane in drinking water should be added to the risk evaluation because the Agency has not established a Safe Drinking Water Act (SDWA) regulatory standard (or Maximum Contaminant Level [MCL]) for 1,4-dioxane. EPA included exposures to the general population via ambient surface waters in the supplemental analysis because there is no nationally recommended Ambient Water Quality Criteria under the Clean Water Act (CWA). The Agency's reasoning to include ambient water, but not drinking water, is unclear and inconsistent with the approach provided in the risk evaluation.	and 9(b)(1). Currently, EPA is evaluating 1,4 Dioxane through the SDWA statutory processes for developing a National Primary Drinking Water regulation. However, EPA has not developed CWA section 304(a) recommended water quality criteria for the protection of aquatic life or human health for 1,4-dioxane. Human exposure to a receptor using the waters for recreation and exposures to aquatic life were evaluated in this risk evaluation under TSCA. • OCSPP has coordinated with the Office of Water regarding 1,4-dioxane contamination in drinking water. In EPA's Preliminary Regulatory Determinations for Contaminants on the Fourth Drinking Water Contaminant Candidate List (85 FR 14098 (Mar. 10, 2020)), EPA found that 1,4-dioxane is occuring in finished drinking water above a health reference level and therefore, for purposes of TSCA section 9(b), EPA has found risk from 1,4-dioxane contamination at certain levels in drinking water that could be addressed under EPA's SDWA
76, 87	• EPA should explain why the Office of Water is relying on the TSCA risk evaluation to make a regulatory determination for 1,4-dioxane, when OCSPP is excluding drinking water exposure from its analysis. ASDWA continues to stress the need to harmonize regulatory approaches between OCSPP and the Office of Water so that potential downstream water contamination from chemicals such as 1,4-dioxane is not left to the state primary agencies and water systems to solve. Preventing contaminants from entering drinking water sources is more effective and less expensive than having to remove them from drinking water has become contaminated. Protecting drinking water sources (and preventing contamination) is essential for sustaining safe drinking water supplies, protecting public health and the economy, and protecting the environment.	
81, 87	• The exclusion of drinking water and other risks misplaces the risk management burden, moving it from manufacturers and commercial users onto water rate payers, local government, and other regulated entities. TSCA should support and minimize the need for controls under other environmental statutes.	
89	• By continuing to omit contaminated drinking water from the evaluation, the supplement fails to account for a source of exposure that contributes to total consumer intake of 1,4-dioxane and greatly adds to the cancer risk from use of consumer products. Including drinking water in the evaluation would require EPA to add ingestion to inhalation and dermal routes of exposure; the draft risk evaluation and supplement do not	

	account for this exposure pathway.	authorities.[1] However, EPA has deferred a determination to regulate 1,4-dioxane under SDWA because SDWA section 1412(b)(1)(B)(ii) requires that EPA determine after opportunity for public comment that regulation of 1,4-dioxane meets all three criteria for regulation under SDWA section 1412(b)(1)(A), and EPA is awaiting new information that can inform the evaluation of these three criteria (i.e. adverse effect, level of public health concern and meaningful opportunity for health risk reduction). EPA will continue to evaluate 1,4-dioxane under SDWA authorities to determine whether or not to regulate 1,4-dioxane in drinking water, and the information produced in the risk evaluation process will be considered by the Office of Water as part of future SDWA actions. • As described above, EPA has regular analytical processes to identify and evaluate drinking water contaminants of potential regulatory concern for public water systems under SDWA. The Office of Water evaluates the regulatory determination criteria
89	• 1,4-Dioxane contamination of drinking water is a national concern. UCMR3 sampling identified 1,4-dioxane levels were above 0.35 mg/L in at least one sample from 6.9 percent of PWSs, serving a total of 29.4 million customers in 37 states. According to the EPA drinking water program, 1,4-dioxane levels of 0.35 mg/L (or 1 ppb) represent "the amount of 1,4-dioxane expected to cause no more than one additional case of cancer in 1 million people who drink and bathe with the water over a lifetime." • In areas of North Carolina, the maximum concentrations reported – 114 and 107 ug/L – are nearly 300 times greater than EPA's one in a million cancer risk level, presenting a significant public health concern. • The UCMR3-based estimates understate the number of people consuming 1,4-dioxane in drinking water at levels of health concern because medium and small water systems may not test regularly for 1,4-dioxane and private wells are not required to test at all. As with other volatile compounds like TCE and PCE, water from municipal systems and private wells is not only ingested but used for bathing and showering, which result in inhalation and dermal exposure.	
89	• The millions of users of contaminated drinking water in Eastern North Carolina and similar "hot spots" in other states comprise PESSs because their exposure is a function of both drinking water consumption and use of consumer products and therefore is greater than exposure by the general population. • EPA is required under TSCA to make unreasonable risk determinations for these highly exposed and susceptible subpopulations. Since drinking water levels in many communities are well in excess of the concentrations deemed by EPA and state regulators to pose a 1 in 1 million cancer risk, the combined exposure from drinking water and consumer product pathways in these communities is likely well above EPA's unreasonable risk benchmark for carcinogenicity.	
89, 82	• The supplement continues to assert that TSCA should not apply "when other EPA offices have expertise and experience to address specific	

	environmental media" and that excluding drinking water from TSCA risk evaluations is necessary to "avoid duplicating efforts taken pursuant to other Agency programs." • However, 1,4-dioxane is NOT being "addressed" under the SDWA. EPA has not promulgated a National Primary Drinking Water regulation for 1,4dioxane and has no plans to do so and there is little prospect that 1,4-dioxane in ground water or drinking water will be regulated by EPA for the foreseeable future. • It contradicts the position that US EPA has taken under its Safe Drinking Water Act ("SDWA") program. Even though US EPA now states in the Supplemental Analysis that the drinking water impacts of 1,4-Dioxane should be considered under the SDWA rather than TSCA, it declined, in March of this year, to make a preliminary regulatory determination under SDWA for 1,4-Dioxane, on the ground it wanted first to complete its TSCA risk evaluation of 1,4-Dioxane. US EPA cannot argue, under the SDWA, that it will consider such impacts under TSCA and then, under TSCA, argue that it will only consider them under the SDWA. • 1,4-Dioxane in ground water is also ignored but is considered a major source of drinking water contamination in "hot spots" such as Long Island, New York and Southern California. • If drinking water sources of exposure are not included in the ongoing TSCA risk evaluation, the risks they present will likely never be identified, evaluated, and reduced. In short, even if EPA is correct that TSCA is a "gap-filling" statute, addressing drinking water contamination in risk evaluations would in fact fill a serious "gap" in regulatory protection. To ignore this gap would violate the spirit and letter of TSCA.	under SDWA Section 1412(b)(1)(A) to determine whether or not to initiate the development of a National Primary Drinking Water Regulation. EPA promulgates National Primary Drinking Water Regulations (NPDWRs) under SDWA when the Agency concludes a contaminant may have adverse health effects, occurs or is substantially likely to occur in public water systems at a level of concern and that regulation, in the sole judgement of the Administrator, presents a meaningful opportunity for health risk reduction. For each contaminant with NPDWRs, EPA sets an enforceable Maximum Contaminant Level (MCL) as close as feasible to a health based, non-enforceable Maximum Contaminant Level Goals (MCLG) or establishes a treatment technique. Feasibility refers to both the ability to treat water to meet the MCL and the ability to monitor water quality at the MCL, SDWA Section 1412(b)(4)(D). Public water systems are generally required to monitor for the regulated chemical based on a standardized monitoring schedule to ensure compliance with the maximum

		contaminant level (MCL). Under SDWA, EPA must also review existing drinking water regulations every 6 years, and if appropriate, revise them. SDWA, originally passed by Congress in 1974, thereby is the main federal statute to protect drinking water by regulating the nation's public drinking water supply and authorizing EPA to set national health-based standards and take other actions to protect against contaminants that may be found in drinking water. • EPA will continue to evaluate 1,4-dioxane under SDWA authorities to determine whether or not to regulate 1,4-dioxane in drinking water, and the information produced in the risk evaluation process will be considered by the Office of Water as part of the current SDWA actions.
89, 81, 83	• EPA's Legal Justification for Including Surface Water Discharges in the Supplement Conflicts with Its Rationale for Excluding Drinking Water Contamination. EPA continues to exclude 1,4-dioxane in drinking water from its evaluation because it is theoretically subject to the SDWA, but points to the absence of regulation under the CWA to justify addressing surface water under TSCA.	• EPA is currently evaluating 1,4-dioxane under SDWA. There is no such evaluation underway under CWA and so EPA is including surface water discharges in this risk evaluation.

	• AMWA would like further explanation as to why the exclusion of a standard under CWA calls for the agency to consider exposure via surface water, but a lack of national standard under SDWA does not. This seems inconsistent and calls into question the agency's decision to exclude drinking water. • EPA's selective invoking of another statute as a basis for its 11th-hour decision to include the ambient water pathway, while excluding other relevant pathways, is contradictory and arbitrary and capricious. The draft TSCA risk evaluation – and now the Supplement – make clear that the TSCA risk evaluation will ignore drinking water exposures, on the basis that they are already addressed by the Office of Water under SDWA, when in fact they are not.	• As described in Section 1.4.2 of the risk evaluation, EPA believes it is both reasonable and prudent to tailor TSCA risk evaluations when other EPA offices have expertise and experience to address specific environmental media, rather than attempt to evaluate and regulate potential exposures and risks from those media under TSCA. EPA has therefore tailored the scope of the risk evaluation for 1,4-dioxane using authorities in TSCA Sections 6(b) and 9(b)(1). Currently, EPA is evaluating 1,4 Dioxane through the SDWA statutory processes for developing a National Primary Drinking Water regulation. However, EPA has not developed CWA section 304(a) recommended water quality criteria for the protection of aquatic life or human health for 1,4-dioxane. Human exposure to a receptor using the waters for recreation and exposures to aquatic life were evaluated in this risk evaluation under TSCA.
89, 83, 86, 78	• EPA's analysis of surface water discharges is inadequate to achieve the purposes of water quality criteria under the CWA or to satisfy the requirements of TSCA. The supplement presents an incomplete picture of 1,4-dioxane releases to surface water because it overlooks the many pathways by which it enters water bodies and the resulting	• EPA disagrees, and believes that the analysis satisfies the requirements of TSCA. In its evaluation of the ambient water, general population pathway, EPA focused its analysis

	contamination of drinking water sources. The surface water discharges analyzed do not include manufacturer of ethoxylated raw materials or cleaning products, etc. It also ignores down the drain releases following use of consumer products. • EPA's evaluation of surface water impacts of 1,4-dioxane discharges is based on only 24 sources, comprising mainly chemical, pharmaceutical and pesticide manufacturers, that EPA admits are "likely not representative of all the releases in the U.S. for 2018." The 24 sources do not include manufacturers of ethoxylated raw materials or finished cleaning products, personal care products or cosmetics formulated from these raw materials. In addition, the supplement identifies several additional groups of 1,4-dioxane dischargers, representing over 1.6 million facilities. • EPA estimates the number of release days per year for these dischargers and calculates representative discharge levels but makes no attempt to estimate the resulting surface water concentrations attributable to each discharger. This is a significant limitation because the large universe of discharging facilities likely has significant cumulative water quality impacts that are broadly distributed geographically. Had EPA's analysis accounted for all of the numerous industrial point-sources of 1,4-dioxane, its modeling of ambient water levels would necessarily have reflected the impact of multiple discharges on specific water bodies. This would be a more realistic scenario than modeling the surface water impact of individual dischargers standing alone, the approach EPA uses in the supplement. • The supplement also ignores "down the drain" releases of 1,4-dioxane following the use of cleaning products, personal care products and cosmetics. Since 1,4-dioxane is difficult to treat and remove, it often passes through POTWs to surface waters, where it mixes with point-source discharges from industrial and commercial sites and contaminates drinking water sources. • For the significant fraction of households that rely on septic systems for disposing of residential wastewater, available information indicates very	using releases from the scoped industrial and/or commercial conditions of use shown in Table 2-2 of the final risk evaluation. The OES with non-zero releases included: manufacturing, industrial uses, function fluids (open-system), spray foam application, and disposal. These were based on reasonably available 1,40-dioxane release data. It also incorporated monitoring data that were submitted during the public comment period and SACC review of the draft risk evaluation. • Regarding body care and cosmetic products, they are excluded from the definition of "chemical substance" per TSCA section 3(2) and are outside the scope of this risk evaluation. • As described in Section 1.4.2 of the risk evaluation, EPA believes it is both reasonable and prudent to tailor TSCA risk evaluations when other EPA offices have expertise and experience to address specific environmental media, rather than attempt to evaluate and regulate potential exposures and risks from those media under TSCA. EPA has therefore tailored the scope of the risk evaluation for 1,4-dioxane using authorities in TSCA Sections 6(b)

	limited removal. Evidence shows that the chemical can be readily transported from septic systems directly into domestic drinking water wells typically relied on by the same households. • EPA continues to ignore 1,4-dioxane's use in oil and gas production (*i.e.*, releases of 1,4-dioxane arising from its use or presence in both hydraulic fracturing fluids and produced water). • EPA's evaluation of general population risks is particularly flawed because it does not evaluate the chronic drinking water risks of the surface water concentrations predicted at the point of release. EPA claims in the supplemental analysis that the agency is not evaluating the drinking water risks of surface water contaminated with 1,4-dioxane because the agency is relying on the Safe Drinking Water Act to regulate drinking water. That claim cannot be justified because EPA has no drinking water standard for 1,4-dioxane now and has no plans to develop such a standard in the future. • Public and peer review comments EPA previously received identified numerous additional omissions related to water exposures that EPA has now failed to include in its Supplement. • EPA's failed to include all exposures through water – including drinking water, groundwater, and sediment, as well as ambient surface water. EPA failed to consider direct exposures to ambient water through activities such as cooking, bathing or showering.	and 9(b)(1). • Related to specific dischargers, all specific discharges included in the summary tables presented in Section 2.2.1.2.3 (Table 2-5) were modeled to estimate site-specific surface water concentrations (see Section 2.4.2.1.1 and Table 2-34). • The releases estimated and used to model predicted surface water concentrations in support of the ambient water, general population exposure pathway were associated with the scoped occupational conditions of use (see Table 2-2 for the OES included in this release assessment). • With respect to oil and gas production (hydraulic fracturing), EPA's review of the FracFocus reports on 1,4-dioxane indicates that the 1,4-dioxane is likely present as an impurity in the ethoxylated alcohols that are also named in the same reports. EPA initially excluded production of 1,4-dioxane as a by-product from certain other chemicals and presence as a contaminant in industrial, commercial and consumer products from the scope of the risk evaluation using EPA's discretion under TSCA section 6(b)(4)(D). While EPA has addressed some

		conditions of use related to 1,4-dioxane as a byproduct in this risk evaluation, EPA expects that 1,4-dioxane exposures associated with the use of ethoxylated alcohols used in hydraulic fracturing fluids would be considered in the scope of a risk evaluation for ethoxylated alcohols. In cases like this, EPA believes its regulatory tools under TSCA section 6(a) are better suited to addressing any unreasonable risks that might arise from these activities through regulation of the activities that generate 1,4-dioxane as an impurity or cause it to be present as a contaminant than they are to addressing them through direct regulation of 1,4-dioxane. This case-by-case approach for byproducts exposures is consistent with the various scenarios explained in the Risk Evaluation Rule, 82 FR at 33730.
89	• Monitoring studies in North Carolina [a summary of findings are provided in the comments] demonstrate the widespread impact of 1,4-dioxane discharges on drinking water quality. The data confirms a relationship between surface water concentrations and elevated levels of 1,4-dioxane in drinking water, and indicate that most of the measured levels in surface water were above the EPA and North Carolina recommended limit of 0.35 ppb for drinking water based on 1,4-dioxane's carcinogenicity. • This analysis would provide a basis for defining the contribution of	• As described in Section 1.4.2 of the risk evaluation, EPA believes it is both reasonable and prudent to tailor TSCA risk evaluations when other EPA offices have expertise and experience to address specific environmental media, rather than attempt to evaluate and regulate potential exposures and risks from

	manufacturing and processing sites and down-the-drain releases of consumer products to 1,4-dioxane levels in drinking water and enable EPA to determine whether these surface water discharges present an unreasonable risk to the health of drinking water users.	those media under TSCA. EPA has therefore tailored the scope of the risk evaluation for 1,4-dioxane using authorities in TSCA Sections 6(b) and 9(b)(1). Currently, EPA is evaluating 1,4 Dioxane through the SDWA statutory processes for developing a National Primary Drinking Water regulation. • EPA has added a footnote to the Executive Summary to clarify that EPA did not identify any legacy uses of 1,4-dioxane. EPA did not evaluate "legacy disposal" (*i.e.,* disposals that have already occurred) in the risk evaluation, because legacy disposal is not a "condition of use" under Safer Chemicals, 943 F.3d 397. • In March 2020, EPA published a Preliminary Regulatory Determinations for Contaminants on the Fourth Drinking Water Contaminant Candidate List pursuant to SDWA authority, see 85 FR 14098. The Agency did not make a preliminary determination under SDWA for 1,4-dioxane because the Agency has not determined whether there is a meaningful opportunity for public health risk reduction. EPA will continue to evaluate 1, 4-dioxane prior to making a regulatory determination. The Regulatory
88	• In the Supplemental Analysis, EPA continues to overlook one of the largest sources of exposure to 1,4-dioxane: contaminated drinking water. 1,4-dioxane has been detected in thousands of drinking water supplies serving more than 88 million people, with unsafe levels of the chemical detected by more than 280 utilities in 26 states. However, EPA did not consider the risks associated with that drinking water contamination in either its initial Risk Evaluation or its Supplemental Analysis. EPA's exclusion of drinking water exposures for 1,4-dioxane has no legal or factual basis. EPA claims that "exposures to general population via drinking water ... fall under the jurisdiction of other environmental statutes administered by EPA," such as the Safe Drinking Water Act ("SDWA"), and thus need not be considered under TSCA. But TSCA does not permit EPA to ignore known exposures and risks resulting from a chemical's conditions of use merely because those exposures may be regulated under other environmental laws. Moreover there is no federal limit on 1,4-dioxane levels in drinking water, and just last March EPA decided against establishing one. EPA cited its ongoing TSCA risk evaluation to justify its failure to commence a rulemaking process for 1,4-dioxane under the SDWA, while at the same time relying on the existence of the SDWA to excuse its failure to consider drinking water exposures in its TSCA risk evaluation. This regulatory shell game violates EPA's obligations under TSCA and leaves millions of people exposed to a known carcinogen in their drinking water.	
86	• Drinking water and air can be contaminated from legacy inputs of dioxane, in addition to ongoing inputs from consumer products. These were omitted.	
86	• Source reduction is recognized as the most effective way to reduce drinking water contamination. Including drinking water in this assessment and regulating dioxane's presence in consumer products	

	would do more to address contamination that the extensive efforts required to set an MCL.	Determination 4 Support Document (USEPA, 2019a) and the Occurrence Data from the Third Unregulated Contaminant Monitoring Rule (UCMR 3) (USEPA, 2019b) present additional information and analyses supporting the Agency's evaluation of 1,4-dioxane. • Sections 2.4.2, 4.2.4, and 5.2 for EPA's evaluation of general population exposures via the ambient water pathway.
85	• The draft risk evaluation excludes numerous significant exposure pathways in which the general population and environment are exposed to 1,4-dioxane—such as the well-documented risks to those exposed to contaminated drinking water—thereby understating the overall risk of 1,4-dioxane exposure.	
84	• In light of recent concerns raised by stakeholders, including state water agencies, we recommend that EPA consider evaluating general population risks associated with drinking water as part of the risk evaluation.	
Aggregate Exposure Comments		
78, 82	• EPA should aggregate the incidental ingestion and dermal exposure risks from swimming instead of evaluating them separately. • The agency has not aggregated dermal and inhalation exposure to single products, when that is clearly the situation for consumers. EPA's failure to combine exposure across these routes results in an understatement of risk for consumers.	• EPA did not aggregate exposure across exposure routes (dermal, inhalation or oral) for occupational, consumer, or general populations exposures. EPA chose not to employ simple additivity of exposure pathways within a condition of use because of the uncertainties present in the current exposure estimation procedures. There is currently no PBPK model available to facilitate evaluation of aggregate exposure from simultaneous exposure through inhalation, dermal, and oral contact with 1,4-dioxane. Without a PBPK model containing a dermal compartment to account for toxicokinetic processes the true internal dose for any given exposure cannot be determined, and

		aggregating exposures by simply adding exposures from multiple routes could inappropriately overestimate total exposure. Conversely, not aggregating exposures in any manner may potentially underestimate total exposure for a given individual. EPA acknowledges in Section 4.3.2 that the decision not to aggregate risk could result in an underestimate of risk. • This approach is consistent with the approach taken and peer reviewed for the other solvent chemicals recently evaluated and finalized.
89, 82	• EPA assumes a single use event per day, but many products are used multiple times (*e.g.,* laundry detergent, dish soap, surface cleaners). Use has been increased due to the COVID pandemic. • EPA needs to recalculate its consumer risk estimates to reflect the combined effects of concurrent dermal and inhalation exposure, use of multiple 1,4-dioxane-containing cleaning products simultaneously and repeated applications of individual products in the course of a day. • EPA is able to calculate a cancer risk that it deems "reasonable" only by artificially considering each 1,4-dioxane source in isolation from others. However, when all sources are combined to mirror actual real-world exposure, the cancer risk is clearly much larger than EPA has estimated. • Inhalation risks from 1,4-dioxane in spray polyurethane foam used in basements, attics, and garages (table 4-3) should be considered together, not room-by-room.	• EPA concluded that there is insufficient information to support analysis of aggregate exposure across multiple conditions of use. EPA therefore did not aggregate risk across multiple consumer products or uses. EPA assumed a single use event per day, per the approach taken and peer reviewed for the other solvent chemicals recently evaluated and finalized. EPA acknowledges in Section 4.3.2 that the decision not to aggregate risk across conditions of use could result in an underestimate of risk. • As described in Section 4.3.2 of the final risk evaluation, inhalation and

		dermal exposures were evaluated on a product-specific basis and are based on use of a single product type within a day, not multiple products. • The analysis of consumer use of SPF products did not assume application would occur in all three rooms of use on the same day; it estimated exposures for all three home spaces (attic, basement, garage) to capture the application scenario likely to lead to the greatest exposure based on zone volume and ventilation rate. These modeled scenarios reflect distinct exposure activities.
78, 86, 85, 83, 82	• Consumer exposure receptors are the same as those whose exposures in ambient water/surface water are assessed following environmental releases to water. These exposures also should be aggregated with the COUs. By excluding aggregate exposures from multiple products and drinking water, this analysis purposefully ignores best available science and underestimates potential exposures. • TSCA requires EPA to "describe whether aggregate or sentinel exposures to a chemical substance under the conditions of use were considered, *and the basis for that consideration*". Here, while EPA has made clear it hasn't aggregated anything, there is no indication it has instead applied a sentinel exposure approach – the term never appears in the Supplement – nor has it described the basis for the approach it has taken. • Concurrent workplace and consumer risks should be aggregated. • EPA fails to consider aggregate exposures under the conditions of use for the general population. The exposures evaluated in the Supplemental Analysis occur in addition to exposures from air, drinking water, soil, sediment, and food. For health outcomes with a threshold level of	• EPA did not aggregate risk across multiple COUs or pathways. EPA concluded that there is insufficient information to support analysis of aggregate exposure across multiple conditions of use. EPA acknowledges in Section 4.3.2 that the decision not to aggregate risk across conditions of use could result in an underestimate of risk. • EPA defines sentinel exposure as "*the exposure to a single chemical substance that represents the plausible upper bound of exposure relative to all other exposures within a broad category of similar or related exposures* (40 CFR Section 702.33)." In this Risk Evaluation,

	exposure (commonly assumed for noncancer outcomes), the exposures evaluated in the Supplemental Analysis could cause consumers to exceed a threshold even if these exposures considered in isolation do not. Thus, evaluations that do not consider additivity to other sources of exposure are incomplete and underestimate health risks by an unknown margin. • EPA is urged to comply with TSCA by considering the risk of impacts to environmental media and to public health as a result of exposures to those media. • EPA admits that "[b]ackground levels of 1,4-dioxane in indoor and outdoor air are not considered or aggregated in this analysis".	EPA considered sentinel exposure the highest exposure given the details of the conditions of use and the potential exposure scenarios. Sentinel exposures for workers are the high-end scenarios with no assumption of PPE use within each OES. EPA considered sentinel exposures in this Risk Evaluation by considering risks to populations who may have upper bound (*e.g.*, high-end, high intensities of use) exposures. EPA's decision for unreasonable risk are based on high-end exposure estimates to capture individuals with sentinel exposure. • In accordance with 40 CFR 702.47 "…EPA will determine whether the chemical substance presents an unreasonable risk of injury to health or the environment under each condition of use within the scope of the risk evaluation…". This approach in the implementing regulations for TSCA risk evaluations is consistent with statutory text in TSCA Section 6(b)(4)(A), which instructs EPA to conduct risk evaluations to determine whether a chemical substance presents an unreasonable risk "under the conditions of use." As described in Section 1.4.2 of the risk evaluation, EPA believes it is both reasonable and prudent to tailor

		TSCA risk evaluations when other EPA offices have expertise and experience to address specific environmental media, rather than attempt to evaluate and regulate potential exposures and risks from those media under TSCA. EPA has therefore tailored the scope of the risk evaluation for 1,4-dioxane using authorities in TSCA Sections 6(b) and 9(b)(1). • The approach of considering consumer exposures on a product-specific basis without the consideration of background or multiple sources of exposure is consistent with the approach taken and peer reviewed for the other solvent chemicals recently evaluated and finalized. This aspect of the evaluation is described in the uncertainties Section 4.3.2
82	• Cancer risks for children 11–15, adolescents 16–20, and adults 21 and over should be summed and considered as a total lifetime increased cancer risk (along with calculations of risk from exposure before age 11).	• For inhalation exposures, a lifetime average daily air concentration (LADC) was predicted in CEM and used to estimate cancer risk. For dermal exposures, a lifetime average daily dose (LADD) was used to estimate cancer risk.
89	• Individuals who receive 1,4-dioxane from multiple sources are clearly PESSs under TSCA by virtue of their elevated exposure.	• EPA agrees that individuals with multiple sources of exposure may be potentially exposed or susceptible subpopulations. EPA has identified

		adult and adolescent workers and ONUs, adult and child consumers and bystanders, and adults and children in the general population as potentially exposed subpopulations.
85	• EPA's failure to consider 1,4-dioxane exposure from air emissions, drinking water and groundwater violates TSCA and results in an assessment of risks to consumers that is incomplete and under-protective. • Subpopulations exposed to 1,4-dioxane from contaminated groundwater may be exposed to higher levels of 1,4-dioxane than the general population	• As described in Section 1.4.2 of the risk evaluation, EPA has determined that drinking water, air emissions, onsite releases to land, disposal, and underground injection pathways fall under the jurisdiction of other EPA-administered statutes or regulatory programs are outside the scope of this risk evaluation. EPA believes it is both reasonable and prudent to tailor TSCA risk evaluations when other EPA offices have expertise and experience to address specific environmental media, rather than attempt to evaluate and regulate potential exposures and risks from those media under TSCA. EPA has therefore tailored the scope of the risk evaluation for 1,4-dioxane using authorities in TSCA Sections 6(b) and 9(b)(1).
Human Health Hazard Comments		
78, 89, 83	• EPA's benchmark MOE for chronic effects does not reflect the lack of data on 1,4-dioxane for critical endpoints. The hazard database for 1,4-dioxane lacks studies that assess the potential for reproductive and developmental effects and developmental neurotoxicity (in light of its known neurotoxic effects in adults). EPA has no dermal toxicity data at all and for developmental toxicity has only a single short-term study;	• As described above, there is no universal list of hazard data required when evaluating chemical risks under TSCA. Furthermore, for 1,4-dioxane, EPA has sufficient, reasonably available hazard information to

	hence, the agency lacks any sub-chronic or chronic reproductive, developmental or neurotoxicity data A 10X UF should be added to reflect these data gaps, increasing the benchmark MOE to 300.	conduct a risk evaluation and support the use of the chosen hazard endpoints. Therefore, EPA did not use a database uncertainty factor for hazard in the 1,4-dioxane risk evaluation.
83, 89	• The supplement's evaluation of health risks does not include chronic non-cancer effects. This omission is all the more curious because EPA identifies such non-cancer effects attributable to 1,4-dioxane exposure and it calculates and displays corresponding dose-response values for these effects. Nowhere does EPA provide any rationale or explanation for this omission. • EPA's final evaluation must estimate chronic noncancer risks to consumers, taking into account all pathways of exposure and subpopulations with elevated exposure levels.	• EPA evaluated cancer risk for consumer exposures because it is the risk driver (*i.e.*, the most sensitive endpoint) for chronic exposure. Based on the lack of cancer risk identified for chronic exposure through consumer products, EPA did not further evaluate chronic non-cancer risks.
83	• With respect to chronic non-cancer dermal effects, in the Supplement (Table 3-1) EPA indicates it has derived a HED of 1.6 mg/kg/day and cites two studies for this value: Kociba et al., 1974 and Kasai et al., 2009. EPA fails provide any explanation of how either or both studies were used to derive the HED, and it needs to do so. To the extent EPA relies on the Kasai et al., 2009 study, EPA may need to apply an additional UF_L uncertainty factor (LOAEL to NOAEL) as this study did not identify a NOAEL.	• The supplement was focused on the addition of new COUs and only provided a summary final PODs used to evaluate risk for consumer and general population exposures. Complete documentation for derivation of the final PODs is in Section 3 and Appendix K of the risk evaluation. EPA did not apply an uncertainty factor for NOAEL to LOAEL extrapolation to the chronic dermal non-cancer POD because the POD is based on the BMDL rather than a LOAEL.
83, 84, 80, 90	• EPA has provided no discussion or description of the basis for its changes to the POD values and CSF either in the Supplement or in the other documents it released along with it, other than the brief statement that the changes were in response to peer review and public comment.	• EPA changed several of the PODs in response to SACC and public comments. The supplemental that was sent for public comment

	With one exception, there are no comments that explain the changes. EPA appears to have made a change consistent with the comments it received from the New Jersey Department of Environmental Protection regarding the agency's earlier rejection of the oral cancer slope factor adopted by IRIS in its 2013 assessment of 1,4-dioxane. EPA has included this value in the Supplement as the starting point for its extrapolation to cancer risk from dermal exposure. Aside from this value, the previous comments from the public or the SACC peer review report do not explain EPA's decision to change some of the POD values. • EPA should make a discussion of the scientific rationale for these changes available for peer and public review before finalizing the risk evaluation.	included a summary table of final PODs, but, because these changes weren't the focus of the supplemental, documentation and rationale for the changes was not included. The documentation for the changes is in the hazard section and appendices of the final risk evaluation. EPA's rationale for changes and responses to previously submitted comments on these topics are presented in the preceding sections of this document. Changes made to PODs in response to SACC and public comment include: 1. The dermal cancer slope factor was modified based on reanalysis of female mouse cancer data. This data was used in the IRIS assessment but had been initially excluded in the draft risk evaluation due to difficulty modeling the data; In response to comments questioning the exclusion of this sensitive data, EPA obtained individual animal data from the original study to support a more robust time-to-tumor modeling approach that allows inclusion of this data 2. EPA corrected an error in dermal POD derivation. By incorporating a dermal adjustment factor in both the hazard and exposure portions of the

		risk calculations of the draft, EPA had effectively compared PODs in terms of *applied* dermal dose to predicted exposures in terms of *absorbed* dermal dose. In the final RE, EPA has revised all dermal PODs to reflect absorbed dermal dose rather than the applied dermal dose calculated in the draft RE. This eliminates the error by putting both the exposure and hazard parts of the risk equation in terms of absorbed dermal dose. EPA made this change in response to SACC comments indicating an error in the approach. 3. Nasal lesions are now classified as a result of systemic delivery (as opposed to portal of entry effects) relevant for dermal and oral exposures as well inhalation exposures. EPA made this change in response to SACC comments.
80, 90	• There is considerable scientific evidence that the mode of action (MOA) of liver and respiratory tract tumors observed in rodents treated with 1,4-dioxane do not arise by a mutagenic mode of action, but instead are related to a threshold-based response that only occurs at high doses. The draft supplemental analysis again errs in using a default linear low dose extrapolation method for calculating theoretical cancer risks. Instead, EPA should use a threshold approach, or at a minimum, present in Tables 4.4 and 4.6 risks calculated using a point of departure based on the threshold MOA side by side with calculations based on unit risk. • The decision to use the female mouse liver tumors from the study by Kano et al. (2009) directly contradicts the 2019 Draft Risk Evaluation	• EPA developed a more thorough MOA analysis that applies the framework outlined in the Guidelines for Carcinogen Risk Assessment to evaluate evidence for proposed mechanisms of carcinogenicity for liver tumors. This analysis is was substantially revised and expanded and moved to an Appendix (Appendix I). The narrative in the body of the RE is now condensed to

	which concluded that "Female mouse hepatocellular carcinoma data from Kano et al. (2009) were not modeled due to the difficulties that were previously noted in the U.S. EPA (2013c) IRIS assessment." ○ EPA has not explained why it has concluded that these significant concerns about the female mouse liver tumors are no longer relevant, nor does the Draft Supplement even indicate that EPA's view of these tumors has changed. ○ The occurrence of female mouse liver tumors is not consistent with other available information ─ including the results of a subchronic study conducted by the same research group (Kano et al. 2008). ○ This conclusion is further supported by the results of a new subchronic study sponsored by ACC and recently published (enclosed). A second article describing the results of toxicogenomic analysis of the livers of the exposed animals has been submitted for publication and will be available shortly. The findings of these two analyses lend further support to the conclusion reached by authoritative bodies around the world that the tumors observed in the laboratory animal studies are the result of a threshold mode of action. • Further, the dermal CSF for the female mouse liver tumors in the draft is roughly the same as the oral CSF for those tumors in the 2013 IRIS assessment. This discrepancy suggests that EPA has not made the appropriate adjustment for converting from oral-to-dermal exposure. The significant difference in the values (two orders of magnitude) for dermal risks derived from the inhalation study by Kasai et al. between the 2019 and 2020 drafts also suggests a problem with the approach taken in the Draft Supplement. It is not clear whether these differences reflect a change in the approach to extrapolating from oral/inhalation to dermal exposures or an error in the calculation.	provide a summary of EPA's major conclusions about MOA. The fundamental conclusions of this section have not changed, but the conclusions are supported by a more robust analysis. As described in above responses, EPA considered the recently published subchronic study submitted by ACC but did not incorporate this evidence into the MOA analysis. While the study may identify thresholds for specific effects evaluated in the study, a 90-day study that does not include tumor endpoints is not able to demonstrate that the key events in question are necessary precursors of liver tumor formation. • The dermal cancer slope factor was modified based on reanalysis of female mouse cancer data in Kano et al (2008). This data was used in the IRIS assessment but had been initially excluded in the draft risk evaluation due to difficulty modeling the data. In response to comments questioning the exclusion of this sensitive data, EPA obtained individual animal data from the original study to support a more robust time-to-tumor modeling approach that allows inclusion of this data. • Derivation of the dermal CSF from

		the female mouse liver tumors is presented in Section 3.2.6 and Appendix K of the risk evaluation. Because oral absorption was assumed to be 100%, the dermal CSF is equal to the oral CSF calculated from the Kano (2008) data. No additional adjustment is required for conversion from an oral dose to an absorbed dermal dose.
90, 83	• In table 4.4, EPA indicates that the calculated theoretical cancer risk value of 1.0 x 10-6 "...exceeds the benchmark of 1 x 10-6." This is obviously incorrect as these numerical values are equal. • EPA fails to identify this unreasonable risk or provide any explanation for dismissing it. EPA's risk determination for surface cleaners erroneously states (p. 74): "For consumers, EPA found that there was no unreasonable risk of non-cancer effects (liver toxicity) from acute inhalation or dermal exposures or of cancer from chronic inhalation or dermal exposures at the high intensity use."	• EPA appreciates this comment. The language has been slightly revised to clarify that values may be equal to the benchmark. • EPA's finding for surface cleaners is based on the acute and chronic consumer exposure analysis described in Section 2.4.3.
88, 89, 83	• In both the draft risk evaluation and Supplemental Analysis, EPA employed a default 10x uncertainty factor to adjust for all human (intra-species) variability. But EPA has no evidence that differences in susceptibility to 1,4-dioxane vary only by a factor of 10. • The Supplemental Analysis falsely asserts that "reasonably available human health data for all routes of exposure evaluated (*i.e.*, dermal and inhalation) indicate that there is no evidence of increased susceptibility for any single group relative to the general population." This claim is contradicted by EPA's own draft risk evaluation, which acknowledged that 1,4-dioxane is metabolized at least in part by Cytochrome P450 ("CYP") enzymes, and that "[v]ariations in CYP enzyme expression may contribute to susceptibility." EPA has also acknowledged that these genetic variations coupled with the effects of certain pre-existing health	• EPA revised the description of PESS in the executive summary of the final risk evaluation to be consistent with more in-depth discussions of PESS later in the document. In the absence of quantitative information on the impact of genetic variability, pre-existing health conditions, lifestage, or other factors on susceptibility across the population, EPA applied an uncertainty factor of 10 to account for interindividual variability. In Section 4.3.6 of the risk evaluation, EPA recognizes this as a source of

	conditions, like fatty liver disease, could alter the metabolism and toxicological activity of 1,4-dioxane. • EPA has previously acknowledged that "a 10-fold factor may ... be too small because of factors that can influence large differences in susceptibility, such as genetic polymorphisms." • Studies have shown that differences in sensitivity to chemical exposures can reach up to 30 fold, in some cases up to 100 fold, due to variability factors like pre-existing health conditions. • We recommend that EPA utilize at minimum a 30x intra-species uncertainty factor for 1,4-dioxane, consistent with the approach employed by California EPA, where, as here, "differences in metabolism and excretion are key to the toxicological activity [of a chemical]," particularly in the context of children's health. • We recommend an additional 10X UF for workers and consumers in recognition of the uncertain range of genetic variability, the very large worker and consumer populations exposed to 1,4-dioxane, and EPA's inability to determine the susceptibility to the substance of children and pregnant women. This would increase the benchmark MOE for non-cancer chronic health effects to 1000X. • While EPA acknowledges "limited data" exist on potential susceptibilities, it proceeds to ignore them by asserting there is a "lack of quantitative information." At a minimum, EPA must account for these susceptibilities in its uncertainty analyses and augment hazard and risk characterizations to reflect these relevant subpopulations, including by considering the use of additional uncertainty factors and/or by adjusting the magnitude of uncertainty factors applied.	uncertainty.
83	• EPA's reliance on route-to-route extrapolation for sub-chronic/chronic dermal effects –necessitated by the total absence of dermal toxicity data –also introduces uncertainty that EPA has failed to account for. As is recommended for route-to-route extrapolation generally and oral-to-dermal extrapolation specifically, EPA should apply an additional uncertainty factor of 10 to account for these uncertainties. • EPA also newly examines risks from acute oral and dermal exposure	• EPA agrees that route-to-route extrapolation is a source of uncertainty in the hazard characterization. As described in Section 3.2.7, EPA concluded that the primary sources of uncertainty are likely to underestimate the POD

	resulting from contact with 1,4-dioxane contaminated ambient surface water. Here EPA relies on Mattie et al., 2012, an inhalation study from which it derived a POD HED of 35.4 mg/kg/day, to evaluate risk. The associated BMOE of 300 EPA applied does not account for either of the route-to-route extrapolations employed (inhalation-to-dermal and inhalation-to-oral). An additional uncertainty factor should apply for the route-to-route extrapolations employed.	rather than overestimate the POD. For example, absorption through lungs is generally expected to be more efficient for solvents. The oral and dermal PODs derived under the assumption of 100% absorption may therefore be artificially low, but are unlikely to be artificially high. Given the cautious assumptions made in the route-to-route extrapolation, EPA concluded that an additional uncertainty factor was not warranted.
83	• EPA did not examine cancer in assessing risks from acute exposures and did not provide any explanation for this decision. For dichloromethane (DCM), the agency explained its decision not to assess acute cancer risks by stating only that the "[r]elationship is not known between a single short-term exposure to DCM [methylene chloride] and the induction of cancer in humans" (p. 699). We can assume that EPA would offer the same rationale in the case of 1,4-dioxane. If so, EPA's rationale is not supported and is unwarranted. • The National Research Council (NRC) states: "The NRC guidance states that the determination of short-term exposure levels will require the translation of risks estimated from continuous long-term exposures to risks associated with short-term exposures. " • EPA did not sufficiently consider such principles related to mode-of-action in deciding not to model acute cancer risk based on chronic exposure data. EPA estimates for excess cancer risk were based on the assumption of linearity in the relationship between 1,4-dioxane exposure and the probability of cancer. Hence, a linear low-dose extrapolation from chronic to acute exposures would be the appropriate approach to take for 1,4-dioxane. • A linear extrapolation from chronic cancer bioassays may even underestimate the cancer risk of short-term exposures. Halmes et al.,	• EPA did not evaluate cancer risks from acute exposure because the relationship between acute exposure and lifetime cancer risk is unknown and there would therefore be substantial uncertainty around such an analysis. This approach is consistent with the approach taken and peer reviewed for the other solvent chemicals recently evaluated and finalized. EPA applied the framework outlined in the Guidelines for Carcinogen Risk Assessment to evaluate evidence for proposed mechanisms of carcinogenicity for liver tumors but did not identify clear evidence in support of a particular MOA.

	2000 lends support to the potential for short-term exposures to result in similar or higher cancer risks than even chronic lifetime exposures. The study used NTP data where both shorter term and full lifetime studies had been conducted.	
Uncertainty Analysis Comments		
83	• EPA's failure to conduct uncertainty analyses to determine the effects of its assumptions, limited data, modeling defaults, and so forth. In the Supplement EPA acknowledges this need. On pages 30 and 49, EPA states: "EPA's approach recognizes the need to include uncertainty analysis." But in fact no uncertainty analysis has been conducted. While EPA identifies factors that contribute to uncertainty, it never evaluates their effect on its conclusions, and its determinations in effect ignore these factors. One small exception is that EPA does present a sensitivity analysis of the consumer exposure model it used, CEM. But that is a stand-alone analysis of the model itself, and does not extend to a characterization of the manner in which EPA uses the model outputs to estimate risks and then make risk determinations for this chemical.	• To the extent possible, EPA describes the potential magnitude of each source of uncertainty (see Section 4.3.2). For several sources of uncertainty, EPA lacks the quantitative information that would be necessary to characterize uncertainty for some parameters. EPA believes that the qualitative and quantitative analyses included in the risk evaluation provide sufficient information to support risk conclusions. As discussed in Section 5.1, EPA, in making a risk determination, takes into account a number of things, including the Agency's confidence in the data used in the risk assessment. This includes an evaluation of the strengths, limitations, and uncertainties associated with the information used to inform the risk estimate and the risk characterization.
83	• With regard to consumer exposures, especially chronic, EPA states it has only moderate confidence in its chronic inhalation exposure estimates and only low to moderate confidence in its chronic dermal exposure estimates. Yet it firmly concludes that none of these exposures presents any unreasonable risk. The basis for these rankings is less than clear and appears quite subjective. EPA describes the factors it states it considers in deciding on a confidence ranking, but never shows how those factors were actually applied to yield the confidence result it assigns to a specific exposure. At the very least EPA should have conducted uncertainty analyses to reflect and address uncertainties engendered by the lack of confidence in the available release and exposure information.	
83	• Overall EPA stated (p. 32): "Based on the above considerations, the general population ambient water exposure assessment scenarios have an overall low to moderate confidence." Despite the significant uncertainties in the available information, however, EPA still draws	

	unqualified conclusions that human exposures to ambient water (from swimming and fish consumption) do not present unreasonable risk. While EPA states that it takes its degree of confidence in available information into account in making risk determinations (pp. 70, 71), EPA never explains how it does so; nor does it rationalize or adjust this particular risk determination with the fact that it has only low to moderate confidence in the data on which it is based. At the very least EPA should have conducted uncertainty analyses that reflect and address uncertainties engendered by the lack of confidence in the available release and exposure information.	
Editorial/Clarity Comments		
82	• In section 4.2.1.2 4.6.2.2 [sic], the last sentence cites sections 2.4.3 and 4.2.3 for methods for consumer exposure assessment and risk characterization. The Supplemental Analysis, however, does not include these sections. (The 2019 Draft Risk Evaluation ("Draft Risk Evaluation") also has no section 2.4.3, and section 4.2.3 covers only hazard identification.)	• EPA has revised section references to accurately reflect contents of the final risk evaluation.
82	• A footnote to table 3-1 states, "HECs are adjusted from the study conditions as described above in Section 3.2.6," but there is no section 3.2.6. • It seems the new methods sections were not ready and were not included in the Supplemental Analysis. The existence of such significant errors calls the overall conclusions of the Supplemental Analysis into question.	• HEC derivation was beyond the scope of the Supplemental Analysis and this footnote should have been excluded. The final risk evaluation includes complete documentation of POD derivation in Section 3.2.6.
82	Several issues of Transparency were identified: • There is no discussion of the revisions to the Points of Departure (PODs) between the Draft Risk Evaluation and the Supplemental Analysis. • The Draft Risk Evaluation describes adjusting PODs for occupational instead of continuous exposure, but the Supplemental Analysis does not describe further adjustment of the PODs for consumer exposure. • 1,4-Dioxane could not be found in the hyperlinked IHSkinPerm© spreadsheet for the permeability coefficient (5.05E-04 cm/hr). Based on	• POD derivation was beyond the of the Supplemental document. Some PODs changed in response to SACC and public comment. The final risk evaluation includes complete documentation of POD derivation in Section 3.2.6. The rationale for specific changes made since the draft in is articulated in above responses to

	the link given in table 28, 1,4-Dioxane is not in the pull-down menu of substances covered by IHSkinPerm© • Certain parameter values used to calculate absorption fractions in table 2-12 are not clear. The Consumer Exposure Model 2.1 User Guide discusses the fraction-absorbed model; however, it does not provide certain scenario-specific or chemical-specific parameters, such as temperature or the gas-phase mass transfer coefficient. • Lines 1264–1266 cite Frasch and Bunge (2015) for modeling to estimate the absorption factor based on chemical-specific data. They modeled four chemicals; none was 1,4-Dioxane. Values used for 1,4-Dioxane should be provided.	SACC and public comments. • IHSkinPerm© allows users to add new chemicals to the program by selecting "User's" in the Database field. Using this option, along with the physical and chemical properties for 1,4-dioxane shown in Table 1-1 of the final risk evaluation, a user is able to estimate the permeability coefficient referenced. • All inputs required to replicate the runs presented are shown in the Supplemental File [Consumer Exposure Assessment Model Input Parameters]. In that file, the gas phase mass transfer coefficient estimated and used within CEM 2.1 is shown as 3.2 m/hr. • The application of the Frasch and Bungle (2015) fraction absorbed estimation to chemicals not specified in the original source is an approach that has undergone peer review when CEM 2.1 was peer reviewed. This application is consistent with the dermal modeling conducted and reviewed in the other recently finalized solvent risk evaluations.
82	• In table 4-13 of the Draft Risk Evaluation, six dermal cancer slope factors range from 1.7e-4 to 6.7e-4 per mg/kg-d, depending on the data and assumptions used. In table 31 of the Supplemental Analysis, however, the three dermal cancer slope factors range from 1.2e-2 to 1.2e-1, indicating much higher cancer risks than previously estimated.	• POD derivation was beyond the of the Supplemental document. Some PODs changed in response to SACC and public comment. The final risk evaluation includes complete

	This begs the question: which prior determinations of no unreasonable risk are erroneous? The 2020 Supplemental Analysis does not acknowledge the underestimate or correct the risk determinations that appeared in the Draft Evaluation. Without explanation of the revised PODs, there can be little confidence that the new risk determinations are not erroneous, too.	documentation of POD derivation in Section 3.2.6. Revised occupational risk estimates based on these new PODs are in Section 4.2. The rationale for specific changes made since the draft in is articulated in above responses to SACC and public comments.
78	• There is some confusion in the text in Section 2.4.3.3 Consumer Exposure Modeling Approach as to what model was used for each scenario. Suggest revising the first sentence to read "Acute exposures via inhalation and acute and chronic dermal contact to consumer products were estimated using EPA's Consumer Exposure Model (CEM) Version 2.1…" "An older version of CEM, available within E-FAST 2014, was used to estimate chronic inhalation exposures…".	• EPA updated this paragraph with this clarification.