Exhibit A

Request for Reconsideration
Denka Performance Elastomer LLC

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

January 25, 2018

Robert Holden
Liskow & Lewis
One Shell Square
701 Poydras Street, Suite 5000
New Orleans, LA 70139

OFFICE OF
RESEARCH AND DEVELOPMENT

Dear Mr. Holden:

This letter is in response to the Request for Correction (RFC) received by the U.S. Environmental Protection Agency (EPA) on June 26, 2017, which was assigned RFC #17002 for tracking purposes. The letter was provided on behalf of Denka Performance Elastomer LLC (DPE). In the RFC letter, DPE states that the *Toxicological Review of Chloroprene (CAS No. 126-99-8) In Support of Summary Information on the Integrated Risk Information System (IRIS)*, disseminated by EPA's Office of Research and Development (ORD) in 2010 (referred to herein as the "IRIS chloroprene assessment"), does not reflect the "best available science" or "sound and objective scientific practices" and requests correction.

Summary of the Request

The DPE RFC requests the IRIS chloroprene assessment be corrected in three ways: 1) the EPA-derived inhalation unit risk (IUR) of 5 x 10^{-4} per ug/m^3 be replaced with a value derived by Ramboll Environ of 3.2 x 10^{-6} per ug/m^3, or withdrawn; 2) the EPA cancer classification of chloroprene as a "likely" human carcinogen be classified instead as a "suggestive" human carcinogen; and 3) the EPA derived Reference Concentration (RfC) be withdrawn pending further IRIS review. The RFC letter indicates, as an alternative, that the EPA immediately withdraw the IRIS IUR and RfC values pending further review.

To support the RFC, DPE provided a document "…organized into six sections: Section I demonstrates that the 2010 IRIS Review constitutes "information" "disseminated" to the public; Section II shows that the 2010 IRIS Review is subject to heightened information quality standards because it is influential scientific information; Section III explains how the 2010 IRIS Review fails to comply with the EPA Guidelines; Section IV shows how EPA's correction of the 2010 IRIS Review would benefit DPE, which has been harmed by its errors; Section V provides DPE's contact information; and Section VI sets forth the relief that DPE is seeking."

The EPA Response to DPE Request for Correction

In the Attachments to this response, EPA addresses the assertions and topics raised in Section III of the RFC as this section is relevant to the science evaluation represented in the IRIS chloroprene assessment under EPA's *Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility and Integrity of Information Disseminated by the Environmental Protection Agency (IQG).* The information and assertions in the other sections are either not in dispute or are not pertinent to the evaluation of science issues under the RFC.

Conclusion

The EPA, after careful review of the RFC submitted by DPE, has concluded that the underlying information and conclusions presented in the *Toxicological Review of Chloroprene (CAS No. 126-99-8) In Support of Summary Information on the Integrated Risk Information System (IRIS)* are consistent with the EPA's Information Quality Guidelines.

Your Right to Appeal

If you are dissatisfied with the response, you may submit a Request for Reconsideration (RFR) as described in EPA's Information Quality Guidelines. The EPA requests that any such RFR be submitted within 90 days of the date of the EPA's response. If you choose to submit a RFR, please send a written request to the EPA Information Quality Guidelines Processing Staff via mail (Information Quality Guidelines Processing Staff, Mail Code 2821T, USEPA, 1200 Pennsylvania Avenue, NW, Washington, DC 20460); or electronic mail (quality@epa.gov). If you submit a RFR, please reference the case number assigned to this original Request for Correction (RFC #17002). Additional information about how to submit an RFR is listed on the EPA Information Quality Guidelines website at http://epa.gov/quality/informationguidelines/index.html.

Sincerely,

Jennifer Orme-Zavaleta, Ph.D.
Principal Deputy Assistant Administrator for Science

Cc: Tina Bahadori, ScD ORD/NCEA Director
Stephen Fine, PhD, Acting Chief Information Officer
David Gray, EPA Region 6 Director of External Affairs
Vincia Holloman, Director of Enterprise Quality Management Division
Anne Idsal, JD, Region 6 Administrator
Kristina Thayer, ORD/NCEA IRIS Division Director
John Vandenberg, ORD/NCEA RTP Division Director

Attachment 1: U.S. EPA Response to the Denka Performance Elastomers (DPE) Request for Correction of the Toxicological Review of Chloroprene (CAS No. 126-99-8) In Support of Summary Information on the Integrated Risk Information System (IRIS)

Attachment 2: Systematic Review of Chloroprene [CASRN 126-99-80] Studies Published Since 2010 IRIS Assessment to Support Consideration of the Denka Request for Correction (RFC). January 2018. USEPA, ORD, NCEA-IRIS, Washington DC.

Attachment 1

U.S. EPA Response to the Denka Performance Elastomers (DPE) Request for Correction (RFC) of the *Toxicological Review of Chloroprene (CAS No. 126-99-8) In Support of Summary Information on the Integrated Risk Information System (IRIS)*

January, 2018

Integrated Risk Information System
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency

The Request

The Denka Performance Elastomers (DPE) Request for Correction (RFC) requests the IRIS chloroprene assessment be corrected in three ways: 1) the EPA-derived inhalation unit risk (IUR) of 5 x 10^{-4} per ug/m^3 be replaced with a value derived by Ramboll Environ of 3.2 x 10^{-6} per ug/m^3, or withdrawn; 2) the EPA cancer classification of chloroprene as a "likely" human carcinogen be classified instead as a "suggestive" human carcinogen; and 3) the EPA derived Reference Concentration (RfC) be withdrawn pending further IRIS review. The RFC letter indicates, as an alternative, that the EPA immediately withdraw the IRIS IUR and RfC values pending further review.

To support the RFC, DPE provided a document "…organized into six sections: Section I demonstrates that the 2010 IRIS Review constitutes "information" "disseminated" to the public; Section II shows that the 2010 IRIS Review is subject to heightened information quality standards because it is influential scientific information; Section III explains how the 2010 IRIS Review fails to comply with the EPA Guidelines; Section IV shows how EPA's correction of the 2010 IRIS Review would benefit DPE, which has been harmed by its errors; Section V provides DPE's contact information; and Section VI sets forth the relief that DPE is seeking."

Response

In this response, the EPA is addressing the assertions and topics raised in Section III of the RFC as this section is relevant to the science evaluation represented in the IRIS chloroprene assessment under EPA's *Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility and Integrity of Information Disseminated by the Environmental Protection Agency (IQG).*

In this response, the EPA is addressing the following topics as raised in the DPE RFC:

A. Epidemiological Evidence Shows No Increase in Cancers Among Workers Highly Exposed to Chloroprene
B. The IUR Does Not Reflect the Best Available Science or Sound and Objective Scientific Practices
    1. The IUR is Primarily Based on Data from the Female Mouse, Which is Uniquely Sensitive to Chloroprene Exposure
    2. The IUR Rests on the Unwarranted Assumption that Different Tumor Types are Statistically Independent
    3. The IUR Rests on the Assumption that Chloroprene Has A Mutagenic Mode of Action, But the Available Evidence Does Not Support that Assumption
    4. The IUR Must Be Corrected By Employing the PBPK Model to Sufficiently Account for Differences in Mice and Humans
    5. The Correct Chloroprene IUR is 156 Times Lower than the Chloroprene IUR Derived by EPA
C. EPA's IUR for Chloroprene is Drastically Higher Than IURs for Similar Chemicals
D. EPA's Classification of Chloroprene as "Likely to be Carcinogenic to Humans" Should Be Reviewed
E. EPA's Reference Concentration (RfC) for Chronic Inhalation Exposure Should Be Reviewed

A. Epidemiological Evidence Shows No Increase in Cancers Among Workers Highly Exposed to Chloroprene

This topic is related to point #2 of the DPE request that the IRIS chloroprene assessment be corrected, i.e., that "the EPA cancer classification of chloroprene as a "likely" human carcinogen be classified instead as a "suggestive" human carcinogen." In drawing the conclusion that chloroprene is a likely human carcinogen, information from epidemiological, toxicological, and mode of action studies were considered (see §§ 4.1, 4.2, 4.3, 4.5, and 4.7 of the IRIS chloroprene assessment). Specifically, the assessment clearly delineates in § 4.7.2 and Table 4-39 the evidence the descriptor "likely to be carcinogenic to humans" was based on, noting both the strengths and weaknesses of the evidence utilized. Drafts of the assessment document were reviewed by internal science experts within EPA, by science reviewers from other federal agencies, and by the White House, and it was externally peer reviewed by independent experts including opportunity for public comment. EPA notes that many of the topics and assertions raised by DPE in the RFC were considered by agency and external peer reviewers during assessment development and external peer review because DuPont (the former owner of the La Place Louisiana facility that currently produces chloroprene) provided extensive comments during the public comment period.

The EPA fully addressed the issues raised in the DPE RFC regarding the identification, evaluation and interpretation of epidemiological evidence during the development and publication of the IRIS chloroprene assessment (see § 4.1). The process for development of the IRIS chloroprene assessment is described in the Introduction to the assessment, and the evaluation of epidemiological evidence is described in Section 4: Hazard Identification. Appendix A of the IRIS chloroprene assessment includes the Summary of External Peer Review and Public Comments and Disposition.

The information presented in the IRIS chloroprene assessment meets the EPA IQC standards of objectivity and utility. The evaluation of the epidemiological evidence, and the consideration of multiple lines of evidence to draw the conclusion that chloroprene is a likely human carcinogen, were supported by the numerous agency review groups and was unanimously supported by the external peer review panel. Further, the following specific points were evaluated based on Charge Question 8 (Appendix A, pages A-10 to A-12) to the review panel which asked "Under the EPA's 2005 *Guidelines for Carcinogen Risk Assessment* (2005, 086237) the Agency concluded that chloroprene is likely to be carcinogenic to humans by all routes of exposure. Please comment on the cancer weight of evidence characterization. Is the cancer weight of evidence characterization scientifically justified"? Six (out of six total) peer reviewers commented that the characterization of chloroprene as "likely to be carcinogenic to humans" was appropriate and clearly justified based on the animal and genotoxicity data. Three reviewers commented that the animal data provided ample evidence of carcinogenesis in both sexes of two rodent species (mouse and rat) at multiple organ sites, many of which were distal to the point-of-contact. In fact, two reviewers further suggested that the strength of the epidemiological evidence was sufficient to change the descriptor to "carcinogenic to humans." No new scientific evidence was provided in the DPE RFC that would alter this conclusion.

B. The IUR Does Not Reflect the Best Available Science or Sound and Objective Scientific Practices

This topic is related to point #1 of the DPE request that the IRIS chloroprene assessment be corrected, i.e., that "the EPA derived inhalation unit risk (IUR) of 5×10^{-4} per ug/m^3 be replaced with a value derived by Ramboll Environ of 3.2×10^{-6} per ug/m^3, or withdrawn." Drafts of the EPA assessment

document were reviewed by internal science experts within EPA, by science reviewers from other federal agencies, and by the White House, and it was externally peer reviewed by independent experts including opportunity for public comment. EPA notes that many of the topics and assertions raised by DPE in the RFC were considered by agency and external peer reviewers during assessment development and external peer review because DuPont (the former owner of the La Place Louisiana facility that currently produces chloroprene) provided extensive comments during the public comment period.

The following 5 subtopics are addressed in turn.

1. *The IUR is Primarily Based on Data from the Female Mouse, Which is Uniquely Sensitive to Chloroprene Exposure*

The EPA fully addressed the issues raised in the DPE RFC regarding the interpretation of evidence of mouse tumor during the development and publication of the IRIS chloroprene assessment. The process for development of the IRIS chloroprene assessment is described in the Introduction to the assessment, and the evaluation of female mouse lung tumor data is described in various subsections of Section 4: Hazard Identification and 5: Dose-Response Assessment. Appendix A of the IRIS chloroprene assessment includes the Summary of External Peer Review and Public Comments and Disposition.

In accordance with the EPA Guidelines for Carcinogen Risk Assessment (2005), in the absence of data to the contrary, EPA utilizes the most sensitive species and sex in estimating cancer risk to humans, which in the case of chloroprene, is the female mouse. The RFC comment that female mice are uniquely sensitive to chloroprene exposure is based on observations of species and sex differences in studies of female and male mice, rats and hamsters. The RFC notes studies "…demonstrated that the female mouse is uniquely sensitive to chloroprene exposure…" and "these differences related to how various species metabolize chloroprene." To this point, Tables 3 and 4 of Yang et al (2012) report that metabolism varies between female and male mice, with Vmax approximately 5 times higher for male mice than for female mice, resulting in an over 5-fold higher internal lung dose metric in the male mice than the female mice at each concentration in the Yang et al (2012) PBPK model. This difference in the dose metric would be expected to produce differences in tumor response between female and male mice if there is a unique sensitivity due to sex differences. This is not the case, however, as the tumor responses in chloroprene-exposed female and male mice are nearly identical (26 and 8% [control], 56 and 57% [12.8 ppm], 72 and 68% [32 ppm], and 86 and 84% [80 ppm]); therefore, the RFC comment is unfounded. Further, it is notable, as stated in the IRIS assessment (see also below), that given the multiplicity of tumor sites observe in female mice across several 2-year bioassays, the IUR is based on tumors from multiple sites. See Attachment 2 for further discussion of pharmacokinetic studies.

The information presented in the IRIS chloroprene assessment meets the EPA IQC standards of objectivity and utility. The derivation of the IUR and the documentation describing this derivation were supported by the numerous review groups and the majority of the external peer review panel. No new scientific evidence was provided in the DPE RFC that would alter the interpretation and application of data from female mouse lung tumors in IUR derivation.

2. The IUR Rests on the Unwarranted Assumption that Different Tumor Types are Statistically Independent

The EPA fully addressed the issues raised in the DPE RFC regarding the interpretation and evaluation of evidence on multiple tumors resulting from exposure to chloroprene in toxicological studies during the development and publication of the IRIS chloroprene assessment (see § 5.4 of the IRIS chloroprene assessment). The process for development of the IRIS chloroprene assessment is described in the Introduction to the assessment, and the evaluation of epidemiological evidence is described in various subsections of Section 4: Hazard Identification and 5: Dose-Response Assessment. Appendix A of the IRIS chloroprene assessment includes the Summary of External Peer Review and Public Comments and Disposition.

The information presented in the IRIS chloroprene assessment meets the EPA IQC standards of objectivity and utility. As indicated in Sections 4 and 5 and Appendix A of the assessment, the identification, evaluation and interpretation of the evidence, including dose-response modeling of multiple tumors consistent with recommendations of the National Research Council (NRC, Science and Judgement in Risk Assessment, 1994), were considered in the derivation of the IUR. Of note, the NRC (1994) document based its recommendation of calculating aggregate carcinogenic potency on the statistical independence of chemical-induced tumors. The NRC conducted a statistical analysis to investigate the degree to which statistically significant correlations exist between tumors in standard National Toxicology Program (NTP) chronic bioassays. The investigation of the independence of tumor types included more than 60 mouse studies and concluded that "[l]ittle evidence was found of tumor-type correlation for most of the tumor-type pairs in control and treated mice…" (pages 230-231, § 11). The IRIS chloroprene assessment noted this NRC investigation in § 5.4.4 as a justification for the assumption of tumor-type independence, and cited the NRC's conclusion that "a general assumption of statistical independence of tumor-type occurrences within animals was not likely to introduce substantial error in assessing carcinogenic potency…". Therefore, while an analysis of statistical independence was not conducted with chloroprene-specific data, EPA's assumption of statistical independence is entirely consistent with the NRC's previous analysis and conclusions.

Further, the derivation of the IUR and the documentation describing this derivation were supported by the numerous review groups and the majority of the external peer review panel. Specifically Charge Question 11 (Appendix A, pages A-15 to A-16) to the review panel asked "Data on hemangiomas/hemangiosarcomas (in all organs) and tumors of the lung (bronchiolar/alveolar adenomas and carcinomas), forestomach, Harderian gland (adenomas and carcinomas), kidney (adenomas), skin and mesentery, mammary gland and liver in B6C3F1 mice were used to estimate the inhalation unit risk. Please comment on the scientific justification and transparency of this analysis. Has the modeling approach been appropriately conducted? Please identify and provide the rationale for any alternative approaches for the determination of the inhalation unit risk and discuss whether such approaches are preferred to EPA's approach." Four out of six reviewers specifically commented that the scientific justification of combining unit risks for all tumor types was scientifically justified and conducted. One of these reviewers also noted that basing the unit risk derivation on one tumor type would underestimate the carcinogenic potential of chloroprene. Two reviewers were silent on the matter, with one of these reviewers simply commenting that "[t]he derivation of the IUR could be made somewhat clearer in the text"). No new scientific evidence, including any statistical analyses, was provided in the DPE RFC that would alter the multitumor modeling used in derivation of the IUR.

3. The IUR Rests on the Assumption that Chloroprene Has A Mutagenic Mode of Action, But the Available Evidence Does Not Support that Assumption

The EPA fully addressed the issues raised in the DPE RFC regarding the interpretation of mode of action evidence from relevant studies during the development and publication of the IRIS chloroprene assessment. The process for development of the IRIS chloroprene assessment is described in the Introduction to the assessment, and the evaluation of epidemiological evidence is described in various subsections of Section 4.7.3: Mode-of-Action Information and 5.4.5: Application of Age-Dependent Adjustment Factors. Appendix A of the IRIS chloroprene assessment includes the Summary of External Peer Review and Public Comments and Disposition.

The information presented in the IRIS chloroprene assessment meets the EPA IQC standards of objectivity and utility. The identification, evaluation and interpretation of the mode of action evidence (§§ 4.5.2 and 4.73 of the IRIS chloroprene assessment) supports the conclusion that chloroprene acts via a mutagenic mode of action. Of note, the conclusions in the IRIS chloroprene assessment about the mode of action were supported by the numerous review groups and unanimously supported by the external peer review panel. Specifically, Charge Question 10 (Appendix A, page A-15) to the review panel asked "A mutagenic mode of carcinogenic action is proposed for chloroprene. Please comment on whether the weight of evidence supports this conclusion. Please comment on whether this determination is scientifically justified. Please comment on data available for chloroprene that may support an alternative mode(s) of action." The panel unanimously concluded that a mutagenic mode of carcinogenic action for chloroprene was appropriate based on the evidence that chloroprene metabolism operates via P450-mediated oxidation to a DNA-reactive epoxide metabolite, which is mutagenic in multiple strains of Salmonella, and the observation of K- and H-ras mutations in tumors obtained from mice exposed to chloroprene. One reviewer specifically noted that the proposed mode of action was consistent with other epoxide-forming carcinogens (i.e., 1,3-butadiene). Public comments were provided to the peer review panel (Dupont written comments and oral comments) that argued against a genotoxic mode of action and supported an alternative mode of action of cytotoxicity and regenerative proliferation. However, three peer reviewers commented that they were not aware of any scientific data that would support an alternative mode of action, with an additional reviewer commenting that while a mutagenic mode of action may not be the only mode of action, it was clearly one possibility. No new scientific evidence was provided in the DPE RFC that would alter this conclusion.

4. The IUR Must Be Corrected By Employing the PBPK Model to Sufficiently Account for Differences in Mice and Humans

The EPA addressed the issues raised in the DPE RFC regarding the application of a physiologically-based pharmacokinetic (PBPK) model in the derivation of the IUR. The process for development of the IRIS chloroprene assessment is described in the Introduction to the assessment, and the evaluation of PBPK modeling approaches is described in Sections 3.5 (Physiologically Based Toxicokinetic Models) and 5.4 (Cancer Assessment). EPA ultimately concluded that the PBPK model available at the time of the assessment was inadequate for calculation of internal dose metrics or interspecies dosimetry extrapolations for a number of reasons, including the lack of sensitivity analyses to indicate whether chamber loss of chloroprene was sensitive to metabolism, the fact that chamber data were fit by varying alveolar ventilation and cardiac output, and the lack of blood or tissue time-course concentration data

for model validation (§ 3.5, pages 20-21). Appendix A of the IRIS chloroprene assessment includes the Summary of External Peer Review and Public Comments and Disposition.

The DPE RFC identifies several new studies (Thomas et al. 2013, Yang et al, 2012, Allen et al, 2014) published since the development of the IRIS chloroprene assessment and asserts that these studies address critical model validation issues identified at that time as a barrier to the application of a PBPK model. With the identification of these studies, and the assertion that the new studies address knowledge gaps present at the time of the IRIS chloroprene assessment, the EPA conducted a systematic review of chloroprene studies published since the 2010 IRIS assessment for chloroprene. This analysis is included as Attachment 2 to this letter. In the EPA analysis, a transparent framework for study identification and evaluation, including PBPK models, is provided.

Seven studies were identified in the EPA systematic review process. The studies were evaluated for their potential impact on the IRIS chloroprene assessment and they represent novel approaches to analyzing existing epidemiologic, toxicological and toxicokinetic data available for chloroprene. As documented in Attachment 2, there are a number of serious concerns regarding the development and/or application of the PBPK models (Yang et al., 2012), including poor model optimization that resulted in underestimates of organ-specific metabolism (i.e., kidney) and unexplained inconsistencies between the internal dose metric and tumor response in male mice.

The U.S. EPA contacted the authors of Yang et al. (2012) to request the model code. Dr. Yang stated that the model code was no longer in her possession. Dr. Harvey Clewell shared several model code packages with the U.S. EPA, but these are poorly documented. In particular, these do not contain a 'readme' file explaining the function of each 'project' and script within the zip file packages. Hence it is not clear which package or files within them, if any, corresponds to the final publication. File dates in the package only extend to 2009, so it seems likely that these are only preliminary results, not the final set of code used by Dr. Yang. Supplemental material to the published article (Yang et al., 2012) provides examples of some of the code used to run the PBPK model, but does not contain a complete set of files sufficient to reproduce the results. In summary, the new studies on chloroprene do not provide a reasonable basis for reassessing the human health effects due to chronic exposures to chloroprene.

The information presented in the IRIS chloroprene assessment meets the EPA IQC standards of objectivity and utility. Drafts of the assessment document were reviewed by Internal experts within EPA, by interagency reviewers from other federal agencies, and by the White House, and externally peer reviewed by independent experts including opportunity for public comment. The derivation of the IUR and the documentation describing this derivation were supported by the numerous review groups and the external peer review panel (see above (Subtopic B.2 of this letter) regarding the external peer review panel's response to Charge Question 11 regarding the use of a multiple tumor approach). EPA fully considered the peer reviewer comments in its revision of the draft IRIS chloroprene assessment and ultimately decided the available PBPK model was not suitable (for reasons outlined above and in Attachment 2 to this letter). In the final IRIS chloroprene assessment, EPA provided more detailed discussions of all aspects of rat, mouse, and human metabolism of chloroprene. The revisions EPA made in response to external peer reviewer comments were thoroughly reviewed by interagency reviewers from other federal agencies and by the White House. Studies identified through a systematic review of the literature of research published since completion of the IRIS chloroprene assessment in 2010 do not provide a basis for re-evaluation of the IUR.

5. The Correct Chloroprene IUR is 156 Times Lower than the Chloroprene IUR Derived by EPA

As noted in response to subtopics A.1-4 above, the EPA fully addressed the issues raised in the DPE RFC regarding the interpretation of evidence and derivation of the IUR for chloroprene exposure by inhalation. The process for development of the IRIS chloroprene assessment is described in the Introduction to the assessment, and the evaluation of evidence is described in various subsections of the assessment. Appendix A of the IRIS chloroprene assessment includes the Summary of External Peer Review and Public Comments and Disposition.

The information presented in the IRIS chloroprene assessment meets the EPA IQC standards of objectivity and utility. As indicated in the assessment, the identification, evaluation and interpretation of the evidence, including dose-response modeling of multiple tumors consistent with recommendations of the NRC (§ 5.4 of the IRIS chloroprene assessment), were considered in the derivation of the IUR. The derivation of the IUR and the documentation describing this derivation were supported by the numerous review groups and the majority of the external peer review panel (see Charge Questions 9 and 11, pages A-14 to A-16). The DPE RFC included an unpublished analysis developed by Ramboll Environ that derived a cancer IUR based only on lung tumors in female mice through application of a PBPK model and the assumption that chloroprene does not have a mutagenic mode of action. As of this moment, EPA is not aware that the analysis proposed by Ramboll Environ has gone through (or is going through) independent peer review. Further, EPA followed the conclusions and recommendations of both the external peer review panel for the chloroprene assessment and the NRC (1994) in pursuing a multitumor modeling approach. Of particular note is the conclusion of the NRC that basing cancer analyses on simply the most potent tumor (in this case lung tumors in female mice) or the number of tumor bearing animals would bias the estimate of a chemical's true carcinogenic potency. As for EPA's conclusion of a genotoxic mode of action and DPE's alternative cytotoxicity/regenerative proliferation mode of action, the chloroprene external peer reviewers were unanimous in their support of a genotoxic mode of action. Further, even if a cytotoxicity/regenerative proliferation mode of action was active in addition to a genotoxic mode of action, the genotoxic mode of action would still drive EPA's cancer derivations in order to protect sensitive early lifestages. The information provided in the DPE RFC does not provide a basis for altering the documented and extensively peer reviewed IRIS chloroprene assessment derivation of the IUR.

C. <u>EPA's IUR for Chloroprene is Drastically Higher Than IURs for Similar Chemicals</u>

This topic is related to point #1 of the DPE request that the IRIS chloroprene assessment be corrected, i.e., that "the EPA derived inhalation unit risk (IUR) of 5×10^{-4} per ug/m^3 be replaced with a value derived by Ramboll Environ of 3.2×10^{-6} per ug/m^3, or withdrawn." As noted above, the EPA fully addressed the issues raised in the DPE RFC regarding the interpretation of evidence and derivation of the IUR for chloroprene exposure by inhalation. The process for development of the IRIS chloroprene assessment is described in the Introduction to the assessment, and the evaluation of evidence is described in various subsections of the assessment (§§ 4.5, 4.7.1, 4.7.3, 6.1 of the IRIS chloroprene assessment). Appendix A of the IRIS chloroprene assessment includes the Summary of External Peer Review and Public Comments and Disposition.

That the IUR differs among chemicals is not surprising as the mechanisms underlying potency of chemicals to produce cancer is known to vary depending on factors such as chemical structure, bioavailability, and metabolic profiles and capacities of tissue types and species. Derivation of an IUR

also depends on the nature of the available database and current understanding of the mode of action for a given chemical.

The IURs for other chemicals identified in the RFC, i.e., 1,3-butadiene, benzene and vinyl chloride, are different from that derived for chloroprene due to differences in the nature and extent of epidemiological and toxicological available for each chemical. These chemicals have structural similarities that support the EPA conclusion that chloroprene is likely to be a carcinogen in humans. As indicated in the IRIS chloroprene assessment, the identification, evaluation and interpretation of the evidence, including dose-response modeling of multiple tumors consistent with recommendations of the National Research Council, was considered in the derivation of the chloroprene IUR.

The information presented in the IRIS chloroprene assessment meets the EPA IQC standards of objectivity and utility. The derivation of the IUR and the documentation describing this derivation were supported by the numerous review groups and the majority of the external peer review panel (see Charge Questions 9 and 11, pages A-14 to A-16). No new scientific evidence was provided in the DPE RFC that would alter the derivation of the IUR.

D. EPA's Classification of Chloroprene as "Likely to be Carcinogenic to Humans" Should Be Reviewed

This topic is related to point #2 of the DPE request that the IRIS chloroprene assessment be corrected, i.e., that "the EPA cancer classification of chloroprene as a "likely" human carcinogen be classified instead as a "suggestive" human carcinogen." The EPA fully addressed the issues raised in the DPE RFC regarding the identification and evaluation of evidence of carcinogenicity during the development and publication of the IRIS chloroprene assessment. The process for development of the IRIS chloroprene assessment is described in the Introduction to the assessment, and the evaluation of evidence of carcinogenicity is described in Section 4: Hazard Identification. Appendix A of the IRIS chloroprene assessment includes the Summary of External Peer Review and Public Comments and Disposition. See EPA response A of this letter, above, for the External Peer Review panel's answer to Charge Question 8 (Appendix A, pages A-10 to A-12), in which the panel unanimously concluded that EPA's characterization of chloroprene as "likely to be carcinogenic to humans" was appropriate and clearly justified based on the animal and genotoxicity data.

The information presented in the IRIS chloroprene assessment meets the EPA IQC standards of objectivity and utility. In drawing the conclusion that chloroprene is a likely human carcinogen, information from epidemiological, toxicological, and mode of action studies were considered (see §§ 4.1, 4.2, 4.3, 4.5, and 4.7 of the IRIS chloroprene assessment). Specifically, the assessment clearly delineates in § 4.7.2 and Table 4-39 the evidence the descriptor "likely to be carcinogenic to humans" was based on, noting both the strengths and weaknesses of the evidence utilized. The evaluation of the carcinogenicity evidence and the conclusion that chloroprene is a likely human carcinogen were supported by the numerous review groups and the external peer review panel. No new scientific evidence was provided in the DPE RFC that would alter the conclusion in the IRIS assessment that chloroprene is appropriately classified as likely to be carcinogenic to humans.

E. EPA's Reference Concentration (RfC) for Chronic Inhalation Exposure Should Be Reviewed

As noted above, the EPA fully addressed the issues raised in the DPE RFC regarding the interpretation of evidence and derivation of the RfC for chloroprene exposure by inhalation (see §§ 4.2, 4.6, and 5.2 of

the IRIS chloroprene assessment). The process for development of the IRIS chloroprene assessment is described in the Introduction to the assessment, and the evaluation of evidence is described in various subsections of the assessment. Appendix A of the IRIS chloroprene assessment includes the Summary of External Peer Review and Public Comments and Disposition. Specifically, Section A.1.2.2 of the IRIS chloroprene assessment provides detailed responses of the external peer review panel on issues related to the suitability of the 2-year NTP study for RfC derivation (Charge Question 4, page A-4), choice of endpoints on which to basis the derivation of the RfC (Charge Question 5, page A-5), the use of Benchmark Dose modeling for RfC derivation (Charge Question 6, page A-7), and the rationale for the selection of the uncertainty factors for the derivation of the RfC (Charge Question 7, page A-9).

The information presented in the IRIS chloroprene assessment meets the EPA IQC standards of objectivity and utility. As indicated in the assessment, the identification, evaluation and interpretation of evidence of non-cancer effects resulting from chloroprene exposure was fully considered in the derivation of the RfC. The derivation of the RfC and the documentation describing this derivation were supported by the numerous review groups and the external peer review panel. No new scientific evidence was provided in the DPE RFC that would alter the development and derivation of the RfC for chloroprene.

Conclusion

The EPA, after careful review of the RFC submitted by DPE, has concluded that the underlying information and conclusions presented in the *Toxicological Review of Chloroprene (CAS No. 126-99-8) In Support of Summary Information on the Integrated Risk Information System (IRIS)* are consistent with the EPA's Information Quality Guidelines.

Attachment 2

Systematic Review of Chloroprene [CASRN 126-99-8] Studies Published Since 2010 IRIS Assessment to Support Consideration of the Denka Request for Correction (RFC)

January, 2018

Integrated Risk Information System
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency

DISCLAIMER

This document has been reviewed in accordance with U.S. Environmental Protection Agency policy and approved for publication.

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List of Abbreviations

ADME	absorption, distribution, metabolism, excretion
BMD	benchmark dose
BMI	body mass index
BW3/4	body-weight scaling to the 3/4 power
C1-MA-I	4-chloro-3-oxobutyl mercapturic acid
C1-MA-II	4-chloro-3-hydroxybutyl mercapturic acid
C1-MA-III	3-chloro-2-hydroxy-3-butenyl mercapturic acid
CASRN	Chemical Abstracts Service registry number
CD	β-chloroprene
CEO	(1-chloroethenyl)oxirane
DHBMA	3,4-dihydroxybutyl mercapturic acid
EPA	U.S. Environmental Protection Agency
HAWC	Health Assessment Workspace Collaborative
HERO	Health and Environmental Research Online
HOBMA	4-hydroxy-3-oxobutyl mercapturic acid
IISRP	International Institute of Synthetic Rubber Producers
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
Km	Michaelis-Menten constant
MA	mercapturic acid
MCMC	Markov-Chain Monte-Carlo
MHBMA	2-hydroxy-3-butenyl mercapturic acid
MOA	mode of action
NATA	National Air Toxics Assessment
PBPK	physiologically based pharmacokinetic
PECO	population, exposure, comparator, and outcome
PK	pharmacokinetic
PBPK	physiologically based pharmacokinetic
PKWG	Pharmacokinetic Working Group
RD	respiratory depression
RFC	Request for Correction
RfC	reference concentration
ROBINS-I	Risk of Bias in Nonrandomized Studies of interventions
SMR	standardized mortality ratio
Vmax	maximum expiratory flow

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1. BACKGROUND

The U.S. Environmental Protection Agency (EPA) completed the most recent Integrated Risk Information System (IRIS) assessment of chloroprene in 2010. In that assessment, the agency concluded that chloroprene is "likely to be carcinogenic to humans" through a mutagenic mode of action (MOA) and that the primary exposure route of concern is the inhalation pathway. Accordingly, the assessment included an inhalation unit risk (IUR), which is an estimate of inhaled cancer potency that can be used to estimate the risk of cancer that would be expected in a population exposed to chloroprene in the air every day over a lifetime.

In 2015, the Office of Air and Radiation released the most recent version of the National Air Toxics Assessment (NATA), a national analysis that combines information about the emissions of specific air pollutants to estimate the risk of developing a particular health effect in a population. This NATA was the first to incorporate information (i.e., the IUR) from the 2010 IRIS assessment for chloroprene, and it identified the census tract in the vicinity of the Denka Performance Elastomers (Denka) facility in La Place, LA (i.e., Lake Pontchartrain Works site) as having an elevated risk for cancer.

In response to this designation on August 9, 2016, scientists from Ramboll Environ, as representatives of Denka briefed Agency scientists on specific issues related to the chloroprene assessment and new studies published since the release of the 2010 IRIS assessment. The conclusion of the Ramboll Environ scientists was that their new analyses provided a sufficient reason for IRIS to re-evaluate the science surrounding chloroprene and to update the IRIS assessment and derive new risk values. Subsequently, on June 26, 2017, a Request for Correction (RFC) was received by EPA from Robert Holden, Attorney for Denka Performance Elastomer LLC.

The purpose of this systematic review is to provide information on EPA's evaluation of the recent studies identified by Ramboll Environ scientists as well as other studies published since the 2010 IRIS assessment. This information will be considered as part of developing the EPA response to specific statements in the RFC.

2. OVERALL OBJECTIVES, SPECIFIC AIMS, AND POPULATION, EXPOSURE, COMPARATOR, AND OUTCOME (PECO) FRAMEWORK

The overall objective of this systematic review is to identify and evaluate human health-related studies of chloroprene published since the 2010 IRIS assessment to determine whether any new evidence is likely to have an impact on the current IRIS toxicity values (2×10^{-2} mg/m^3 reference concentration [RfC] or 3×10^{-4} mg/m^3 IUR).

2.1. SPECIFIC AIMS

- Identify literature pertaining to the health hazards of chloroprene as outlined in the population, exposure, comparator, and outcome (PECO) framework.
- Conduct study evaluation (risk of bias and sensitivity) for individual epidemiological and animal toxicity studies.
- Conduct study evaluation (reporting quality and applicability) for individual (physiologically based pharmacokinetic [PBPK], absorption, distribution, metabolism, excretion [ADME]) studies and any mechanistic studies prioritized according to the PECO framework.
- Summarize findings and assess whether any new evidence is likely to have an impact on the current IRIS toxicity values (2×10^{-2} mg/m^3 RfC or 3×10^{-4} mg/m^3 IUR).

2.2. POPULATION, EXPOSURE, COMPARATOR, AND OUTCOME (PECO) FRAMEWORK

A PECO framework (see Table 1) is used as an aid to focus the research question(s), search terms, and inclusion/exclusion criteria in a systematic review.

Table 1. Population, exposure, comparator, and outcome (PECO) framework

PECO Element	Evidence
Population	**Human:** Any population (occupational, general population, including children and other sensitive population). The following study designs will be considered most informative: controlled exposure, cohort, case-control, or cross-sectional. Note: Case reports and case series will be tracked during study screening but are not the primary focus of this assessment.
	Animal: Nonhuman mammalian animal species (whole organism) of any life stage (including preconception, in utero, lactation, peripubertal, and adult stages).
	Nonmammalian model systems/in vitro/in silico: Nonmammalian model systems such as fish, amphibians, birds, invertebrates, e.g., *Caenorhabditis elegans*, etc.; human or animal cells, tissues, or biochemical reactions (e.g., ligand binding assays) with in vitro exposure regimens; bioinformatics pathways of disease analysis; or high throughput screening data. These studies are tagged during title and abstract/full-text screening and an iterative approach is used to prioritize for further analysis based on likelihood of the study to impact hazard conclusions or inform toxicity value derivation. Studies that do not undergo further analysis will be classified as PECO-relevant supplemental information.
Exposure	Exposure based on administered dose or concentration, biomonitoring data (e.g., urine, blood, or other specimens), environmental or occupational-setting measures (e.g., air, water levels), or job title or residence. The potential for human exposure to chloroprene primarily is via inhalation and perhaps by the dermal route. ADME and PBPK studies will also be included. Relevant forms are listed below: • Chloroprene (CASRN 126-99-8) or its metabolites, such as (1-chloroethenyl)oxirane or (2-chloro-2-ethenyl)oxirane • Mixture studies will be included if they include a chloroprene-only group (or one of its metabolites)
Comparator	**Human:** A comparison or reference population exposed to lower levels (or no exposure/exposure below detection levels) or to chloroprene for shorter periods of time.
	Animal and in vitro: Quantitative exposure vs. lower or no exposure with concurrent vehicle control group.
Outcome	• All health outcomes (both cancer and noncancer) • ADME and PBPK studies

CASRN = Chemical Abstract Service registry number.

3. METHODS

3.1. LITERATURE SEARCH STRATEGIES

The literature search focused on studies published since completion of the 2010 IRIS Agency Review Draft of the "Toxicological Review of Chloroprene," which covered the literature up through August 2010. The literature search focused only on the chemical name with no limitations on evidence streams (i.e., human, animal, in vitro, in silico) or health outcomes. The databases listed below were searched for the date range of January 1, 2010 through November 3, 2017 using EPA's Health and Environmental Research Online (HERO) database.[1] Full details of the search strategy for each database are presented in Appendix A.

- PubMed (National Library of Medicine)
- Web of Science (Thomson Reuters)
- ToxLine (National Library of Medicine)

3.2. SCREENING PROCESS

Two screeners independently conducted a title and abstract screen of the search results using DistillerSR[2] to identify study records that met the PECO eligibility criteria. In addition to adherence to PECO eligibility criteria, the exclusion criteria noted below were applied.

- Records pertinent to the PECO framework but not containing original data, such as reviews, editorials, or commentaries (the reference lists from these materials, however, are reviewed to identify PECO-relevant studies that may have been missed during database searching).
- Studies that have not been peer reviewed (e.g., conference abstracts, technical reports, theses/dissertations, working papers from research groups or committees, and white papers).

[1]EPA's HERO database provides access to the scientific literature behind EPA science assessments. The database includes more than 600,000 scientific references and data from the peer-reviewed literature used by EPA to develop its regulations.
[2]DistillerSR is a web-based systematic review software used to screen studies available at https://www.evidencepartners.com/products/distillersr-systematic-review-software.

Records that were not excluded based on title and abstract screening advanced to full-text review. Full-text copies of potentially relevant records identified from title and abstract screening were retrieved, stored in the HERO database, and independently assessed by two screeners to confirm eligibility according to the PECO eligibility criteria. At both title/abstract and full-text review levels, screening conflicts were resolved by discussion between the primary screeners with consultation by a third reviewer or technical advisor (if needed) to resolve any remaining disagreements. For citations with no abstract, the articles are initially screened based on all or some of the following: title relevance (title should indicate clear relevance), page numbers (articles two pages in length or less are assumed to be conference reports, editorials, or letters), and PubMed Medical Subject Headings. Assessment of eligibility status of any non-English publications was facilitated by native-language speakers at EPA or Google Translator. During title/abstract or full-text level screening, studies that were not directly relevant to the PECO framework, but could provide supporting information, were categorized (or "tagged") relative to the type of supporting information they provided (e.g., review, commentary, or letter with no original data; exposure only). Conflict resolution is not required during the screening process to identify supporting information (i.e., tagging by a single screener is sufficient to identify the study as potential supportive information).

3.3. STUDY EVALUATION

3.3.1. Epidemiology Studies (Risk of Bias and Sensitivity)

Key concerns for study evaluation were potential *bias* (factors that affect the magnitude and/or direction of an effect) and *insensitivity* (factors that limit the ability of a study to detect a true effect). Bias can result in false positives and negatives, while study sensitivity primarily focuses on the latter. Epidemiology studies were evaluated for bias and study sensitivity in the following domains: exposure measures, outcome measures, participant selection, potential confounding, analysis, selection of reported results, and study sensitivity (see Table 2).

Table 2. Domains of evaluation for epidemiology studies

Domain	Example information
Exposure measures	Source(s) of exposure (consumer products, occupational, an industrial accident) and source(s) of exposure data, blinding to outcome, level of detail for job history data, timing of measurements, type of biomarker(s), assay information, reliability data from repeated-measure studies, validation studies.
Outcome measures	Source of outcome (effect) measure, blinding to exposure status or level, method of measurement/classification, incident vs. prevalent disease, evidence from validation studies, prevalence (or distribution summary statistics for continuous measures).
Participant selection	Study design, timing and location of the study, and who was included? Recruitment process, exclusion and inclusion criteria, type of controls, total participants eligible, comparison between participants and nonparticipants (or followed and not followed), final analysis group. Does the study include potential vulnerable/susceptible groups or life stages?
Potential confounding	Background research on key confounders for specific populations or settings; participant characteristic data, by group; strategy/approach for consideration of potential confounding; strength of associations between exposure and potential confounders and between potential confounders and outcome; degree of exposure to the confounder in the population.
Analysis	Extent (and if applicable, treatment) of missing data for exposure, outcome, and confounders, approach to modeling, classification of exposure and outcome variables (continuous vs. categorical), testing of assumptions, sample size for specific analyses, relevant sensitivity analyses.
Selective reporting	Are results presented with adequate detail for all of the endpoints and exposure measures of interest? Are results presented for the full sample as well as for specified subgroups? Were stratified analyses (effect modification) motivated by a specific hypothesis?
Sensitivity	What are the ages of participants (e.g., not too young in studies of pubertal development)? What is the length of follow-up (for outcomes with long latency periods)? Choice of referent group, the exposure range, and level of exposure contrast between groups is critical (i.e., the extent to which the "unexposed group" is truly unexposed, and the prevalence of exposure in the group designated as "exposed").

The principles and framework for evaluating epidemiology studies are based on the Cochrane Risk of Bias in Nonrandomized Studies of interventions (ROBINS-I) (Sterne et al., 2016) but modified to address environmental and occupational exposures. The underlying philosophy of ROBINS-I is to describe attributes of an "ideal" study with respect to each of the evaluation domains (e.g., exposure measurement, outcome classification, etc.). Core and prompting questions are used to collect information to guide evaluation of each domain (see Appendix B). Core questions are considered key concepts while prompting questions help the reviewer focus on relevant details under each key domain. In addition, the expected direction of bias is explicitly considered and the impact of a potential bias is incorporated into the study evaluation process. Emphasis is placed on discerning a bias that would be expected to produce a substantive change in the effect estimate. For each study, in each domain question, reviewers reach a consensus on a value of **Good**, **Adequate**, **Poor**, or **Critically Deficient**. These terms are defined as follows:

- A **Good** classification is intended to represent a perfect or close-to-ideal study design and execution.
- An **Adequate** classification represents studies that may have some limitations, but the judgment is made that those limitations are not likely to be severe or to have a substantive impact on the results.
- A **Poor** classification denotes biases or deficiencies that could materially affect the interpretation of the study.
- A **Critically Deficient** classification would represent a flaw that is so serious that the study could not be used.

Emphasis was placed on discerning bias that could substantively change an effect estimate, considering also the expected direction of the bias. Low sensitivity is a bias towards the null. Once the evaluation domains have been classified, these ratings are combined to reach an overall study confidence classification of **High**, **Medium**, **Low**, or **Uninformative**. This classification is based on the classifications in the evaluation domains and will include consideration of the likely impact of the noted deficiencies in bias and sensitivity on the results. Studies with critical deficiencies in any evaluation domain will be classified as **Uninformative**. Other classifications will generally follow a sorting such that **High Confidence** studies would have the highest evaluation ("Good") for all or most domains; **Low Confidence** studies would have a "Poor" evaluation for one or more domains (unless the impact of the particular limitation[s] is judged to be unlikely to be severe), and **Medium Confidence** studies are in between these groups (e.g., most domains receiving a mid-level **Adequate** evaluation, with no limitations judged to be severe). Study evaluation is conducted with at least two reviewers independently assessing each study, with inclusion of a pilot phase to assess and refine the evaluation process, comparison of decisions and reaching consensus among reviewers, and when necessary, resolution of differences by discussion between the reviewers, the chemical assessment team, or technical experts.

3.3.2. Animal Studies (Risk of Bias and Sensitivity)

No animal bioassay studies were identified in the literature search. If present, they would have been evaluated using the animal study quality assessment approach outlined in Appendix C.

3.3.3. Pharmacokinetic (PK)/Physiologically Based Pharmacokinetic (PBPK) Reporting Quality and Applicability

Judgments on the suitability of a model are separated into two categories: scientific and technical (Table 3). The scientific criteria focus on whether the biology, chemistry, and other information available for chemical MOA(s) are justified (i.e., preferably with citations to support use) and represented by the model structure and equations. The scientific criteria are judged based

on information presented in the publication or report that describes the model and do not require evaluation of the computer code. Preliminary technical criteria include availability of the computer code and completeness of parameter listing and documentation. Studies that meet the preliminary scientific and technical criteria proceed to in-depth technical evaluation, which includes a thorough review and testing of the computational code and quality assurance of all parameters and data used in the modeling against original publications, reports, or sources. The in-depth technical and scientific analyses focus on the accurate implementation of the conceptual model in the computational code, use of scientifically supported and biologically consistent parameters in the model, accurate incorporation of parameters and data from their sources, and reproducibility of model results reported in journal publications and other documents. This approach stresses: (1) clarity in the documentation of model purpose, structure, and biological characterization; (2) validation of mathematical descriptions, parameter values, data, and computer implementation; and (3) evaluation of each plausible dose metric. The in-depth analysis is used to evaluate the potential value and cost of developing a new model or substantially revising an existing one.

Table 3. Criteria of evaluation for physiologically based pharmacokinetic (PBPK) models

Criteria	Example information
Scientific	Biological basis for the model is accurate. • Consistent with mechanisms that significantly impact dosimetry. • Predicts dose metrics expected to be relevant. • Applicable for relevant route(s) of exposure.
	Consideration of model fidelity to the biological system strengthens the scientific basis of the assessment relative to standard exposure-based extrapolation (default) approaches. • Can the model describe critical behavior, such as nonlinear kinetics in a relevant dose range, better than the default (i.e., $BW^{3/4}$ scaling)? • Is the available metric a better predictor of risk than default? Specifically, model-based metrics may correlate better than the applied doses with animal/human dose-response data. Degree of certainty in model predictions vs. default is also a factor. For example, while target tissue metrics are generally considered better than blood concentration metrics, lack of data to validate tissue predictions when blood data are available may lead to a choice of the latter.
	Principle of parsimony • Model complexity or biological scale, including number and parameterization of (sub)compartments (e.g., tissue or subcellular levels) should be commensurate with data available to identify parameters.
	Model describes existing PK data reasonably well, both in "shape" (matches curvature, inflection points, peak concentration time, etc.) and quantitatively (e.g., within a factor of 2−3).
	Model equations are consistent with biochemical understanding and biological plausibility.
Initial technical	Well-documented model code is readily available to EPA and public.
	Set of published parameters clearly identified, including origin/derivation.

Criteria	Example information
	Parameters do not vary unpredictably with dose (e.g., any dose dependence in absorption constants is predictable across the dose ranges relevant for animal and human modeling).
	Sensitivity and uncertainty analysis has been conducted for relevant exposure levels (local sensitivity analysis is sufficient, though global provides more information). • If a sensitivity analysis was not conducted, the PKWG would suggest this as additional work before using the model in the risk assessment. • A sound explanation should be provided when sensitivity of the dose metric to model parameters differs from what is reasonably expected based on experience.

$BW^{3/4}$= body-weight scaling to the 3/4 power; PK = pharmacokinetic; PKWG = Pharmacokinetic Working Group

3.4. DATA ABSTRACTION OF STUDY METHODS AND RESULTS

Information on study design and results from epidemiology and animal toxicology studies were extracted into the Health Assessment Workspace Collaborative (HAWC).[3] Key information from identified PK/PBPK models are summarized in tabular format. Data abstraction was performed by one member of the evaluation team and checked by one to two other members. Any discrepancies in data abstraction were resolved by discussion or consultation with a third member of the evaluation team.

[3]HAWC is a modular, content management system designed to store, display, and synthesize multiple data sources for the purpose of producing human health assessments of chemicals. This online application documents the overall workflow of developing an assessment, from literature search and systematic review, to data extraction (human epidemiology, animal bioassay, and in vitro assay), dose-response analysis, and finally, visualization to facilitate evidence synthesis.

4. RESULTS

4.1. LITERATURE SEARCH RESULTS

The database searches yielded 182 unique records, with no additional records identified from other sources. All studies published after the 2010 IRIS assessment that were cited in the request for correction were identified during database searching. Of the 182 studies identified, 165 were excluded during title and abstract screening, 17 were reviewed at the full-text level, and 9 studies were considered relevant to the PECO eligibility criteria (see Figure 1). Two of the nine studies were considered PECO-relevant "supplemental material" and not further evaluated, leaving seven studies evaluated for impact on 2010 IRIS assessment conclusions (see Table 4).

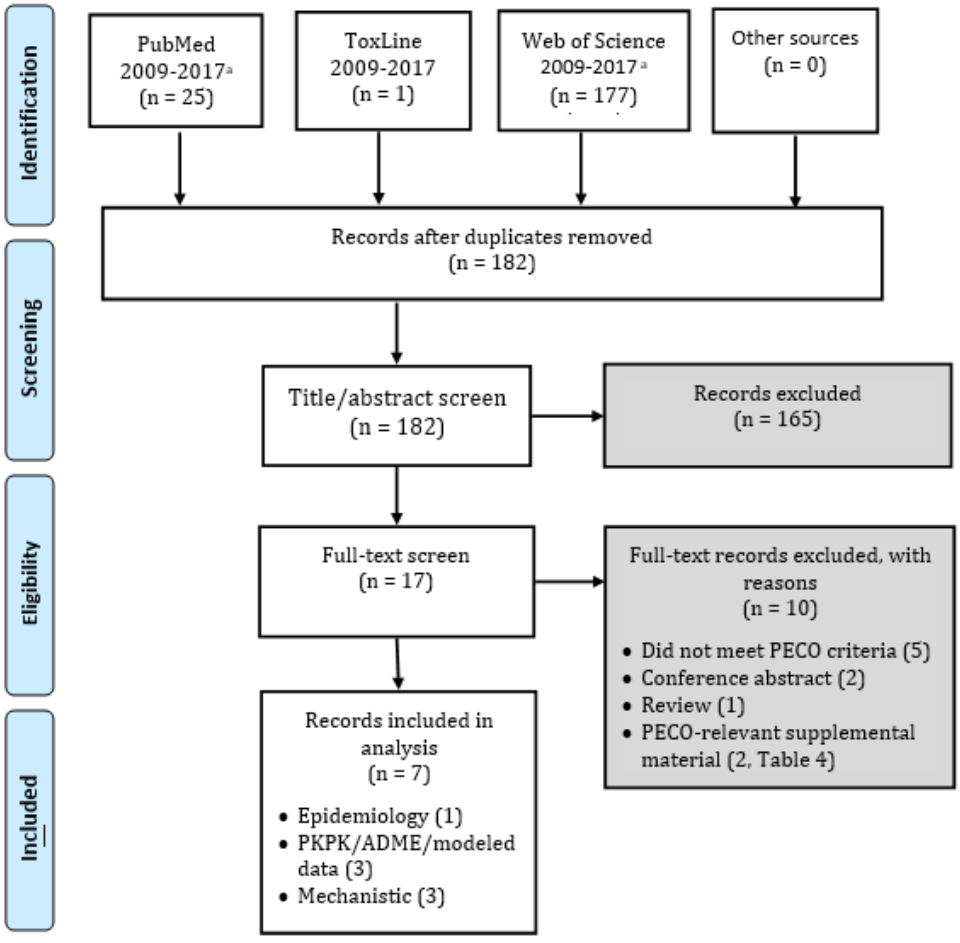

Figure 1. Study flow selection diagram.

Table 4. Included and population, exposure, comparator, and outcome (PECO)-relevant supplemental material studies

Epidemiology
1. Garcia, E; Hurley, S; Nelson, DO; Hertz, A; Reynolds, P. (2015). Hazardous air pollutants and breast cancer risk in California teachers: a cohort study. Environ Health 14: 14. http://dx.doi.org/10.1186/1476-069X-14-14.
PBPK, ADME, dose-response models
2. Allen, BC; Van Landingham, C; Yang, Y; Youk, AO; Marsh, GM; Esmen, N; Gentry, PR; Clewell, HJ; Himmelstein, MW. (2014). A constrained maximum likelihood approach to evaluate the impact of dose metric on cancer risk assessment: application to β-chloroprene. Regul Toxicol Pharmacol 70: 203-213. http://dx.doi.org/10.1016/j.yrtph.2014.07.001.
3. Eckert, E; Leng, G; Gries, W; Göen, T. (2013). Excretion of mercapturic acids in human urine after occupational exposure to 2-chloroprene. Arch Toxicol 87: 1095-1102. http://dx.doi.org/10.1007/s00204-013-1016-6.
4. Yang, Y; Himmelstein, MW; Clewell, HJ. (2012). Kinetic modeling of β-chloroprene metabolism: Probabilistic in vitro-in vivo extrapolation of metabolism in the lung, liver and kidneys of mice, rats and humans. Toxicol In Vitro 26: 1047-1055. http://dx.doi.org/10.1016/j.tiv.2012.04.004
Mechanistic
5. Guo, Y; Xing, Y. (2016). Weighted gene co-expression network analysis of pneumocytes under exposure to a carcinogenic dose of chloroprene. Life Sci 151: 339-347. http://dx.doi.org/10.1016/j.lfs.2016.02.074.
6. Thomas, RS; Himmelstein, MW; Clewell, HJ; Yang, Y; Healy, E; Black, MB; Andersen, ME. (2013). Cross-species transcriptomic analysis of mouse and rat lung exposed to chloroprene. Toxicol Sci 131: 629-640. http://dx.doi.org/10.1093/toxsci/kfs314.
7. Wadugu, BA; Ng, C; Bartley, BL; Rowe, RJ; Millard, JT. (2010). DNA interstrand cross-linking activity of (1-Chloroethenyl)oxirane, a metabolite of beta-chloroprene. Chem Res Toxicol 23: 235-239. http://dx.doi.org/10.1021/tx9003769.
PECO-relevant supplemental material
8. Gulec, C; Coban, N; Ozsait-Selcuk, B; Sirma-Ekmekci, S; Yildirim, O; Erginel-Unaltuna, N. (2017). Identification of potential target genes of ROR-alpha in THP1 and HUVEC cell lines. Exp Cell Res 353: 6-15. http://dx.doi.org/10.1016/j.yexcr.2017.02.028.
9. Rickert, A; Hartung, B; Kardel, B; Teloh, J; Daldrup, T. (2012). A fatal intoxication by chloroprene. Forensic Sci Int 215: 110-113. http://dx.doi.org/10.1016/j.forsciint.2011.03.029.

4.2. STUDY SUMMARIES AND ANALYSIS

4.2.1. Epidemiology Studies

Garcia, E; Hurley, S; Nelson, DO; Hertz, A; Reynolds, P. (2015). Hazardous air pollutants and breast cancer risk in California teachers: a cohort study. Environ Health 14: 14. http://dx.doi.org/10.1186/1476-069X-14-14.

Garcia et al. (2015), in a prospective cohort study of over 112,000 women in California with over 15 years of follow-up, examined the relationship between invasive breast cancer incidence and census tract levels of modeled concentrations of hazardous air pollutants shown to be mammary gland carcinogens. In models assessing the entire cohort, stratifying by age and adjusting for race, an increased risk of breast cancer from exposure to chloroprene was observed among higher quintiles of concentration (Quintiles 4 and 5) as compared to the referent group (Quintiles 1 through 3). Following additional adjustments for multiple comparisons, this relationship did not remain statistically significant. In a sub-group analysis stratifying by age and adjusting for race, a statistically significant association of increased breast cancer risk from exposure to chloroprene (Quintile 5) was found in the BMI $\geq$ 25 subgroup after adjusting for multiple comparisons. Discernable patterns of risk with increasing chloroprene exposure in susceptible population subsets are not clear in this study and may be due to chance. The overall results from this study should be interpreted with caution because exposure estimates were limited to modeled annual average ambient air concentrations from 2002 only and did not account for other exposure sources or routes other than inhalation. The results of this study do not impact the current IRIS hazard conclusions or toxicity values.

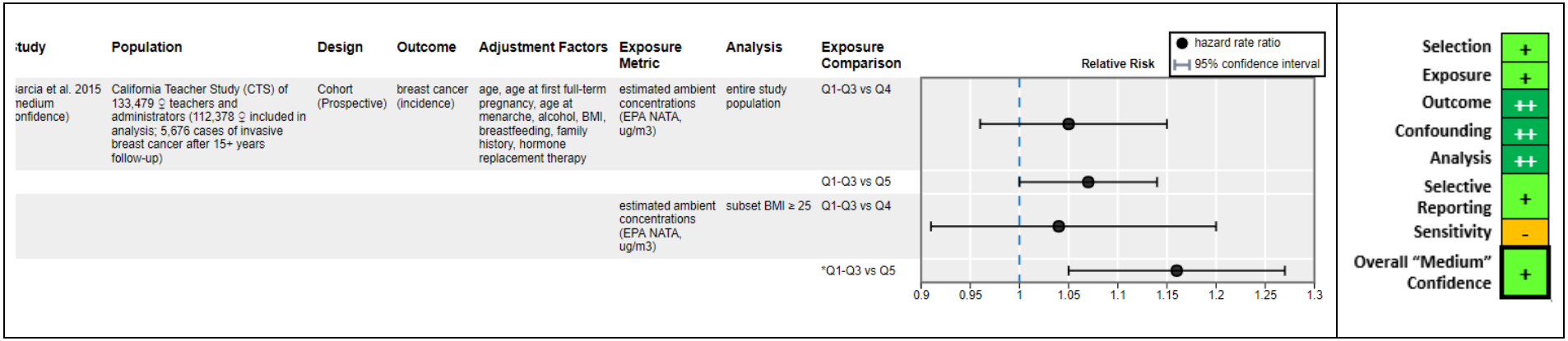

Figure 2. Chloroprene exposure and breast cancer incidence (Garcia et al., 2015).

CTS = California Teacher Study; Q2 = Quintile 2; Q3 = Quintile 3. The study authors collapsed the lower (Q2 and Q3 chloroprene quartiles) into the referent population (Q1) for HR comparison purposes when a larger portion of the study participants had same concentration value; Authors indicated that 71% of women in the CTS had exposure levels of "zero"; the minimum detectable value was ~1E-9 µg/m3 and maximum detectable value was ~1E-2 µg/m3. *The test for trend for chloroprene was statistically elevated at p<0.04. Click to see interactive data graphic and the risk of bias and sensitivity analysis in HAWC.

Thomas, RS; Himmelstein, MW; Clewell, HJ; Yang, Y; Healy, E; Black, MB; Andersen, ME. (2013). Cross-species transcriptomic analysis of mouse and rat lung exposed to chloroprene. Toxicol Sci 131: 629-640. http://dx.doi.org/10.1093/toxsci/kfs314.

Thomas et al. (2013) conducted a transcriptomic dose-response analysis to identify possible MOAs to explain differences in cross-species lung tumor rates between female B6C3F1/Crl mice and F344/NCrl rats. The animals were exposed for either 5 or 15 days at chloroprene levels of 0.3, 3, 13, or 90 ppm (mice) or 5, 30, 90, or 200 ppm (rats). Following exposure, the animals were sacrificed and their lungs evaluated for histopathology and gene expression via microarray analysis. Following the microarray analysis, a transcriptional benchmark dose (BMD) analysis was conducted on genes shown to be up- or downregulated via gene expression analysis of variance (ANOVA). Histopathology revealed minimal epithelial hyperplasia in most mice exposed to 90 ppm for 5 or 15 days, while no changes were noted in exposed rats. The total number of differentially expressed genes in mice and rats were observed to increase with increasing dose. Differences in gene expression were minimal between mice exposed for 5 or 15 days whereas differences were larger in exposed rats. No genes were differentially expressed at 5 or 30 ppm in rats exposed for 5 days, but rats exposed for 15 days had differentially expressed genes at doses ≥30 ppm. The total number of differentially expressed genes were much larger in rats exposed for 5 versus 15 days. Following transcriptional BMD analysis, the most sensitive pathways in mice were observed to have lower median BMD values (1.12−6.43 ppm) versus those in rats (8.04−29.00). Thomas et al. (2013) observed that induction of Cyp2e1, responsible for the initial oxidation of chloroprene, is similar in the lungs of female rats and mice for exposure levels up to 90 ppm; the mean activity increased by a factor of approximately 1.2- to 1.3-fold, but the change was not statistically significantly different. Cyp2e1 mRNA levels in female rats (exposed to 200 ppm chloroprene for either 5 or 15 days) were increased significantly 1.4-fold over controls; this exposure level was not evaluated in mice, but given the similarity in the trend for mice up to 90 ppm, it appears that mice would have responded similarly to rats at 200 ppm. Conversely, epoxide hydrolase mRNA was induced in mice at >13 ppm (5 or 15 days) and >3 ppm (5 days only), but not rats. Thomas et al. (2013) states "It is not yet known whether the changes in Cyp2e1 and Ephx1 mRNAs are translated into increased enzyme activity, but the ultimate result would be a narrowing of the cross-species differences in the activation-to-detoxification ranges."

The most notable limitation of the Thomas et al. (2013) study for the purpose of evaluating whole-body metabolism is that induction in the kidney and liver and induction in male mice were not evaluated. Thus, the data cannot be used to elucidate the impact of repeated exposure on either whole-body dosimetry or gender differences (or lack thereof) in tumor incidence. Another significant limitation is the length of exposure used. While the limitation of the exposure durations to 5 and 15 days may be useful for identifying affected gene pathways, it remains unclear how these up or down regulations in gene expression relate to possible MOAs of the effects due to chronic exposures to chloroprene as addressed in the 2010 assessment. Also notably missing from the

analysis is any data on humans. While characterizing possible explanations for interspecies differences seen between mice and rats, characterizing differences between mice and humans would have been more informative because mice served as the basis of the cancer analysis to estimate risk in exposed human populations. Thus, the results of this study do not impact the current IRIS toxicity values.

Guo, Y; Xing, Y. (2016). Weighted gene co-expression network analysis of pneumocytes under exposure to a carcinogenic dose of chloroprene. Life Sci 151: 339-347. http://dx.doi.org/10.1016/j.lfs.2016.02.074.

Guo and Xing (2016) used the transcriptional data for mice from Thomas et al. (2013) to perform a weighted gene-expression network analysis. Based on the in vivo bioassay results, mice in this study were separated into noncarcinogenic (0.3 and 2 ppm) and carcinogenic (13 and 90 ppm) groups for analysis. The microarray data were normalized and 2,434 genes were identified as being differentially expressed between the two groups; these differentially expressed genes were used to construct a weighted gene coexpression network wherein gene modules and hub genes were identified. A total of 21 gene modules were identified with 12 modules having significantly different gene expression patterns between the noncarcinogenic and carcinogenic groups. For each of these 12 gene modules, a hub gene (genes with high gene significance, module membership, and intramodular interconnectivity) was identified and its possible role in the origin of lung cancer was determined. Hub genes were found to play a role in inflammatory processes (*CFTR*), signaling pathways that can activate *Ras* (*HIP1*), metabolism of chloroprene (*EPHX1*), and control of cell division (*CCND2*). A total of 41 pathways were enriched in the gene modules of interest. Most notably, in the module related to steroid hormone stimulus, the mismatch repair pathway was the most enriched. It is plausible that this pathway is enriched in response to DNA damage induced by exposure to chloroprene. Consensus on approaches to quantitatively integrate these types of genomic results or on how to apply them to replace or even refine risk assessments are not yet currently available. As such, the results of this study do not impact the current IRIS toxicity values.

4.2.2. Physiologically Based Pharmacokinetic (PBPK), Absorption, Distribution, Metabolism, Excretion (ADME), Dose-Response Model

Yang, Y; Himmelstein, MW; Clewell, HJ. (2012). Kinetic modeling of β-chloroprene metabolism: Probabilistic in vitro-in vivo extrapolation of metabolism in the lung, liver and kidneys of mice, rats and humans. Toxicol In Vitro 26: 1047-1055. http://dx.doi.org/10.1016/j.tiv.2012.04.004.

Yang et al. (2012) presents the results of the refinement of an existing deterministic PBPK model and the development of a new probabilistic PBPK model (see Table 5). Upon review, there are many apparent concerns about the results presented in this study. These concerns are outlined in Table 6, and are separated into two categories: technical and scientific. These assessments were made based upon the materials available in Yang et al. (2012), and comments submitted to *Docket ID: EPA-HQ-ORD-2009-0217.*

Table 5. Pharmacokinetic (PK)/Physiologically Based Pharmacokinetic (PBPK) model descriptive summary of Yang et al. (2012)

Author	Yang et al. (2012)			
Contact Email	yyang@thehamner.org			
Contact Phone	Tel.: +1 919 558 1310; fax: +1 919 558 1300			
Sponsor	DuPont			
Model Summary				
Species	Mice, rats, humans			
Strain	B6C3F1 mice, F344/*N* rats			
Sex	M/F			
Life-Stage	Adult			
Exposure Routes	Inhalation			
Tissue Dosimetry	Lung	Liver	Kidneys	
Model Evaluation				
Language	ACSL 11.8.4			
Code Available:	Sample scripts available in supplemental material. Requests made for full model code. Final in vivo model code should be available.		Effort to recreate model	Significant effort without code
Code Received:	Code for in vitro model received, appears to be complete workspaces; some in vivo model code files received, but they are likely not final. Availability of scripts and in vivo data uncertain.		Migration to new PBPK platform (e.g., R/MCSim)	Unknown effort
Structure Evaluated	Yes			
Math Evaluated	Partially			
Code Evaluated	No			
Available PK Data	Yes (in vitro headspace concentrations)			

F = female; M = male.

Table 6. Technical and scientific evaluation of the Yang et al. (2012) model and analysis

Criteria type and notes	Potential impact on dose-response analysis
Technical (available code): All data and model codes from the Yang et al. (2012) publication are not published or publicly available. PBPK code is necessary for a quality assurance and quality control review by EPA. As a result, EPA cannot evaluate the internal validity of the Yang et al. (2012) PBPK modeling methods or results, or results that are dependent on this model [i.e., Allen et al. (2014)]. Furthermore, code must be translated to a different platform given the discontinuation of acslX software.	Unknown
Scientific (biological basis) and technical (parameters): Female mouse lung metabolism and internal doses in Yang et al. (2012) are not consistent with results for male mice. V_{max} is approximately 5 times higher for male mice than for female mice, yet the tumor response is similar. This has implications for biological basis for the site-specific dose-response, and parameterization of extra-hepatic metabolism (more details provided in subsection below). Also, lung metabolism does not account for tumor responses at other sites, which also need to be incorporated into a risk assessment.	An unknown but major impact due to the importance of the proposed lung internal dose metric. Further evaluation needed if whole-body metabolism is used as a dose metric.
Scientific (model fidelity) and technical (parameters): Female mouse liver and kidney metabolism may be underestimated in Yang et al. (2012). For liver metabolism, this is apparent on the log-scale for predictions of chloroprene headspace concentration data provided in Figure 2b of Yang et al. (2012), and Figures 5 and 25 of Study IISRP-17520-1388 (submitted to EPA-HQ-ORD-2009-0217). The underestimation occurs for both the point estimate results and the Monte Carlo results. Also, because the molecular form of enzymes does not vary between tissues within an individual, or males and females of a species, the K_m for metabolism should be likewise constant across tissues and between sexes.	By mass balance, the error would lead to increased mouse lung metabolism. Increasing mouse internal lung dose would lead to an increased human equivalent concentration if solely applying the lung dose metric (under-estimating human risk). If whole-body metabolism is used to evaluate tumor dose-response in various sites, the impact may be minimal.
Technical (parameters): Possible errors in model optimization for kidney metabolism. Female mouse kidney metabolism approaches zero in MCMC optimization. Parameterization of extra-hepatic metabolism may not be correct (more details provided in subsection below).	

Table 6. Technical and scientific evaluation of the Yang et al. (2012) model and analysis (continued)

Criteria type and notes	Potential impact on dose-response analysis
Technical (MCMC/statistics): likely underestimation of uncertainty, overestimation of significance of differences in parameters between species and sexes: The calculation of likelihood used in the MCMC analysis appears to assume that serially collected samples from each incubation (experimental unit) are treated as independent (i.e., if 20 time points were collected, these are treated as 20 independent samples). But if only a single incubation is conducted, with serial sampling of the headspace, the actual *n* is 1, and the likelihood calculation needs to account for the autocorrelation among repeated measures from a single experimental unit.	Mean parameter values from the MCMC analysis may still be considered sufficient for evaluation of dose-response, but nominal information on the degree of variance or significance of differences between male and female mice, for example, will not be considered. Information from the human microsomal incubations is not sufficient to evaluate interindividual variability.
Technical: model validation vs. in vivo data. The model's ability to reproduce in-vivo PK data [i.e., from Himmelstein et al. (2004a)] has not been evaluated. Of concern is that Himmelstein et al. (2004a) had to reduce alveolar ventilation and total blood flow values predicted from the in vitro data by 50% to match the in vivo PK data presented there. Mice are well known to suppress respiration (RD) and cardiac output in response to irritant gases. However, this response would be dose dependent. A search for RD data for chloroprene in mice was unsuccessful.	Unknown impact on risk predictions. Reductions in ventilation and blood flow needed to match in vivo PK data should assumed to also apply to bioassay conditions, barring data that the response is not chronic. A non-dose-dependent reduction of 50% (i.e., at all exposure levels) may be acceptable. Reduction would only be assumed to occur during periods of exposure.

IISRP = International Institute of Synthetic Rubber Producers; K_m = Michaelis-Menten constant; MCMC = Markov-Chain Monte-Carlo; RD = respiratory depression; V_{max} = maximum expiratory flow.

Other observations regarding Yang et al. (2012) specific to ADME, internal dose, and model/data fitting

Tables 3 and 4 of Yang et al. (2012) report the lung V_{max} to be approximately five times higher for male mice than for female mice. Not surprisingly, the male mouse internal lung dose metric is over fivefold higher than the female mouse at each exposure concentration [Table 5 of Yang et al. (2012)]. However, the tumor profiles between male and female mice are very similar: 26 and 8% (control), 56 and 57% (12.8 ppm), 72 and 68% (32 ppm), and 86 and 84% (80 ppm) (NTP, 1998). Because the fundamental premise of this series of papers is that mouse lung tumors may not be relevant to humans given the large differences in lung metabolism, the reported differences in the internal dose metrics between male mice and female mice should have been explained by the authors. If tumor response can be better explained by using internal dose vs. external concentration, it is unclear how such large differences in metabolism do not translate to differences in tumor incidence. The difference of internal dose between male and female mice is similar to that between female mice and humans [Table 5 of Yang et al. (2012)]. The difference between male and

female mouse internal dose metrics (male/female value) was 5.6-, 5.7-, and 5.4-fold for 12.8, 32, and 80 ppm, respectively. The difference between female mice and humans (female mice/human value) was 7.4, 4.8, and 2.5 at those same doses. The subsequent dose-response analysis by Allen et al. (2014) only incorporates female mouse data, and no rationale for the omission of male mouse data are provided. It cannot be determined whether this discrepancy reflects on the usability or validity of the model because it is possible that site-specific metabolism truly differs substantially between male mice and female mice. However, the discrepancy indicates that the site-specific dose metric may not be appropriate for dose-response modeling and animal-to-human extrapolation.

There are also inconsistencies in the kidney metabolic rates. Anomalies are apparent in the output distributions of the metabolic parameters V_{max} and Michaelis-Menten constant (K_m) for female mice [Figure S6 of Yang et al. (2012) supplementary materials, and Figure 20 of the International Institute of Synthetic Rubber Producers (IISRP)-17520-1388 study]. Unlike for male mice, the probability samples cluster around zero for female mice. The underestimation only occurs for the Monte Carlo results, and the difference between point estimates and Monte Carlo estimates (which are a factor of 10 lower) is attributed only to "background loss rate." It is possible that there was an error in the Markov-Chain Monte-Carlo (MCMC) optimization (i.e., the prior distribution failed to properly incorporate in vitro data, which indicate that kidney metabolism is not zero), and that kidney metabolism is greatly underpredicted in female mice. More reasonable results may have been obtained under the assumption that K_m for Cyp2e1 does not vary between tissues or between males and females (i.e., that only the V_{max} varies between tissues and sexes). To implement this assumption under Bayesian analysis, a hierarchical approach is required to account for the commonality of the K_m within a species. At a minimum, the K_m estimated from the liver data for one sex should be assumed to apply and treated as a fixed constant when evaluating data from the other sex and other tissues.

The model has not been evaluated for its ability to predict in vivo PK data (i.e., there has been no validation of the model). If reductions in respiration rate and cardiac output (total blood flow) are required to match the in vivo data, similar to results of Himmelstein et al. (2004a), then these may be attributed to respiratory depression (RD) which is a response that occurs particularly in mice from exposure to irritant gases. However, such a response would be expected to be dose dependent (lower RD at lower exposure levels). Further, barring data which show that it is not a persistent response, the response should be assumed to also occur during bioassay exposures, but only during periods of exposure.

Other in vivo or in vitro data sets may need to be evaluated further to test model fidelity or validate model parameters. In the chloroprene docket is a report in which blood chloroprene was measured in mice following single (6-hour) and repeated (5- or 15-day) inhalation exposures. Chloroprene blood levels were higher following single exposures, which was postulated to be because of higher minute volume due to stress. The authors conclude that this blood data is suitable for validation of a PBPK model, but it is unclear whether the data were used for the

validation of the PBPK model in Yang et al. (2012). The report did not investigate chloroprene levels in the organs of interest (namely the lungs, liver, or kidneys).

The metabolic data used to parameterize both the deterministic and probabilistic PBPK models were generated via in vitro headspace experiments where chloroprene was added to closed vials with lung, liver, or kidney microsomal preparations and the disappearance of chloroprene from the vial headspace was measured. Microsomes are derived from the endoplasmic reticulum that contain Phase I and II metabolizing enzymes; microsomes are not present in living cells and are not capable of transcribing mRNA. Thomas et al. (2013) stated that induction of metabolizing enzymes appears to differ between rats and mice, based on data in female rats and mice. However, while Cyp2e1 mRNA levels in female rats (exposed to 200 ppm chloroprene for either 5 or 15 days) were significantly increased over controls, this exposure level was not evaluated in mice. At 90 ppm, female mice and rats had similar levels of Cyp2e1 induction, though not statistically significant vs. controls. Conversely, epoxide hydrolase mRNA was induced in mice at >13 ppm (5 or 15 days) and >3 ppm (5 days only), but not rats. The lack of Cy2e1 induction in the female mouse lung from exposure to 90 ppm chloroprene is supported by an unpublished report submitted to the chloroprene docket (*EPA-HQ-ORD-2009-0217-0009*, report IISRP-12828-1406). This report stated that, "after 15 days of inhalation exposure to β-Chloroprene, no dose-dependent alterations were observed in total CYP content or CYP 1A2, 2B1/2, 2E1, 3A2 or 4A1/2/3 content." Thomas et al. (2013) stated "It is not yet known whether the changes in Cyp2e1 [in rat] and Ephx1 [in mice] mRNAs are translated into increased enzyme activity, but the ultimate result would be a narrowing of the cross-species differences in the activation-to-detoxification ranges." Further evaluation of data is needed to determine the impact (if any) induction would have in humans at environmentally relevant concentrations.

More significantly, data explicitly evaluating metabolic induction in the liver or kidney of female mice or rats, or in any tissue of male mice or rats, are not available. Thus, the possible impact of induction on whole-body metabolism or kinetics in these species, or any difference between males and females, is unknown. PK data submitted to *Docket ID: EPA-HQ-ORD-2009-0217* show a 5.4-fold decrease in chloroprene blood concentration after 15 days of exposure to 13 ppm chloroprene in female mice and approximately 2-fold reductions after 15 days of exposure to 32 and 90 ppm, indicating significant whole-body metabolic induction at these exposure levels. However, if tumor risk is assumed to be proportional to the rate of chloroprene oxidation, the failure to account for this induction in the model is likely to over-estimate the cancer slope factor (i.e., underestimate the dose [rate of metabolism] associated with a particular tumor response). Thus, this inadequacy in the model, under the proposed model application, would result in an error on the side of caution.

Eckert, E; Leng, G; Gries, W; Göen, T. (2013). Excretion of mercapturic acids in human urine after occupational exposure to 2-chloroprene. Arch Toxicol 87: 1095-1102. http://dx.doi.org/10.1007/s00204-013-1016-6. (see Table 7)

Table 7. Absorption, distribution, metabolism, excretion (ADME) inventory/summary of Eckert et al. (2013)

Subjects	14 occupationally exposed individuals (males aged 25–57, median age 43), 30 individuals without occupational exposure (14 males, 16 females, aged 21–63, median age 30). Half of participants in both groups stated as smokers.		
Route	Dermal	**Duration**	N/A
Analyte(s)	C1-MA-I, C1-MA-III, MHBMA, HOBMA, DHBMA	**Matrices**	Urine
Exposure	Human biomonitoring pilot study. Significant dermal exposure assumed by the occupational hygienist of the plant. 2-Chloroprene measured in workplace air at <0.1 ppm, and therefore inhalation exposure was assumed negligible.		
Notes	• Elevated levels of the mercapturic acids C1-MA-III, MHBMA, HOBMA, and DHBMA were found in the urine samples of the exposed group. • C1-MA-I and C1-MA-II were not detected in any of the samples. • HOBMA and DHBMA were found in all analyzed urine samples.		

C1-MA-I = 4-chloro-3-oxobutyl MA; C1-MA-II = 4-chloro-3-hydroxybutyl mercapturic acid; C1-MA-III = 3-chloro-2-hydroxy-3-butenyl MA; DHBMA = 3,4-dihydroxybutyl MA; HOBMA = 4-hydroxy-3-oxobutyl MA; MA = mercapturic acid; MHBMA = 2-hydroxy-3-butenyl MA.

Allen, BC; Van Landingham, C; Yang, Y; Youk, AO; Marsh, GM; Esmen, N; Gentry, PR; Clewell, HJ; Himmelstein, MW. (2014). A constrained maximum likelihood approach to evaluate the impact of dose metric on cancer risk assessment: application to β-chloroprene. Regul Toxicol Pharmacol 70: 203-213. http://dx.doi.org/10.1016/j.yrtph.2014.07.001.

The methodology of Allen et al. (2014) has potential for reconciling dose-response relationships from humans and animals when it is not feasible to consider both data types on compatible dose and response scales. However, the reported chloroprene analysis did not use the hazard identification conclusions and dose-response approaches that the 2010 IRIS assessment relied on, so not surprisingly, it estimated a different inhalation unit risk for respiratory cancer than the IRIS assessment. In addition, the use of the PBPK metrics of Yang et al. (2012) for both humans and mice as critical inputs had an unclear impact, owing to the unexplained different rates of chloroprene metabolism in the lung between female and male mice and the unknown impact on projected human internal dose.

The primary difference concerns the human response data for respiratory cancer. The Allen et al. (2014) analysis was based solely on the standardized mortality ratios (SMRs) with external comparison (using U.S. respiratory cancer rates) from the epidemiological study by Marsh et al. (2007). In general, analyses based on internal controls are considered more valid and relevant given concerns including biases such as the healthy worker and healthy worker survivor effects.

Therefore, these SMRs may represent biased estimates, so the slope of zero for the Louisville cohort likely underestimated the magnitude of human responses.

Although there was insufficient support for dose-response estimation, EPA concluded in the 2010 assessment that there was an association of respiratory cancer with increasing chloroprene exposure. The most compelling evidence in the Marsh et al. (2007) paper was the consistent associations, using internal controls, in every upper cumulative exposure quartiles (3 and 4) in the other three plants (odds ratio [OR] range: 1.9–2.9), as well as ORs in excess of 1.0 for low-level exposures in two out of three plants for Quartile 2. Additionally, the cumulative exposure for the Louisville referent group (<4.747 ppm*year) overlapped the exposures in 2nd quartile for the Maydown plant and the 2nd and 3rd quartiles for the Pontchartrain and Grenoble plants. EPA's interpretation of the human evidence was supported by the external peer-review panel; therefore, the choice of the Louisville cohort alone for the Allen et al. (2014) analysis is curious. Given the associations seen in the Maydown, Pontchartrain, and Grenoble cohorts among participants with low exposure levels, the reference choice for the Louisville cohort could attenuate the ability to detect associations at low exposure levels. This would lead to an underestimated slope for the association between chloroprene exposure and lung cancer in that cohort and thus lead to an underestimate of the IUR using the approach of Allen et al. (2014) when combining animal and human data.

Another difference in hazard identification conclusions between the Allen et al. (2014) and the 2010 IRIS assessment concerns multiple tumors observed in mice (and rats), and less sufficient evidence in humans to rule out this possibility. Concerning dose-response approaches, Allen et al. (2014) used a dose-response model that ignored data for decreased time to death with tumor in the mice. Although the human evidence did not support a model including this factor, earlier appearance of tumors was noted in several human studies. Both considerations contributed to a lower potency estimate in mice in the Allen et al. (2014) analysis.

Allen et al. (2014) omitted key information that would clarify applicability of the analysis. First, additional specifics of the dose-response point that both models were constrained to fit would have facilitated a better understanding of the analysis. That is, the cumulative human exposure (either in ppm-years or μmole of metabolite/g lung/day*years) corresponding to the daily PBPK dose of 0.00352 μmole of metabolite/g lung/day was not provided, nor was the response (or range of responses in the uncertainty analysis) estimated at that exposure point.

A second point of needed clarification concerns the final ~1,000-fold range of slope factors, which apparently reflects an uncertainty analysis that only considered the impact of assignments of chloroprene exposures in the Louisville cohort. Without information to clarify what was done, the "maximum-likelihood estimate" within this range then appears to be the slope factor estimate associated with the highest maximum-likelihood combined model fit among all maximum-likelihood estimates from 1,500 different characterizations of the Louisville exposure data. Therefore, both limits of this range, as well as the central tendency estimate, are likely

underestimated by considering only dose-response inputs that minimize estimates of human and animal potency, as opposed to considering the full range of interpretations consistent with the available data. Note: The EPA inhalation unit risk is an upper bound and not directly comparable to a maximum-likelihood estimate.

4.2.3. Carcinogenicity and Mode-of-Action (MOA) Considerations

In their comments on the chloroprene assessment, Ramboll Environ scientists questioned the scientific support for a genotoxic MOA for chloroprene, and instead proposed an alternative MOA involving hyperplasia, induced cell proliferation, and increased expression of pre-existing mutations. The 2010 assessment does not discount the possibility of additional carcinogenic MOAs, and even acknowledges that alternative MOAs may be present at high doses given the decrease in K-ras A to T transversions seen at high doses (i.e., 80 ppm). However, the evidence presented in the 2010 IRIS assessment clearly supports that genotoxicity is a possible MOA. Ramboll Environ scientists note that A to T transversions have been observed in spontaneous mouse lung tumors, but this particular transversion (CAA → CTA at codon 61) was not observed in any historical National Toxicology Program controls, thus decreasing the chance that chloroprene exposure could be increasing the expression of pre-existing mutations. Further, the proposed genotoxic MOA for chloroprene was unanimously supported by the external peer-review committee that reviewed the assessment.

Also, interestingly, most of the studies on which Ramboll Environ scientists cite to support their proposed application of the PBPK model also conclude or report that chloroprene may be operative via a mutagenic MOA. For example, the three Himmelstein toxicokinetic papers all make statements in their introductions regarding the mutagenicity of chloroprene. Himmelstein et al. (2001a) and Himmelstein et al. (2004b) stated that in some tests, but not others, chloroprene appears to be genotoxic. Himmelstein et al. (2004a) stated more strongly that "[t]he mechanistic steps by which CD [β-chloroprene] exposure leads to rodent tumors, while not understood fully, strongly suggest a genotoxic mode of action." Himmelstein et al. (2001b) tested the mutagenicity and clastogenicity of (1-chloroethenyl)oxirane and concluded that "results suggested that CEO [(1-chloroethenyl)oxirane]-induced mutagenicity, but not clastogenicity, may contributed to CD-induced carcinogenicity." The three papers under current consideration (Allen et al., 2014; Thomas et al., 2013; Yang et al., 2012) also made strong statements regarding chloroprene's mutagenicity:

Thomas et al. (2013)—"[t]he current hypothesized mode of action for chloroprene involves bioactivation to a mutagenic metabolite, leading to DNA damage and increased tumors."

Yang et al. (2012)—"[o]ne reactive intermediate formed is the epoxide (1-chloroethenyl)oxirane which was mutagenic in the Ames assay, but not clastogenic at cytotoxic concentrations in vivo. This epoxide also shows reactivity with DNA in vitro and is a potential cross-linking agent."

Allen et al. (2014)—"[t]he initial step in metabolism is oxidation forming a stable epoxide, (1-chloroethenyl)oxirane, a genotoxicant that might be involved in the observed carcinogenicity in animals."

5. CONCLUSIONS

5.1. IMPACT OF NEW LITERATURE ON 2010 INTEGRATED RISK INFORMATION SYSTEM (IRIS) CONCLUSIONS

The seven studies evaluated above represent novel approaches to analyzing existing epidemiologic, toxicological, and toxicokinetic data available for chloroprene. However, as is evident in the discussions of those studies, it is the opinion of the EPA that these studies do not present sufficient evidence or provide adequate rationale for re-evaluating the entire chloroprene toxicity database. Of particular note, there are a number of serious concerns surrounding the development and/or application of the PBPK models (Yang et al., 2012), including poor model optimization of the derived metabolic parameters. A number of issues would need to be addressed in order to update or adapt the Yang et al. (2012) PBPK model for use in revising the chloroprene dose-response assessment. For instance, for the model to be used EPA would need the PBPK code to be replicable on publicly-available software. Due to the discontinuation of the acslX modeling platform, the Yang et al. (2012) model (which includes all model files and scripts) would need to be converted to a different platform. In addition, a revised Yang et al. (2012) model should address the technical and scientific evaluation issues outlined in Table 6, a number of which might substantively impact the dose-response analysis. Finally, the model would need to undergo peer review for it to be considered for potential use in any future assessment of chloroprene health risks.

Thomas et al. (2013) provide only information on gene expression resulting from acute exposures, and likely does not reflect changes in gene expression or MOAs due to chronic exposure, limiting its utility in a chronic human health assessment. Last, the combined dose-response analysis (Allen et al., 2014) relied on judgments that underestimated risk in female mice and particularly underestimated human risk, given existing data. The validity of PBPK model results used by Allen et al. (2014) are also dependent on further evaluations needed for the Yang et al. (2012) model. Collectively, there is low confidence in the published conclusions that human risk of respiratory cancer is up to 100-fold less than that in female mice.

Ultimately, the Agency stands behind the conclusions made in the 2010 IRIS Toxicological Review of Chloroprene, including the derived cancer values. The new studies on chloroprene do not provide a reasonable basis for reassessing the human health effects due to chronic chloroprene exposure.

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APPENDICES

APPENDIX A. LITERATURE SEARCH STRATEGIES

Table A-1. Literature search strategies

WOS	((TS="Chloroprene" OR TS="1,3-Butadiene, 2-chloro-" OR TS="2-Chloor-1,3-butadieen" OR TS="2-Chlor-1,3-butadien" OR TS="2-Chlorbuta-1,3-dien" OR TS="2-chloro-1,3-butadiene" OR TS="2-Chloro-1,3-butadiène" OR TS="2-chlorobuta-1,3-diene" OR TS="Chloropren") AND PY=(2010−2017))	Results: 157
PUBMED	(("Chloroprene" OR "1,3-Butadiene, 2-chloro-" OR "2-Chloor-1,3-butadieen" OR "2-Chlor-1,3-butadien" OR "2-Chlorbuta-1,3-dien" OR "2-chloro-1,3-butadiene" OR "2-Chloro-1,3-butadiène" OR "2-chlorobuta-1,3-diene" OR "Chloropren") AND ("2010/01/01"[Date - Publication]: "3000"[Date - Publication]))	Results: 24
TOXNET	@AND+@OR+(Chloroprene+"1,3-Butadiene, 2-chloro-"+"2-Chloor-1,3-butadieen"+ "2-Chlor-1,3-butadien"+"2-Chlorbuta-1,3-dien"+"2-chloro-1,3-butadiene"+ "2-Chloro-1,3-butadiène"+"2-chlorobuta-1,3-diene"+"Chloropren"+ @term+@rn+126-99-8)+(@RANGE+yr+2010+2017)+@NOT+@org+pubmed+pubdart+ crisp+tscats	Results: 1

APPENDIX B. CORE AND PROMPTING QUESTIONS TO ASSESS RISK OF BIAS AND SENSITIVITY IN EPIDEMIOLOGY STUDIES

Table B-1. Core and prompting questions to assess risk of bias and sensitivity in epidemiology studies

Core question	Example prompting questions	Example follow-up questions
Exposure Does the exposure measure reliably distinguish between levels of exposure in a time window considered most relevant for a causal effect with respect to the development of the outcome?	For all: • Does the exposure measure capture the major source(s) of variability in exposure among the participants, considering intensity, frequency, and duration of exposure? • Does the exposure measure reflect a relevant time window? If not, can the relationship between measures in this time and the relevant time window be estimated reliably? • Was the exposure measurement likely to be affected by a knowledge of the outcome or by the presence of the outcome (i.e., reverse causality)? For case-control studies of occupational exposures: • Is exposure based on a comprehensive job history describing tasks, setting, time period, and use of specific materials? For biomarkers of exposure, general population: • Is a standard assay used? What are the intra- and interassay coefficients of variation? Is the assay likely to be affected by contamination? Are values less than the limit of detection dealt with adequately? • What exposure time period is reflected by the biomarker? If the half-life is short, what is the correlation between serial measurements of exposure?	Is the degree of exposure misclassification likely to vary by exposure level? If the correlation between exposure measurements is moderate, is there an adequate statistical approach to ameliorate variability in measurements? If there is a concern about the potential for bias, what is the predicted direction or distortion of the bias on the effect estimate (if there is enough information)?

Table B-1. Core and prompting questions to assess risk of bias and sensitivity in epidemiology studies (continued)

Core question	Example prompting questions	Example follow-up questions
Outcome Does the outcome measure reliably distinguish the presence or absence (or degree of severity) of the outcome?	For all: • Is disease ascertainment likely to be affected by knowledge of, or presence of, exposure (e.g., consider access to health care, if based on self-reported history of diagnosis)? For case-control studies: • Is the non-diseased comparison group (e.g., controls in a case-control study) based on objective criteria with little or no likelihood of inclusion of people with the disease? For mortality measures: • How well does cause of death data reflect occurrence of the disease in an individual? How well do mortality data reflect incidence of the disease? For diagnosis of disease measures: • Is diagnosis based on standard clinical criteria? If based on self-report of diagnosis, what is the validity of this measure? For laboratory-based measures (e.g., hormone levels): • Is a standard assay used? Does the assay have an acceptable level of inter-assay variability? Is the sensitivity of the assay appropriate for the outcome measure in this study population?	Is there a concern that any outcome misclassification is non-differential, differential, or both? What is the predicted direction or distortion of the bias on the effect estimate (if there is enough information)?

Table B-1. Core and prompting questions to assess risk of bias and sensitivity in epidemiology studies (continued)

Core question	Example prompting questions	Example follow-up questions
Participant selection Is there evidence that selection into or out of the study (or analysis sample) was jointly related to exposure and to outcome?	For longitudinal cohort: • Did participants volunteer for the cohort based on knowledge of exposure and/or preclinical disease symptoms? Was entry into the cohort or continuation in the cohort related to exposure and outcome? For occupational cohort: • Did entry into the cohort begin with the start of the exposure? • Was follow-up or outcome assessment incomplete and if so, was follow-up related to both exposure and outcome status? • Could exposure produce symptoms that would result in a change in work assignment/work status ("healthy worker survivor effect")? For case-control study: • Were controls representative of population and time periods from which cases were drawn? • Are hospital controls selected from a group whose reason for admission is independent of exposure? • Could recruitment strategies, eligibility criteria, or participation rates result in differential participation relating to both disease and exposure? For population-based survey: • Was recruitment based on advertisement to people with knowledge of exposure, outcome, and hypothesis?	Were differences in participant enrollment and follow-up evaluated to assess bias? If there is a concern about the potential for bias, what is the predicted direction or distortion of the bias on the effect estimate (if there is enough information)? Were appropriate analyses performed to address changing exposures over time in relation to symptoms? Is there a comparison of participants and non-participants to address whether or not differential selection is likely?

Table B-1. Core and prompting questions to assess risk of bias and sensitivity in epidemiology studies (continued)

Core question	Example prompting questions	Example follow-up questions
Confounding Is confounding of the effect of the exposure likely?	• Is confounding adequately addressed by considerations in… a. … participant selection (matching or restriction)? b. … accurate information on potential confounders, and statistical adjustment procedures? c. … lack of association between confounder and outcome, or confounder and exposure in the study? d. … information from other sources? • Is the assessment of confounders based on a thoughtful review of published literature, potential relationships (e.g., as can be gained through directed acyclic graphing), minimizing potential over-control (e.g., inclusion of a variable on the pathway between exposure and outcome)?	If there is a concern about the potential for bias, what is the predicted direction or distortion of the bias on the effect estimate (if there is enough information)?
Analysis Does the analysis strategy and presentation convey the necessary familiarity with the data and assumptions?	• Are missing outcome, exposure, and covariate data recognized and, if necessary, accounted for in the analysis? • Does the analysis appropriately consider variable distributions and modeling assumptions? • Does the analysis appropriately consider subgroups of interest (e.g., based on variability in exposure level or duration, susceptible subgroups)? • Is an appropriate analysis used for the study design? • Is effect modification considered, based on considerations developed a priori? • Does the study include additional analyses addressing potential biases or limitations (i.e., sensitivity analyses)?	If there is a concern about the potential for bias, what is the predicted direction or distortion of the bias on the effect estimate (if there is enough information)?

APPENDIX C. ASSESSMENT OF RISK OF BIAS AND SENSITIVITY IN ANIMAL STUDIES

Evaluation of animal studies to assess risk of bias and sensitivity was conducted for the following domains: reporting quality, selection or performance bias, confounding/variable control, reporting or attrition bias, exposure methods sensitivity, and outcome measures and results display (see Table C-1).

Table C-1. Domains of evaluation for animal studies

Domain	Metric	Criteria
Reporting quality	Reporting of information necessary for study evaluation	Key information necessary for study evaluation (study would be deemed critically deficient if not reported[a]): • Species, test article description, levels and duration of exposure, endpoints investigated, qualitative or quantitative results. Important information, which should also be reported, is listed below. The brackets contain secondary information that would ideally be reported and, based on the needs of a given assessment, may be considered important, or key, information. • *Test animal*—strain, sex, source (e.g., vendor), husbandry procedures (e.g., housing, feed, mating), [baseline health (e.g., colony monitoring procedures), age or body weight at start of study]. • *Exposure methods*—test article source, description of vehicle control, route of administration, methods of administration (e.g., gavage volume, exposure chamber), [information on stability, purity, analytical verification methods]. • *Experimental design*—periodicity of exposure, animal age/life stage during exposure and at endpoint evaluation(s), [timing of endpoint evaluation(s) (e.g., latency between exposure and testing)]. • *Endpoint evaluations*—procedural details to understand how endpoints were measured; procedural controls, including information on positive and negative controls; [related details (e.g., biological matrix or specific region of tissue/organ evaluated); information on other manipulations (e.g., surgery, co-treatment)]. • *Results presentation*—presents findings for all endpoints of interest that were investigated, information on variability, experimental units assessed, sample size, statistical procedures, (related details, e.g., maternal toxicity in developmental studies, handling of early mortality in long-term bioassays). *Note*: Studies adhering to GLP (good laboratory practices) or to testing guidelines established by (inter)national agencies are assumed to be of good reporting quality.

Table C-1. Domains of evaluation for animal studies (continued)

Domain	Metric	Criteria
Selection or performance bias	Allocation of animals to experimental groups	Ideally, animal studies are randomized, with each animal or litter having an equal chance of being assigned to any experimental group, including controls, and allocation procedures sufficiently described. Less ideally, but generally adequate or good, are studies indicating normalization of experimental groups before exposure, for example according to body weight or litter, but without indication of randomization. The least preferred situation is studies with no indication of how groups were assigned.
	Blinding of investigators, particularly during outcome assessment	Good studies will conceal the treatment groups from the researchers conducting the endpoint evaluations (and, in rare but ideal situations, from all research personnel and technicians). Concern regarding blinding may be attenuated when outcome measures are more objective (e.g., as is the case of obtaining organ weights) or measurement is automated using computer-driven systems (e.g., as is the case in many behavioral assessments).
Confounding/variable control	Control for variables across experimental groups	In a good study, outside of the (chemical) exposure of interest, all variables will be controlled for and consistent across experimental groups. Concern regarding additional variables, introduced intentionally or unintentionally, may be mitigated by knowledge or inferences regarding the likelihood and extent to which the variable can influence the endpoint(s) of interest. A very important example to consider is whether the exposure was sufficiently controlled to attribute the effects of exposure to the compound of interest alone. Generally, well-conducted exposures will not have any evidence of coexposures and will include experimental controls that minimize the potential for confounding (e.g., use of a suitable vehicle control). Other examples of variables that may be uncontrolled or inconsistent across experimental groups include protective or toxic factors that could mask or exacerbate effects, diet composition, or surgical procedures (e.g., ovariectomy).
Reporting or attrition bias	Lack of selective data reporting and unaccounted for loss of animals	In a good study, information is reported on all pre-specified outcomes and comparisons for all animals, across treatment groups and scheduled sacrifices. Aspects to consider include whether all study animals were accounted for in the results (if not, are explanations, such as death while on study, and adjustments provided) and whether expected comparisons or certain groups were excluded from the analyses. In some studies, the outcomes evaluated must be inferred (e.g., a suite of standard measures in a guideline study). *Note*: This metric does not address whether quantitative data were reported, nor considers statistical test methods.

Table C-1. Domains of evaluation for animal studies (continued)

Domain	Metric	Criteria
Exposure methods sensitivity	Characterization of the exposure to the compound of interest	Consider whether there are notable issues that raise doubt about the reliability of the exposure levels, or of exposure to the compound of interest. Depending on the chemical being assessed, this may include considering factors such as the stability and composition (e.g., purity, isomeric composition) of the test article, exposure generation and analytic verification methods (including whether the tested levels and spacing between exposure groups is resolvable using current methods), and details of exposure methods (e.g., inhalation chamber type; gavage volume). In some cases, exposure biomarkers in blood, urine, or tissues of treated animals can mitigate concerns regarding inaccurate dosing (dependent on the validity of the biomarker for the chemical of interest). *Note*: While this identifies uncertainties in dose-response, it is typically not a valid reason for exclusion from Hazard ID.
	Use of the exposure design for the endpoint of interest	Based on the known or presumed biological progression of the outcomes being evaluated, consider whether there are notable concerns regarding the timing, frequency, or duration of exposure. For example, better developmental studies will cover a greater proportion of the developmental window thought to be critical to the system of interest, while better studies for assessing cancer or other chronic outcomes will be of longer duration. Studies that expose animals infrequently or sporadically, or, conversely, on a continuous basis (which, depending on the exposure level, can impact food/water consumption, sleep cycles, or pregnancy/maternal care), might introduce additional complications.
Outcomes measures and results display	Sensitivity and specificity of the endpoint evaluations	Consider whether there are notable concerns about aspects of the procedures for, or the timing of, the endpoint evaluations. Based on the endpoint evaluation protocol used for the endpoints of interest, specific considerations will typically include: • Concerns regarding the sensitivity of the specific protocols for evaluating the endpoint of interest (i.e., assays can differ dramatically in terms of their ability to detect effects) and/or their timing (i.e., the age of animals at assessment can be critical to the appropriateness and sensitivity of the evaluation). This includes both overestimates or underestimates of the true effect, as well as a much higher (or lower) probability for detecting the effect(s) being assessed. • Concerns regarding the specificity and validity of the protocols. This includes the use of appropriate protocol controls to rule out nonspecific effects, which can often be inferred from established guidelines or historical assay data. It may be considered useful for insensitive, complex, or novel protocols to include positive and/or negative controls. • Concerns regarding adequate sampling. This includes both the experimental unit (e.g., litter, animal) and endpoint (e.g., number of slides evaluated). This is typically inferred from historical knowledge of the assay or comparable assays. *Notes*: Human relevance of the endpoint is not addressed during study evaluation; for under sampling without blinding (e.g., sampling bias), this will typically lead to gross overestimates of effect; sample size is generally not a reason for exclusion.

Table C-1. Domains of evaluation for animal studies (continued)

Domain	Metric	Criteria
Outcomes measures and results display (continued)	Usability and transparency of the presented data	Consider whether the results are analyzed or presented in a way that limits concerns regarding the reliability of the findings. Items that will typically be important to consider include: • Concern that the level of detail provided does not allow for an informed interpretation of the results (e.g., authors' conclusions without quantitative data; discussing neoplasms without distinguishing between benign and malignant tumors; not presenting variability). • Concern that the way in which the data were analyzed, compared, or presented is inappropriate or misleading. Examples include failing to control for litter effects (e.g., when presenting pup data rather than the preferred litter data), pooling results from males and females or across lesion types, failing to address observed or presumed toxicity (e.g., in assessed animals; in dams) when exposure levels are known or expected to be highly toxic, incomplete presentation of the data (e.g., presenting continuous data as dichotomized), or non-preferred display of results (e.g., using a different readout than is expected for that assay). The evaluator should support how or why, and to what extent, this might mislead interpretations. *Notes*: Concerns regarding the statistical methods applied are not addressed during study evaluation, but should be flagged for review by a statistician. Missing information related to this metric should typically be requested from the study authors.
Other	(Optional)	Example 1: Control for other threats to internal validity. This exceptional metric might be used to consider animal husbandry concerns, reports of predosing toxicity or infection, etc. Example 2: Lack of concern for sensitivity of the animal model. This exceptional metric should be used only when there is demonstrated evidence of differences in model (e.g., species, sex, strain) sensitivity. This does not address the human relevance of the animal model.

Exhibit B

Request for Reconsideration
Denka Performance Elastomer LLC

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April 6, 2018

Via Electronic Mail & Federal Express
Jennifer Orme-Zavaleta, Ph.D.
Principal Deputy Assistant Administrator for Science
United States Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, D.C. 20460

Re: Chloroprene Request for Correction #17002
Follow-up Request for EPA Review of PBPK Workplan
Our File: 165671-00

Dear Dr. Orme-Zavaleta:

On behalf of Denka Performance Elastomer LLC (DPE), I acknowledge receipt of EPA's denial, dated January 25, 2018, of DPE's Request for Correction (RFC) #17002 concerning the 2010 Toxicological Review of Chloroprene. DPE is very disappointed with the EPA denial, and believes the EPA should reconsider its denial. As outlined in the EPA denial, DPE plans to file a timely Request for Reconsideration.

DPE's interest, as it is EPA's, is to seek the application of the best available science to this matter. EPA recognizes that it established the inhalation unit risk (IUR) for chloroprene based on the default assumption that human beings are as sensitive to chloroprene exposure as the most sensitive species in the laboratory. Attachment 1 to the January 25 denial explained, "In accordance with the EPA Guidelines for Carcinogen Risk Assessment (2005), in the absence of data to the contrary, EPA uses the most sensitive species and sex in establishing the cancer risk to humans, which, in the case of chloroprene, is the female mouse." EPA Denial, Attachment 1, at 3.

The January 25 denial includes a cover letter and attachments 1 and 2. The attachments provide details about why EPA does not consider any currently available physiologically-based pharmacokinetic (PBPK) models to be sufficiently validated to be used to adjust the mouse-based IUR to more accurately indicate potential human response. EPA's denial states that, among other things, it contacted Dr. Harvey Clewell in an effort to obtain computer code for some of the most recent PBPK models for chloroprene.

DPE has now retained Dr. Clewell, who recently joined Ramboll Environ, to assist in developing a PBPK model that addresses the validation issues raised in the EPA denial. Attached for your reference is a copy of the "Workplan to Provide a Physiologically-Based Pharmacokinetic (PBPK) Model to Support the Inhalation Unit Risk (IUR) for chloroprene)," dated March 23, 2018. Dr. Clewell and Ramboll Environ have designed the workplan to address EPA's stated validation concerns, and to deliver to EPA the computer code that EPA can utilize for its own validation review. Dr. Clewell and Ramboll Environ believe they can complete this task in 4 to 6 months.

Although DPE has instructed Dr. Clewell and Ramboll Environ to proceed with this work, we would highly value EPA's review and comment on the workplan because it is DPE's intention to provide EPA with a PBPK model that meets EPA's validation and other requirements. Towards this objective, perhaps a meeting with you and your staff to discuss this path forward would be beneficial. It might also be desirable to form a joint industry-EPA working group to help develop this PBPK model on such an accelerated schedule.

We will be contacting your office shortly to follow up on this request. Thank you for your attention to this.

Yours very truly,

Robert E. Holden
Attorney for Denka Performance Elastomer LLC

REH/lhc/kb
Encls.
cc: *(Via Electronic Mail):*
Tina Bahadori, Sc.D. ORD/NCEA Director
Stephen Fine, Ph.D. Acting Chief Information Officer
David Gray, EPA Region 6 Director of External Affairs
Vincia Holloman, Director of Enterprise Quality Management Division
Anne Idsal, J.D., Region 6 Administrator
John Vandenberg, ORD/NCEA RTP Division Director
Kistina Thayer, ORD/NCEA IRIS Division Director
Richard Yamada, Ph.D. Deputy Assistant Administrator, Office of Research & Development
Samantha Dravis, Associate Administrator for Policy, Office of Policy, EPA

Intended for

Denka Performance Elastomer, LLC

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Date

March 23, 2018

WORKPLAN TO PROVIDE A PHYSIOLOGICALLY-BASED PHARMACOKINETIC (PBPK) MODEL TO SUPPORT THE INHALATION UNIT RISK (IUR) FOR CHLOROPRENE

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CONTENTS

1 INTRODUCTION

Multiple physiologically-based pharmacokinetic (PBPK) models available in the published, peer-reviewed scientific literature (Allen et al. 2014; Himmelstein et al. 2004; Thomas et al. 2013; Yang et al. 2012) have been evaluated and applied in the estimation of potential cancer risks following inhalation exposure to chloroprene (CAS No. 126-99-8). Several of these were identified by the U.S. Environmental Protection Agency's (USEPA) Integrated Risk Information System (IRIS) Toxicological Review of Chloroprene (USEPA 2010) and in a recent Request for Correction (RFC) of the Inhalation Unit Risk (IUR) submitted by Denka Performance Elastomer, LLC (DPE 2017). As noted in USEPA's Denial of the RFC (USEPA 2018), one of the key reasons for the denial was the lack of model validation, noting limitations and uncertainties that need to be addressed. Also lacking was the underlying code for these models to fully evaluate and consider them in the estimation of the IUR for chloroprene. All the published models rely upon the same underlying in vivo and in vitro data and PBPK models.

We outline below an approach for addressing the limitations and uncertainties raised by the USEPA that have prevented the use of these models in the development of the IUR for chloroprene, and provide the model code(s) needed to allow for full review of the available peer-reviewed models by USEPA and their application in the estimation of an IUR for chloroprene. This workplan primarily is intended to guide the process of scientifically evaluating and improving the PBPK model for chloroprene in support of an updated and more scientifically justifiable IUR. An ancillary objective is to provide USEPA a clear representation of the model refinement process and facilitate USEPA's possible review and input at each stage.

2 PROPOSED APPROACH

As noted in the response to the RFC dated January 25, 2018, USEPA was unable to locate and obtain the final code associated with the published PBPK models. USEPA (2018) noted that PBPK code is necessary for a quality assurance and quality control review by USEPA. Because the final code is not available, USEPA cannot evaluate the internal validity of the Yang et al. (2012) PBPK modeling methods or results, or results that are dependent on this model [i.e. Allen et al. (2014)]. Further complicating this, the software platform for these models (ACSL) is no longer available; therefore, migration to a new platform, such as R, will be necessary. The proposed approach to validating the PBPK model will be focused on addressing the comments that have been provided by USEPA in the IRIS (2010) assessment, as well as the Denial of the RFC (USEPA 2018), that were discussed as limitations and uncertainties with the PBPK model for chloroprene. The workplan further describes additional analyses to be conducted using the existing model to address these limitations and uncertainties, which will provide the USEPA with the necessary PBPK model code that would allow for a quality review and application of the model in the estimation of the IUR.

The uncertainties remaining in the application of the PBPK models that have been noted by USEPA in the IRIS Assessment (USEPA 2010) and the response to the RFC (USEPA 2018) are related to four specific areas:

- Justification for selected parameters in the in vivo/in vitro models
- Ability to reproduce in vivo pharmacokinetic data
- Estimation of uncertainty in the model using Markov Chain Monte Carlo (MCMC) analyses
- Reproduction of PBPK model code in an available operating platform

How we plan to address each of these areas of uncertainty is discussed in the following sections.

2.1 Justification for selected parameters in the *in vivo*/*in vitro* models

USEPA (2010) noted that the PBPK model reported in Himmelstein et al. (2004) currently predicts blood chloroprene and delivery of chloroprene to metabolizing tissues based on metabolic constants and partition coefficients based on in vitro data. Loss of chamber chloroprene is attributed to uptake and metabolism by test animals and was used to test the metabolic parameters and validate the model. However, Himmelstein et al. (2004) did not provide results of sensitivity analyses indicating whether chamber loss was sensitive to metabolism, and therefore it is uncertain whether chamber loss is useful for testing the metabolic parameters used in the model. We will conduct a sensitivity analysis using the current ASCL model in vitro and in vivo code and the results provided to USEPA for consideration.

The USEPA has further noted that the female mouse lung metabolism and internal doses in Yang et al. (2012) are not consistent with results for male mice. Vmax is approximately five times higher for male mice than for female mice, yet the tumor response is similar. This has implications for biological basis for the site-specific dose-response, and parameterization of extra-hepatic metabolism. Additional analyses will be conducted to evaluate the uncertainty in the Vmax estimates. The results of these analyses will determine if pharmacokinetic differences can explain the sex-specific differences in response in the mouse, or if there is evidence of pharmacodynamic differences or sex-specific sensitivity.

The dose metrics relied upon in all the modeling publications have focused on metabolism in the liver, lung or kidney. The USEPA has noted that lung metabolism does not account for tumor responses at other sites outside the lung, which also need to be incorporated into a risk assessment. Additional analyses will be conducted to determine if data are available to suggest significant metabolic capability

in organ systems other than the liver, lung or kidney and how critical the potential contribution of this metabolism might be to the overall composite risk.

2.2 Ability to reproduce *in vivo* pharmacokinetic data

In the IRIS Assessment (USEPA 2010), the USEPA noted that the model's ability to reproduce in-vivo PK data [i.e. from Himmelstein et al. (2004)] has not been evaluated. In the chloroprene docket is a report in which blood chloroprene was measured in mice following single (6-hour) and repeated (5- or 15-day) inhalation exposures (unpublished). Chloroprene blood levels were higher following single exposures, which was postulated to be because of higher minute volume due to stress. The authors conclude that these blood data are suitable for validation of a PBPK model, but it is unclear whether the data were used for the validation of the PBPK model in Yang et al. (2012). The report did not investigate chloroprene levels in the organs of interest (namely the lungs, liver, or kidneys). Additional simulations will be conducted to determine if the in vivo model can be validated using the datasets in the mouse provided in the chloroprene docket (DuPont 2009).

Of additional concern in the IRIS Assessment (USEPA 2010) was that Himmelstein et al. (2004) had to reduce alveolar ventilation and total blood flow values predicted from the in vitro data by 50% to match the in vivo PK data presented. Mice are well known to suppress respiration (RD) and cardiac output in response to irritant gases. However, the response would be dose dependent. Change in respiration and cardiac output is necessary to fit the available data and has been observed with and incorporated into models for other compounds. Although there are no data specific to chloroprene to characterize respiratory and cardiac output suppression, additional analyses will be conducted to increase the confidence in this adjustment and to find additional scientific data to support this adjustment.

2.3 Estimation of uncertainty in the model using Markov Chain Monte Carlo (MCMC) analyses

In the 2010 IRIS assessment, USEPA noted the need to use distributions of the PBPK model parameters to represent variability in intra-population rates of chemical absorption, distribution, metabolism, and elimination to estimate human variability. The MCMC analyses conducted as part of the Yang et al. (2012) publication was to investigate potential variability in parameters, but also understand the potential uncertainty and its impact on estimating potential cancer risks from exposure to chloroprene. So, while Yang et al. (2012) addresses part of USEPA's (2010) comments, additional relevant comments were noted in the USEPA (2018) response to the RFC. USEPA (2018) questions the form of the log-likelihood function used in the MCMC analysis and suggests that the autocorrelation among repeated measures from a single experimental unit has not been considered. USEPA (2018) also noted that the female mouse kidney metabolism approaches zero in the MCMC optimization and that parameterization of extra-hepatic metabolism may be incorrect.

For liver metabolism, this is apparent on the log-scale for predictions of chloroprene headspace concentration data provided in Figure 2b of Yang et al. (2012), and Figures 5 and 25 of Study IISRP-17520-1388 (submitted to EPA-HQ-ORD-2009-0217). The underestimation occurs for both the point estimate results and the Monte Carlo results. Also, because the molecular form of enzymes does not vary between tissues within an individual, or males and females of a species, the Km for metabolism should be likewise constant across tissues and between sexes.

The MCMC analyses conducted by Yang et al. (2012) will be revisited to address these comments.

2.4 Reproduction of PBPK model code in an available operating platform

As noted in the USEPA (2018) response to the RFC, while several model code packages were shared with the USEPA by Dr. Harvey Clewell, these are poorly documented and do not provide sufficient instructions that allow the EPA to review or apply the available models now. Once the comments

previously outlined have been addressed, the final step in the workplan will be to provide a complete model code with adequate documentation and files to reproduce critical results needed for the quality review of the model and the application in the estimation of the IUR. Both the code for the in vivo and in vitro components of the model will be provided allowing the USEPA to reproduce the PBPK results from Himmelstein et al. (2004), Yang et al. (2012), Thomas et al. (2013) and Allen et al. (2014). The code will be provided in the R platform, with the necessary scripts to reproduce the analyses conducted as part of the workplan as well as the results provided in the publications.

3 SCHEDULE

We plan to communicate closely with the USEPA to ensure that the remaining questions and uncertainties associated with the review and application of the PBPK model for chloroprene have been addressed. We anticipate that we will be able to provide the needed model code, addressing the remaining uncertainties, to the USEPA within 4 to 6 months following acceptance of the workplan.

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May 17, 2018

Via Electronic Mail & Federal Express
Jennifer Orme-Zavaleta, Ph.D.
Principal Deputy Assistant Administrator for Science
United States Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, D.C. 20460

Re: Chloroprene Request for Correction #17002
Status Report on PBPK Model Development for Chloroprene
Our File: 165671-00

Dear Dr. Orme-Zavaleta:

On April 6, 2018, on behalf of Denka Performance Elastomer LLC (DPE), we sent you a letter expressing DPE's intention to provide EPA with a Physiologically-Based Pharmacokinetic (PBPK) model that meets EPA's validation concerns and other requirements. As you know, the 2010 Toxicological Review of Chloroprene developed an inhalation unit risk (IUR) for chloroprene based on the most sensitive species (the female mouse) in laboratory exposure studies. As described in the EPA Cancer Guidelines (2005), the preferred approach for developing an IUR relevant to humans based on laboratory results from other animal species is through the use of PBPK models when these are available. Our letter of April 6, 2018, included a copy of our proposed "Workplan to Provide a Physiologically-Based Pharmacokinetic (PBPK) Model to Support the Inhalation Unit Risk (IUR) for Chloroprene," dated March 23, 2018, prepared by experts at Ramboll. The Ramboll team includes Dr. Harvey Clewell as a lead scientist, who was instrumental in work related to the development of PBPK models for chloroprene.

In the time since sending the April 6, 2018, letter, we have worked with Dr. Clewell and the Ramboll team to develop and document a PBPK model that addresses the technical questions and comments from EPA on prior chloroprene PBPK models. Dr. Clewell reports that his work updating and validating the chloroprene PBPK model is now close to complete. Dr. Clewell believes that the updated model resolves EPA's concerns. Ramboll is now in a position to provide EPA the computer code so that EPA can undertake its own validation of the model.

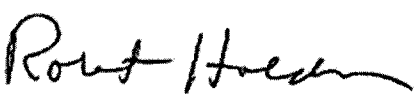
Although the updated PBPK modeling work is close to complete, DPE values EPA's review and comment on this model and would like to understand what the next steps are for providing this model to EPA. We specifically request:

- The opportunity to provide the PBPK model computer code and documentation to EPA for review;
- Guidance from EPA on best practices for obtaining peer review of the PBPK model and underlying data; and
- Guidance from EPA concerning next steps for correcting the IUR based on the EPA vetted and peer reviewed PBPK model.

The application of a PBPK model is an important step towards the application of the best available science in a chloroprene risk assessment. Without the application of a PBPK model, the IUR overestimates the human risk of chloroprene exposure. Correcting the erroneous IUR is an urgent matter for DPE, as the current IUR is creating immense burdens on DPE's Neoprene manufacturing facility in LaPlace, Louisiana, and threatens the long-term viability of the facility.

We are looking forward to working closely with you on this collaborative effort. We would like to schedule a meeting or a telephone conference with you to discuss the EPA review of the updated chloroprene PBPK model and a path forward. We will be in touch with your office to follow up on this request.

Yours very truly,



Robert E. Holden
Attorney for Denka Performance Elastomer LLC

REH/kb

cc: *(Via Electronic Mail):*
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Kistina Thayer, ORD/NCEA IRIS Division Director
Richard Yamada, Ph.D. Deputy Assistant Administrator, Office of Research & Development
Samantha Dravis, Associate Administrator for Policy, Office of Policy, EPA

June 13, 2018

EPA comments on DPE Workplan to provide a physiologically-based pharmacokinetic (PBPK) model to support the inhalation unit risk for chloroprene

A document titled "Workplan to provide a physiologically-based pharmacokinetic (PBPK) model to support the inhalation unit risk for chloroprene" dated March 23, 2018 was provided to EPA on April 6, 2018, on behalf of Denka Performance Elastomers (DPE). The April 6 letter indicated DPE would be in contact regarding the workplan and on May 17, 2018 a letter on behalf of DPE was received that indicated the PBPK model development was proceeding.

We appreciate the opportunity to comment on the proposed workplan for PBPK modeling of chloroprene. We have some thoughts to offer on the approach to quality assurance and review of PBPK models in risk assessment applications as well as some specific thoughts on chloroprene PK modeling.

Approach to quality assurance and documentation

The Pharmacokinetic Workgroup (PKWG) at the U.S. EPA has developed a Quality Assurance Process Plan (QAPP) for computational modeling, focused on PBPK models, which we sent previously for your consideration. Prior to application of a PK model in its assessment work, NCEA will conduct a review according to this QAPP. Such review will be significantly facilitated if corresponding documentation is created during the modeling process. It is much easier to record this information as the modeling is being conducted than to attempt to reconstruct the information later.

Model data

One component of the QAPP is that the data used for model calibration and evaluation should be validated against the original source and need to be made publicly available along with the model code and supporting scripts. If data have been digitized from published figures, then extraction of data from the figures is documented. (To do this an image of the figure with full citation and a copy of the spreadsheet, csv, etc., with the initially digitized values can be saved in a "model data" folder. One method of validation is to plot the digitized data in Excel with a clear background and overlay the plot on the figure image, to assure the plot of digitized points and original points in the image align. If the data are copied from a table, then the reference, table, number, etc., should be provided, with a copy of the document.)

If the data are converted from the originally published units or otherwise mathematically manipulated, it is most helpful if the calculations for the conversion/calculations are embedded as "live" cell-equations in Excel. The resulting set of values matching those used in the PBPK model files (csv or scripts) can be highlighted. A text description of the conversion, with units identified, should also be included, either in the spreadsheet or in an appendix for the report. Alternatively, well-documented computer programs (e.g., R or Python scripts) that modify, filter, and/or pre-process the data can be provided.

Model parameters

Like model data, full documentation of the source/derivation of all parameters is necessary. A source citation alone is often not sufficient to determine how a parameter value in a PBPK model was obtained. For example, Brown et al. (1997) lists the brain weight (fraction) in mice in 3 different tables (Tables 4, 8,

and 21), with different values in each. The specific table or page in the cited source must be identified. If an allometric coefficient for cardiac output (CO) has been derived from a reported value for total CO, provide the calculation with units shown. Calculations embedded in an Excel spreadsheet are easiest to verify. It is particularly important to provide the derivation where data from multiple sources or tables have been combined. For example, a wide range of allometric coefficients for CO and alveolar ventilation appear in the PBPK literature, and it can be very difficult to determine how a specific value was derived.

Chloroprene science issues

Single vs. repeated exposures and respiratory depression, and animal-human extrapolation

In section 2.2 it is noted that higher chloroprene levels may have occurred after single inhalation exposures compared to repeated exposures due to stress, leading to heightened ventilation during the initial exposure. We note that in the Himmelstein et al (2004b) model, the selected ventilation and cardiac output rates for all species were set generally a factor of 2 lower than standard physiological values for modeling of gas uptake experiments but then were set to the standard values when calculating internal doses for bioassays. Using higher values for the bioassays would lead to higher predicted internal doses, hence lower tumor slope factors, but may be inconsistent with the in vivo PK data. While visual observation of reduced breathing frequency in animals during chloroprene exposure has been noted, a reduction in breathing frequency can be off-set by increased tidal volume, so observations of changes in frequency are not authoritative evidence for a reduction in the total amount inhaled per time (i.e., minute ventilation). The U.S. EPA is not aware of quantitative ventilation data for chloroprene-exposed animals. Reduction in these parameters required to fit in vivo PK may simply be adjustments to compensate for other modeling errors.

Regarding differences between acute and long-term exposure, it might be appropriate to assume that the initial response is overcome under bioassay conditions, with the bulk of the bioassay occurring after the animals have acclimatized to the exposures. Visual observations of animal respiration during chloroprene exposures are consistent with this hypothesis. However, if RD data are not available for chloroprene, we suggest that they be collected for both naïve and pre-exposed animals, to support what is otherwise a hypothesis being made to fit specific data sets. In general, we recommend that the model be calibrated to match data for repeated exposures to best represent the bioassay conditions, but otherwise the parameters should be consistent with those needed to match any available PK data.

Finally, RD should be described as a continuous function of exposure concentration, alveolar concentration, or lung tissue concentration, with normal ventilation at zero concentration, rather than as only occurring at zero or full response, to allow for appropriate analysis of the range of bioassay exposures.

Number of parameters and consistency across tissues and genders

Since the form of the key metabolizing enzyme, specifically the CYP, should not vary between males and females or between tissues of the same species, a reasonable initial assumption is that the value of Km is the same across these components of the analysis. Enforcing this equality would reduce the number of fitted parameters, hence improve the statistical certainty in model results, unless this restriction can be shown to significantly degrade model fits (i.e., that relaxing the condition significantly improves the

statistical likelihood of the data vs. model predictions). Hence, we suggest that the analysis be conducted in this way, being parsimonious in the number of fitted parameters.

MCMC analysis

While Bayesian parameter estimation via Markov chain Monte Carlo (MCMC) methods provides useful information about uncertainty in model parameters, the EPA recognizes that such analysis can be more time- and work-intensive than standard methods for obtaining point estimates for model parameters (e.g., least squares, maximum likelihood, or maximum a posteriori parameter estimation). Further, to properly characterize parameter uncertainty, the full set of original experimental data would be required (i.e., data for each individual animal or human subject as opposed to summary data) and attaining convergence of MCMC chains for PBPK model parameters can be difficult and time-consuming. The most likely application for an animal (mouse) PBPK model would involve using point estimates of the parameter values in the PBPK model to estimate internal doses under bioassay conditions. The statistical modeling typically used by EPA (i.e., using BMDS software, MS_Combo tool) uses a fixed measure of dose for each exposure group. This statistical model addresses uncertainty in the dose-response assessment by estimating uncertainty in the response metric. Hence an MCMC analysis is not something that the U.S. EPA needs for its subsequent application of the PBPK model and more time-efficient methods for obtaining point estimates of PBPK model parameters and outputs could be used, although the uncertainty information from such an analysis might be useful for evaluating the PBPK model.

Likelihood Calculation for Serial Samples

When evaluating the improvement in model fit resulting from an additional parameter (e.g., using a different value for Km in the liver vs. the lung) and for MCMC analysis, the likelihood calculation should account for the expected correlation among serial samples from the same experimental unit. Specifically, serial samples taken from a gas uptake chamber or incubation vial are not independent observations and the likelihood calculation should reflect the correlation (Klein et al., 2012).

Dose metrics

There are multiple measures of internal dose that could be considered as potential dose metrics for chloroprene. For chloroprene a key factor is that the combined risk of tumors across all tumor-bearing sites should be evaluated; i.e. the approach used in the 2010 IRIS assessment which was supported during external peer-review. It has been proposed that the tissue-specific rate of metabolism be used as a measure of tumor risk for the lung, but such a metric could not be rationally applied to tumor-bearing sites that lack metabolism (e.g., mammary tissue). That the majority of oxidative metabolism measured by Himmelstein et al. (2004a) appeared to go to 2-chloro-2-ethenyloxirane (2-CEO), which is unstable in aqueous media, is supportive of an assumption that most of the metabolites affecting tissues in which metabolism occurs are those formed in that tissue. However, it is still possible that a fraction of 2-CEO survives long enough to reach other tissues and that (1-chloroethenyl)oxirane (1-CEO), which is more stable, also contributes to toxicity. Hence whole-body metabolism (total of metabolism in liver, lung, and kidneys) will also be evaluated by the U.S. EPA as an appropriate dose metric. Whole-body metabolism is also less uncertain than tissue-specific metabolism, since it can be validated by in vivo gas uptake and blood concentration data (see below).

Scale-up of in vitro data

The microsomal preparations used for different species and organs come from a variety of sources and were not tested contemporaneously in the same laboratory. For example, microsomes for male mice and rats (liver and lung) were purchased from one of two commercial suppliers and metabolic activity was measured by Himmelstein et al (2004a); for female mice and rats (liver and lung), prepared in house and activity measured nearly a decade later by Yang et al (2012). Human microsomes for different tissues were purchased from differing commercial sources and tested by either Himmelstein et al (2004a) or Yang et al (2012). It is noted that the difference between Vmax/Km for the female vs. male mouse lung is over 6-fold (Yang et al., 2012, Table 4), while the lung tumor incidence is nearly identical. The discrepancy between the estimated difference in lung metabolic parameters and tumor incidence raises the question as to how much the differences in microsome source (including animal colonies and housing), microsome preparation, in vitro incubation method, and chemical analyses may have led to artifactual results. While the method for microsome preparation from the liver is well-established and standardized, lung microsomes require careful dissection of the tissue and are more likely to vary between laboratories and individuals performing the preparation. Hence, this question carries over to the reported difference between mouse and human lung metabolism: to what extent are these real vs. the result of uncontrolled experimental variability? An option that might be considered is to conduct a limited additional set of in vitro experiments, across tissues, genders, and species for which existing data are being analyzed, but contemporaneously with all other experimental factors controlled as carefully as possible. The resulting data could then be checked for consistency with the existing data.

While the U.S. EPA will fully consider a revised model in the absence of these suggested additional data, it is less likely to make use of lung-specific metabolism as an internal metric given the uncertainty noted here. Hepatic metabolism, which is the majority of whole-body metabolism, is more similar for male and female mice, hence more consistent with the observed tumor incidence.

The PK models of Yang (2012) and Himmelstein (2004b) estimate in vivo metabolic rates by direct scale up of the in vitro estimates of Vmax and km. (IVIVE scaling, done using literature values for microsomal protein content per gram tissue.) While the in vitro measurements of P450 metabolism have a lengthy history of providing important information on kinetic processes, direct scale up of in vitro to in vivo rates entails multiple uncertainties. For example, Wambaugh et al. (2015) compared IVIVE predictions to in vivo data across a set of chemicals and showed discrepancies frequently up to a factor of 10, which we interpret as the current level of uncertainty in IVIVE extrapolation. That level of uncertainty is higher than is considered acceptable for use of a PBPK model in an IRIS Toxicological Review (which differs from the use-case of hazard identification and risk ranking advocated by Wambaugh et al. (2015)). Hence, for the PBPK model to be accepted for use, the scaling must be validated by showing that model predictions match the in vivo gas uptake data of Himmelstein et al. (2004b) for male mice and rats, and the blood concentration data submitted to the docket. In general, model predictions should be within a factor of 2 of the in vivo data, though there may be some outliers. If correction factors must be applied to the scaling to achieve this level of agreement between model predictions and these in vivo PK data, then those same factors should be applied consistently (also, across tissues for IVIVE calculations) when estimating internal doses for the animal bioassays and for evaluation of the internal dose-exposure relationship in humans.

Key Points

- A full set of model data, that the EPA can then make publicly available, is needed for the model to be used if a revision of the IRIS Toxicological Review is warranted.
- Given the different sources of in vitro PK data as noted, the nominal difference between mouse and human lung metabolism appears to be highly uncertain. In the absence of new validating (in vitro) data, lung-specific metabolism is considered too uncertain to use as a dose metric for tumor response in that site.
- Model code should be well-documented and allow for an independent reviewer to easily reproduce any results.
- If sources and calculations for model parameters are not fully documented, this is likely to delay significantly EPA's QA review of the model, hence possible use in consideration of the case for correction.
- The number of fitted parameters should be kept to a minimum to bound statistical uncertainty.
- The model must be validated or otherwise tuned to match existing in vivo PK data for rats and mice, both gas uptake and blood concentration data.
- If parameters need to be adjusted to match the in vivo PK data, then the adjustment should be consistent between data sets. For example, if different scaling factors are needed to fit mice vs. rat data, then it is not clear how the model can be reliably extrapolated to humans.
- Respiratory depression, if included, should be described as a continuous function of exposure concentration or another appropriate dose metric. The difference between acute PK studies and long-term bioassays should be rationally considered.
- While MCMC analysis has advantages, it is not necessary.
- Any analysis of parameter or internal dose uncertainty and significance of differences in parameters or internal dose between experimental groups (e.g., male vs. female mice) needs to be based on an appropriate calculation of statistical likelihood, given the experimental design. Serial samples from the same experimental unit are not independent.

References

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Klein, M., Neerchal, N., Sinha, B., Chiu, W., White, P. 2012. Statistical inferences from serially correlated methylene chloride data. The Indian Journal of Statistics. 74-B, Part 2, 211-37.

Exhibit C

Request for Reconsideration
Denka Performance Elastomer LLC

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June 26, 2017

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Via Federal Express and Electronic Mail (quality@epa.gov)
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Re: Request for Correction - Toxicological Review of Chloroprene (CAS No. 126-99-8) In Support of Summary Information on the Integrated Risk Information System (IRIS)

Dear Sir or Madam:

This Request for Correction is submitted under the Information Quality Act[1] and the U.S. Environmental Protection Agency's (EPA or the Agency) implementing guidelines (EPA Guidelines),[2] as well as the guidelines of the Office of Management and Budget (OMB)[3] and other applicable law, on behalf of Denka Performance Elastomer LLC (DPE).

DPE petitions EPA to correct information disseminated in the EPA document entitled "Toxicological Review of Chloroprene (CAS No. 126-99-8) In Support of Summary Information on the Integrated Risk Information System (IRIS)"[4] (the 2010 IRIS Review). The 2010 IRIS Review does not comply with the EPA Guidelines for the reasons summarized below and detailed in the toxicological and epidemiological expert review prepared by Drs. Kenneth Mundt, Robinan Gentry, and Sonja Sax, prominent scientists with Ramboll Environ, attached as Exhibit 1 (the Ramboll Environ Report). In sum, the 2010 IRIS Review provides conclusions and advice to the public that do not reflect the "best available science" or "sound and objective scientific

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1 Section 515(a) of the Treasury and General Government Appropriations Act for Fiscal Year 2001, P.L. 106-554; 44 U.S.C. § 3516 (notes).

2 EPA, Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by the Environmental Protection Agency (Oct. 2002).

3 67 Fed. Reg. 8452 (Feb. 22, 2002).

4 EPA/635/R-09/010F (September 2010).

practices" required under the EPA Guidelines.[5] Specifically, the 2010 IRIS Review should be corrected in three particular ways:

1. The 2010 IRIS Review establishes an erroneous human inhalation unit risk (IUR) of 5 x 10^{-4} per $\mu g/m^3$ expected excess cancers per lifetime (70 years) of exposure. An IUR is a basic cornerstone of quantitative air pollution risk assessment science. Ramboll Environ concludes that the IRIS IUR is 156 times too high and should be replaced with a more accurate value of 3.2 x 10^{-6} per $\mu g/m^3$, or the IUR should be withdrawn pending further review by EPA.
2. The 2010 IRIS Review classifies chloroprene as a "likely" human carcinogen based on erroneous interpretations of available data, particularly in the rejection of the primary conclusions of the leading epidemiological study of chloroprene that showed no linkage between worker exposure to chloroprene and the incidence of cancer. Chloroprene should instead be classified as a chemical for which there is evidence only suggestive of human carcinogenicity.
3. The Reference Concentration (RfC) for noncancer inhalation exposure risks reflects many of the same methodological errors as the IUR, and should be withdrawn pending further IRIS review.

DPE has been harmed by the erroneous information in the 2010 IRIS Review and EPA's failure to comply with the information quality guidelines. By way of background, DPE acquired the Neoprene production facility in LaPlace, Louisiana from DuPont on November 1, 2015. Chloroprene is the base feedstock for Neoprene, and DPE is in compliance with its air permits, all of which authorize chloroprene emissions. However, based in large part on the erroneous IUR – which was the primary input to the risk calculations in EPA's 2011 National Air Toxics Assessment (NATA) study published on December 17, 2015, right after DPE acquired the facility – EPA, the Louisiana Department of Environmental Quality (LDEQ), and many members of the public in Louisiana's St. John the Baptist Parish have turned DPE's air emissions into an environmental *cause célèbre*. Based on the erroneous IUR and the facility's emission characteristics, the NATA study erroneously identifies DPE's facility as associated with the highest offsite cancer risks of any chemical facility in the United States. This does not comport with data from the Louisiana Tumor Registry, which indicates that St. John the Baptist Parish has one of the lower cancer rates of any parish in the state.[6]

Since acquiring the facility, DPE has committed to spend approximately $18 million on pollution controls in order to reduce chloroprene emissions by approximately 85% below the facility's 2014 emissions. However, these dramatic emission reductions may not be sufficient to satisfy EPA emission reduction requirements based on the erroneous IUR and the emission profile of the facility.

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5 EPA Guidelines at p. 22.

6 https://statecancerprofiles.cancer.gov/incidencerates/index.php?stateFIPS=22&cancer=001&race=00&sex=0&age=001&type=incd&sortVariableName=rate&sortOrder=default#results.

The only ambient standard applicable to chloroprene is a Louisiana 8-hour standard of 857 $\mu g/m^3$. Even though there is no more stringent regulation, EPA has declared: "Based on this [IUR] value" in the 2010 IRIS Review, the appropriate risk level of "100-in-1 million" is 0.2 $\mu g/m^3$ on an annual average basis.[7] DPE's state-of-the-art emission reduction projects technologically cannot achieve this extraordinarily low ambient target.

Moreover, as a result of the erroneous IUR, DPE has suffered severe reputational damages. Public statements by EPA have led the public to expect the attainment of this extraordinarily low value of 0.2 $\mu g/m^3$. Citizen activists picket the facility and local schools wearing red t-shirts emblazoned with "Only 0.2 will do."

The damages to DPE resulting from the erroneous IUR, the classification of chloroprene as a "likely" human carcinogen, the RfC, and the related NATA findings are more fully summarized in the letter from Koki Tabuchi, DPE CEO, to EPA Administrator Scott Pruitt, dated June 26, 2017 (attached as Exhibit 3). For DPE, this matter is at a crisis point.

The Information Quality Act, its implementing guidelines, and public policy must be applied here to correct the 2010 IRIS Review. Under the EPA Guidelines, influential information like the 2010 IRIS Review is required to be based on the "best available science" and "sound and objective scientific practices." Public policy similarly argues for good science to provide the basis for chloroprene emission controls. Notwithstanding the significant amount of agency work that went into the compilation of the 2010 IRIS Review, the Review falls short of these information quality standards because it calculates the IUR with one unreasonably conservative assumption on top of another, without consideration of the full body of available scientific evidence.

As discussed further below, the 2010 IRIS Review preceded important reform initiatives recommended by the National Research Council (NRC) of the National Academies of Sciences in 2011 and 2014, which Congress and EPA have since embraced. The 2010 IRIS Review needs to be corrected in accordance with these reforms.

As the Ramboll Environ Report shows, the most significant error in the 2010 IRIS Review was EPA's failure to follow its own (and the NRC's) recommended method for estimating potential cancer risks in humans when relying on animal laboratory toxicity studies: physiologically based pharmacokinetic (PBPK) modeling. It is well established that interspecies differences in cancer susceptibility result from differences in how various species (including humans) metabolize chloroprene. These differences can and should be accounted for with PBPK modeling, resulting in a more appropriate and scientifically substantiated IUR. The Ramboll

[7] Memo from John Vandenberg, Director, Research Triangle Park Division, National Center for Environmental Assessment, Office of Research and Development, EPA, to Wren Stenger, Division Director, Multimedia Planning and Permitting Division, EPA Region 6, "EPA's Integrated Risk Information System (IRIS) Assessment of Chloroprene," dated May 25, 2016 (Exhibit 2) (Vandenberg Memo).

Environ Report calculates a PBPK-adjusted IUR value of 3.2×10^{-6} per $\mu g/m^3$, which is far more scientifically justified and appropriate than the IUR value contained in the 2010 IRIS Review.

Because the 2010 IRIS Review fails to comply with the EPA Guidelines, DPE requests that EPA take the following corrective action:

- Immediately issue notice to the public that the 2010 IRIS Review has been suspended (or withdrawn), pending further review;[8] and
- Review and revise the 2010 IRIS Review to reflect the best available science and sound and objective scientific practices, before reinstating it, including the following actions as suggested by the Ramboll Environ Report:
    - Replace the 2010 IRIS IUR of 5×10^{-4} excess cancers per $\mu g/m^3$ of chloroprene exposure with the best available and weight-of-evidence value of 3.2×10^{-6} per $\mu g/m^3$;
    - Lower the risk classification of chloroprene from "likely to be carcinogenic to humans" to a chemical for which there is only "suggestive evidence of carcinogenic potential"; and
    - Correct the Reference Concentration (RfC) for chronic inhalation exposure noncancer health effects to address the same fundamental difference between rodent and human susceptibility to chloroprene health effects.

Alternatively, DPE requests that EPA *immediately withdraw only the incorrect IUR and RfC values pending further review*, and then correct those values to reflect the best available science and sound and objective scientific practices.

DPE's Request for Correction is organized into six sections: Section I demonstrates that the 2010 IRIS Review constitutes "information" "disseminated" to the public; Section II shows that the 2010 IRIS Review is subject to heightened information quality standards because it is influential scientific information; Section III explains how the 2010 IRIS Review fails to comply with the EPA Guidelines; Section IV shows how EPA's correction of the 2010 IRIS Review would benefit DPE, which has been harmed by its errors; Section V provides DPE's contact information; and Section VI sets forth the relief that DPE is seeking.

I. The 2010 IRIS Review is Information Disseminated to the Public

The EPA Guidelines apply to "information" that EPA "disseminates" to the public.[9] "Information" in this context "generally includes any communication or representation of

[8] In response to similar requests for correction relating to deficient or unsound IRIS assessments, EPA has withdrawn those assessments. *See, e.g.*, Oct. 24, 2012 Letters from Monica Jones, Director, Quality Staff, Office of Environmental Information, to Methanol Institute (regarding IRIS toxicological review of methanol) and to Bergeson & Campbell (regarding IRIS toxicological review of inorganic arsenic).

[9] EPA Guidelines at p. 15.

knowledge such as facts or data, in any medium or form" including on a webpage.[10] For purposes of the EPA Guidelines, EPA "disseminates" information to the public "when EPA initiates or sponsors the distribution of information to the public."[11]

Clearly, the 2010 IRIS Review meets these threshold requirements. First, it is "information." Among other things, the 2010 IRIS Review classifies chloroprene as "*likely to be carcinogenic to humans*."[12] The 2010 IRIS Review also establishes a chronic cancer human inhalation unit risk estimate (or IUR) of 5 x 10^{-4} per $\mu g/m^3$. The IUR is a fundamental cornerstone of air pollution risk assessment modeling. Further, for noncancer effects, the 2010 IRIS Review establishes a Reference Concentration (RfC) for chronic inhalation exposure of 2 x 10^{-2} mg/m^3.[13]

Second, there is no question that EPA is responsible for distributing the 2010 IRIS Review to the public. EPA released the 2010 IRIS Review to the public in September 2010 by posting it on its website.[14] The 2010 IRIS Review is still prominently featured on EPA's website to this day.[15]

II. As Influential Scientific Information, the 2010 IRIS Review is Subject to a Heightened Standard of Quality

The EPA Guidelines require "influential" scientific information to meet a "higher degree of quality."[16] In particular, EPA has established very rigorous standards for "influential scientific risk assessment information."[17] These stringent quality standards are applicable here.

First, the 2010 IRIS Review clearly constitutes "influential" risk assessment information. The term "influential" means that EPA can "reasonably determine that dissemination of the information will have or does have a clear and substantial impact (i.e., potential change or effect)

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10 EPA Guidelines at p. 15.

11 EPA Guidelines at p. 15.

12 2010 IRIS Review at pp. 96-97 (emphasis in original).

13 2010 IRIS Review at p. 123.

14 *See, e.g.*, https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=236845 (last visited June 21, 2017) (attaching 2010 IRIS Review).

15 *See id; see also* https://www.epa.gov/la/laplace-louisiana-frequent-questions#carcinogen-determination (last visited June 21, 2017) (discussing 2010 IRIS Review).

16 EPA Guidelines at p. 19-20. Likewise, OMB has declared that: "The more important the information, the higher the quality standards to which it should be held." 67 Fed. Reg. at 8452.

17 EPA Guidelines at pp. 20-23.

on important public policies or private sector decisions."[18] The 2010 IRIS Review fits within this definition. Indeed, EPA has expressly acknowledged that IRIS assessments, such as the one at issue, generally constitute "influential" information for purposes of its information quality guidelines.[19]

The 2010 IRIS Review is particularly influential. EPA has emphasized that the 2010 IRIS Review "was developed using a robust, transparent, and public process and represents the Agency's top tier source of toxicity information on chloroprene." Vandenberg Memo at 2 (Exhibit 2). Moreover, based on the IUR in the 2010 IRIS Review, EPA's 2011 National Air Toxics Assessment (NATA) identified DPE's facility as having the highest offsite cancer risk in the United States,[20] where "the facility total is higher [than] the 2nd highest facility by 2 orders of magnitude."[21] Further, following the NATA study, EPA and LDEQ pressed DPE to radically reduce its facility emissions in order to meet an annual average ambient air target of 0.2 $\mu g/m^3$ for chloroprene.[22] This ambient target is based on the IUR from the 2010 IRIS Review. Accordingly, DPE is installing state-of-the-art emission reduction devices at a capital cost of approximately $18 million to decrease its chloroprene emissions.[23] However, even these significant measures will not be sufficient to meet the 0.2 $\mu g/m^3$ ambient target, placing DPE's future viability at risk.

For influential scientific risk assessment information like the 2010 IRIS Review, the EPA Guidelines require EPA to ensure that:

> (A) The substance of the information is *accurate, reliable and unbiased.* This involves the use of:
>
> (i) *the best available science and supporting studies conducted in accordance with sound and objective scientific practices,* including, when available, peer reviewed science and supporting studies; and
> (ii) data collected by *accepted methods* or *best available methods* (if the reliability of the method and the nature of the decision justifies the use of the data).

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18 EPA Guidelines at p. 19.

19 70 Fed. Reg. 17766, 17770 (April 7, 2005).

20 *See, e.g.*, https://www.epa.gov/la/laplace-louisiana-frequent-questions#highest-risks (last visited June 21, 2017) ("The top 6 census tracts with the highest NATA-estimated cancer risks nationally are in Louisiana due to Denka (formerly DuPont) chloroprene emissions.").

21 Email from K. Petersen, LDEQ, to D. Grego, DuPont, dated June 25, 2015 (Exhibit 4) (comment relating to preliminary NATA risk assessment calculations).

22 *See, e.g.*, Letter from Chuck Carr Brown, Secretary, LDEQ, to DPE (May 27, 2016) (Exhibit 5).

23 *See* Letter from DPE to EPA Administrator Pruitt (Exhibit 3).

EPA Guidelines at p. 22 (emphases added).

In calling for the use of "best available science," the EPA Guidelines expressly recognize that "scientific knowledge about risk is rapidly changing and … risk information may need to be updated over time."[24] The EPA Guidelines specify that an "influential" risk assessment should be updated when *inter alia* the assessment will have a "clear and substantial impact" on private sector decisions.[25] The "clear and substantial impact" standard is met here, in light of the decisions that DPE is compelled to make and the significant resources it must expend in responding to the directive from EPA and LDEQ for DPE to radically reduce its chloroprene emissions.

Moreover, the "best available science" standard clearly encompasses recent pertinent recommendations from the National Academies of Sciences National Research Council (NRC). In particular, following EPA's issuance of the 2010 IRIS Review, the NRC recommended major changes to IRIS's methodology in 2011[26] and 2014;[27] and Congress repeatedly instructed EPA in 2012, 2014, and 2015 to enhance and improve the IRIS methodology to address the NRC recommendations.[28] EPA, in turn, advised Congress that it would be and was implementing these changes.[29] The NRC's recommendations for modified IRIS risk assessment methods plainly represent the "best available science" and "sound and objective scientific practices" required by the EPA Guidelines. Further, EPA's current IRIS Program Multi-Year Agenda expressly recognizes the importance of updating IRIS values.[30] However, on August 9, 2016, Ramboll Environ scientists met with EPA IRIS staff members to discuss their concerns about the 2010 IRIS Review. At that meeting, EPA staff indicated that they are unable to undertake the

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24 EPA Guidelines at p. 23.

25 EPA Guidelines at p. 23.

26 National Research Council, Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde (2011).

27 National Research Council, Review of EPA's Integrated Risk Information System (IRIS) Process, at 3 (2014).

28 H.R. Rep. No. 112-331 at 1072 (Dec. 15, 2011) (Conference Committee joint explanatory statement accompanying 2012 Consolidated Appropriations Act); 160 Cong. Rec. H475, H977 (Jan. 15, 2014) (explanatory statement accompanying 2014 Consolidated Appropriations Act); H. R. Rep. No. 113-551 at 59 (July 23, 2014), *cited in* 160 Cong. Rec. H9307, H9766 (Dec. 11, 2014) (explanatory statement accompanying Consolidated and Further Continuing Appropriations Act of 2015).

29 *See* U.S. Environmental Protection Agency Office of Research and Development, EPA's Integrated Risk Information System Program Progress Report and Report to Congress at 11 (June 2012); U.S. Environmental Protection Agency Office of Research and Development, EPA's Integrated Risk Information Program Progress Report and Report to Congress at 3 (Feb. 2015).

30 IRIS Program Multi-Year Agenda (Dec. 2015) (https://www.epa.gov/iris/iris-agenda).

requisite work to employ the best available science to update the inaccurate chloroprene assessment primarily due to "resource constraints."[31]

III. The 2010 IRIS Review Fails to Comply with the EPA Guidelines

As shown below (and explained in greater depth in the Ramboll Environ Report), the 2010 IRIS Review does not reflect the "best available science" or "sound and objective scientific practices" required by the EPA Guidelines. Accordingly, the 2010 IRIS Review must be corrected.

In sum, the IUR is flawed and must be replaced with a more scientifically rigorous value. The IUR is based on the faulty assumption that carcinogenic results reported in the most sensitive species and gender in the laboratory – the female mouse – can be used to predict the potential for carcinogenic risk in the human without fully considering differences in the way mice and humans metabolize chloroprene. To correct this error, EPA should have employed a PBPK model to adjust for cross-species differences in susceptibility to chloroprene risks.

Moreover, the extraordinarily high IUR in the 2010 IRIS Review is not consistent with the epidemiological data, which do not demonstrate higher rates of cancers in humans occupationally-exposed to chloroprene compared with the general, unexposed population. The 2010 IRIS Review rejected the conclusion from the leading epidemiological study on chloroprene that there are not higher rates of cancer following chloroprene exposure in workers. Indeed, the data showed that many of the study cohorts had a lower incidence of cancer than the control or unexposed population. The 2010 IRIS Review, however, substituted its own interpretation of that study, selectively highlighting the *appearance* of a higher (but not statistically significant) risk of certain cancers among more highly chloroprene-exposed groups compared with the risk in the least exposed group. This difference is based on a relative deficit (that is, fewer than would be expected in the general population) in the comparison group, likely due to chance, and not due to increased risk among the exposed workers.

Ramboll Environ demonstrates in their report that reliance on the IUR in the 2010 IRIS Review results in an estimate of expected cancer much larger than those reported in the epidemiological data. In contrast, reliance on the PBPK-adjusted IUR value produces an estimate of expected cancers that is consistent with the epidemiological results. In addition, the PBPK-adjusted value is more in line with the IURs for similar chemicals in the environment, such as vinyl chloride, 1,3-butadiene, and benzene.

A. Epidemiological Evidence Shows No Increase in Cancers Among Workers Highly Exposed to Chloroprene

The 2010 IRIS Review classified chloroprene as "likely to be carcinogenic to humans" in part based on EPA's interpretation of "an association between liver cancer risk and occupational

[31] Letter from Kenneth A. Mundt, Ramboll Environ, to John Vandenberg, Director of Research at National Center for Environmental Assessment, EPA (Aug. 23, 2016) (Exhibit 6).

exposure to chloroprene" and "suggestive evidence of an association between lung cancer risk and occupational exposure."[32] However, EPA's evaluation of the epidemiological evidence in the 2010 IRIS Review was flawed because it failed to take into account required quality criteria set forth in EPA's "Guidelines for Carcinogen Risk Assessment" (2005), which are largely consistent with NRC's recommendations (NRC 2014). In sum, the 2010 IRIS Review gave equal weight to poor quality Russian, Armenian, and Chinese epidemiological studies, and erroneously interpreted and rejected the conclusions of the leading epidemiological study to support a finding of a linkage between chloroprene exposure in workers and the incidence of cancer.[33]

When Ramboll Environ applied the NRC and EPA criteria, it reached largely opposite conclusions from those of the 2010 IRIS Review: Ramboll Environ's appropriate weighing and synthesis of the epidemiological evidence demonstrated that chloroprene exposure is unlikely to cause lung or liver cancer at the occupational exposure levels encountered in the underlying studies. Furthermore, in contrast with EPA's interpretation, the lack of any clear cancer risk is consistent with the results from the animal studies demonstrating significant differences across species in the carcinogenic potential of chloroprene, and the mechanistic evidence that humans are far less sensitive to chloroprene.

Using an approach consistent with EPA (2005) and NRC (2014), Bukowski (2009) evaluated the quality and weight-of-evidence associated with eight mortality studies of seven chloroprene-exposed cohorts from six countries. Bukowski found that the four-cohort Marsh *et al.* (2007 a, b) study was by far the most methodologically rigorous study to date, having the largest overall cohort size and follow-up and therefore the highest statistical power. Under EPA (2005) and NRC (2014), the Marsh *et al.* (2007 a, b) study *should* have been given more weight than the other studies. In the 2010 IRIS Review, however, EPA failed to do that. To the contrary, the 2010 IRIS Review actually misinterpreted the Marsh *et al.* study to reach the opposite conclusions from those of the study authors.

Marsh et al. (2007 a, b) found no excess cancer mortality among chloroprene-exposed workers. Specifically, Marsh *et al.* concluded that "persons exposed to chloroprene … did not have elevated risks of mortality from any of the causes of death examined, including all cancers combined and lung and liver cancer, the cancer sites of *a priori* interest."[34] The Marsh study calculated standardized mortality rates (SMRs), the ratio of cancer mortality in exposed classes of workers to the general population, for its epidemiological evaluation. Marsh evaluated 15 categories of exposed workers and concluded that there was no elevated cancer risk to the exposed workers.

EPA, however, rejected this primary finding, and instead relied on a statistically insignificant evaluation of three calculated SMRs greater than 1.00 for three small subgroups of exposed workers. As the Ramboll Environ Report notes, however, these three subgroups used

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32 Ramboll Environ Report at p. 15.

33 *See* Ramboll Environ Report at pp. 15-23.

34 G.M. Marsh *et al.*, Chemico-Biological Interactions 166 (2007) 285-300, at p. 298.

for comparison were so small that the findings may have been due entirely to chance. In particular, each of these comparison groups exhibited a deficit (that is, fewer than expected based on general population rates) of liver cancers. There were only two to six liver cancer deaths in the comparison groups, making that subgroup analysis statistically unreliable. Because of the deficit of cases in the comparison group, Marsh *et al.* (2007 a, b) pointed out that there is an apparent but *statistically non-significant elevation* (that is, an elevation *likely due to chance*) in risk among the exposed groups. Even if these subgroup analyses were appropriate and representative of overall study findings, the failure to achieve statistical significance should have been noted and taken into account. Quite simply, Marsh *et al.* (2007 a, b) does not demonstrate a causal association between chloroprene exposure and lung or liver cancer.

Furthermore, EPA gave equal weight to epidemiological studies from Armenia (Bulbulyan *et al*. 1999), Russia (Bulbulyan *et al.* 1998), and China (Li *et al*. 1989). Under the NRC's recommendations, however, *less* weight should be accorded to these particular studies because they contain significant limitations. For instance, the results of these studies are statistically weak due to small study populations in which the expected number of specific cancer deaths is often less than two. These studies also contain inaccurate reference population rates leading to improper estimates of expected deaths. Additionally, these studies do not control for other causes of cancer in those regions (*e.g.*, in China, where there are high rates of liver cancer due to hepatitis B viral infection and aflatoxin exposure, and in Armenia and Russia, where there are high levels of tobacco use and alcohol consumption).[35]

Taken as a whole, the epidemiological evidence on chloroprene and cancer is insufficient to conclude that chloroprene is a human carcinogen. Further, this evidence is consistent with the toxicological hypothesis that humans are less sensitive than animals to the possible carcinogenic effects of chloroprene, and also supports the conclusion by Allen *et al*. (2014) that a modified cancer IUR that accounts for animal-to-human extrapolations is needed (as further discussed below).

As a "validity check," Ramboll Environ calculated the expected cancer rates for the Marsh study group exposure levels with both the 2010 IUR calculated by EPA and a PBPK-adjusted IUR. As stated in the Ramboll Environ Report:

> Marsh et al. (2007a) reported less than one excess liver cancer death when compared to US rates, and a deficit of about two liver cancer deaths when compared to the more appropriate local country rates. In contrast, using the 2010 Review IUR and mean reported chloroprene exposures, approximately 15 excess liver cancer deaths should have been observed. Repeating this exercise using the risk estimate derived by Allen et al. (2014), we showed that the estimated excess cancer risk estimates were consistent with the observed cases reported by Marsh et al. (2007a).

[35] These limitations have not been rectified by investigators in subsequent analyses of these cohorts since their original publication.

Ramboll Environ Report at p. 51. In short, use of the 2010 IUR calculated by EPA drastically over-predicts cancers among chloroprene-exposed workers, while a PBPK-adjusted IUR leads to predictions in accord with the results from studies of workers occupationally exposed to chloroprene.

B. The IUR Does Not Reflect the Best Available Science or Sound and Objective Scientific Practices

The IUR in the 2010 IRIS Review does not reflect the "best available science" or "sound and objective scientific practices." Accordingly, the IUR must be withdrawn and corrected.

1. The IUR is Primarily Based on Data from the Female Mouse, Which is Uniquely Sensitive to Chloroprene Exposure

In developing the IUR, EPA relied on the studies conducted by the National Toxicology Program (NTP) in mice and rats (NTP 1998), and a study conducted by Trochimowicz *et al.* (1998) in rats and hamsters. The animal data showed very little consistency across species in tumor incidence and sites. Based on the number of tumors and tumor sites, the female mouse was determined by EPA to be the most sensitive species and gender, with the incidence of lung tumors statistically elevated at all exposure levels in both female and male mice. Rats were found to be less sensitive to chloroprene exposure than mice.

Statistically significant increased lung tumor incidence was not observed in any other animal species evaluated. The incidence of liver tumors in mice were statistically increased only in female mice at the highest exposure level (80 parts per million [ppm]), and no significant increase in the incidence of liver tumors was observed in rats or hamsters. For other tumor sites, statistically increased incidences were found primarily at the highest exposure levels (i.e., 80 ppm). In the study by Trochimowicz *et al.* (1998), there were few statistically significant increases in tumor incidence, no statistically significant trends observed with increasing concentration, and, in hamsters, only a small proportion of animals (20% or less) had any observed tumors.

These results indicated substantial species differences and demonstrated that the female mouse is uniquely sensitive to chloroprene exposure, with lung tumors being the most sensitive endpoint. In addition, the fact that rats are less sensitive to chloroprene exposure than mice points to significant species differences that cannot be disregarded in the human carcinogenicity evaluation. These differences relate to how various species metabolize chloroprene. EPA's IUR, however, failed to take these differences into consideration, and simply assumes that humans metabolize chloroprene in the same manner as a select strain of female mice and therefore are as sensitive to chloroprene as these female mice.[36]

[36] *See* Ramboll Environ Report at pp. 7-8, 39-40.

2. The IUR Rests on the Unwarranted Assumption that Different Tumor Types are Statistically Independent

In deriving the IUR for chloroprene, EPA used a composite value that was based on multiple tumor types, rather than its standard approach of using the most sensitive species, gender, and endpoint. EPA's composite approach is based on the assumption that the different tumor types are statistically independent. But, as shown in the Ramboll Environ Report, the underlying data do not demonstrate mechanistic or biological independence.[37] In other words, the mechanism of action in multiple tissues could be due to dependent events; for example, a liver tumor could be dependent on the generation of the same metabolite that leads to the development of a lung tumor.

As further discussed in the Ramboll Environ Report, EPA's assumption that multiple tumor types are independent led EPA to consider individual animals multiple times if they had multiple types of tumors. This approach significantly overstates the carcinogenicity of chloroprene. Indeed, EPA itself recognized in the 2010 IRIS Review that if the assumption of independence is not valid, then the assumption would overestimate risk.[38] As Ramboll Environ points out, this assumption alone led EPA to overestimate risk by 50%. EPA then further magnified that overestimation by rounding its composite inhalation IUR up to a single digit, resulting in an even more overly conservative value.[39]

3. The IUR Rests on the Assumption that Chloroprene Has A Mutagenic Mode of Action, But the Available Evidence Does Not Support that Assumption

At the final step in calculating the IUR for chloroprene, EPA applied an age-dependent upward adjustment factor based on its hypothesis that chloroprene has a mutagenic mode of action. This upward adjustment was not warranted because the available evidence does not support a mutagenic mode of action for chloroprene.

The term "mode of action" (MOA) describes the sequence of key events and processes, starting with the interaction of a chemical and a cell, leading to cancer formation. The 2010 IRIS Review hypothesized that chloroprene could have a mutagenic MOA (where "mutagenic" refers to the capacity of the chemical to react with or bind to DNA in a manner that causes mutations).

However, an evaluation consistent with the NRC (2011, 2014) recommendations shows chloroprene's genotoxicity profile lacks several attributes necessary to conclude that there is a mutagenic MOA, including negative findings from an *in vivo* test of genotoxicity and lack of consistent findings of point mutation induction in *in vitro* and *in vivo* studies.

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37 Ramboll Environ Report at p. 27.

38 2010 IRIS Review at p. 123.

39 Ramboll Environ Report at p. 28.

Overall, unlike known carcinogens such as 1,3-butadiene, the evidence does not support a mutagenic MOA for chloroprene. We refer the Agency to the more detailed discussion of the foregoing points presented in the Ramboll Environ Report.[40] The result, though, is clear: the evidence does not support making an adjustment to the IUR on the basis of a hypothesized mutagenic MOA.

4. The IUR Must Be Corrected By Employing the PBPK Model to Sufficiently Account for Differences in Mice and Humans

In light of the difference in tumor incidence between the female mouse and other species, as well as the lack of evidence for a mutagenic MOA, it is important to evaluate the pharmacokinetics that may explain the profound cross-species differences. Himmelstein *et al*. (2004 a, b) developed a chloroprene physiologically based pharmacokinetic (PBPK) model to help explain the divergent results observed across animal species. The model estimated the disposition of chloroprene in the lungs of mice, rats, and hamsters following inhalation exposure. Using this model, Himmelstein *et al.* (2004 a, b) showed greater correspondence between the amount of metabolized chloroprene in lung tissue (internal dose) and the tumor incidence results than results based on inhaled concentration. This finding supported the hypothesis that chloroprene metabolites are responsible for the observed tumor incidence in animals, and that because different animals metabolize chloroprene at different rates, toxicity across species will differ. Himmelstein *et al.*'s (2004 a, b) results confirmed that the mouse is the most sensitive species and that humans are likely to be comparatively less sensitive to the effects of chloroprene exposure.

EPA claimed that it did not use the PBPK model developed by Himmelstein *et al.* (2004 a, b) to inform the IUR in the 2010 IRIS Review because the data required to validate the model had not been published. However, all of the quantitative data necessary to refine and verify the critical parameters for the existing peer-reviewed PBPK model for chloroprene (Himmelstein *et al.* 2004b) were available at that time and could have been applied to adjust the cancer unit risk to account for species-specific target-tissue dosimetry. Further, since the 2010 IRIS Review was issued, these data have been published, and the model has been validated (Thomas *et al.* 2013, Yang *et al.* 2012, Allen *et al.* 2014). In particular, Allen *et al.* (2014) derived an IUR based on PBPK results that was 100 times lower than EPA's value, using a method which integrates both the animal and human evidence. Importantly, the IUR reported by Allen *et al.* (2014) is comparable to IURs for similar compounds, such as vinyl chloride, which have stronger and more consistent epidemiological evidence of human carcinogenicity than chloroprene.

The NRC (2014) has advised that, if sufficient and relevant quantitative information is available, PBPK models should be constructed to assist in the determination of tissue dosimetry, species-to-species extrapolation of dose, and route-to-route extrapolation. Indeed, in the 2010 IRIS Review itself, EPA acknowledged: "Ideally, a PBPK model for the internal dose(s) of the reactive metabolite(s) would decrease some of the quantitative uncertainty in interspecies extrapolation; however, current PBPK models are inadequate for this purpose."[41] Now, in 2017,

[40] *See* Ramboll Environ Report at pp. 9-14, 29.

[41] 2010 IRIS Review at p. 141.

adequate PBPK models certainly do exist. They have been peer-reviewed, published, and validated. There simply is no good excuse for ignoring them.

In sum, the IUR should be reassessed based on the validated PBPK model, which will lead to a much more accurate IUR.[42]

5. The Correct Chloroprene IUR is 156 Times Lower than the Chloroprene IUR Derived by EPA

As explained in detail in Exhibit 1, Ramboll Environ recalculated the IUR to correct the scientific deficiencies identified above.[43] In particular, Ramboll Environ applied a PBPK model to account for species-specific pharmacokinetic differences. Additionally, Ramboll Environ's IUR contains no upward adjustment for a mutagenic MOA, because such an adjustment is not supported by the available evidence.

Based on this approach, Ramboll Environ calculated an IUR of 3.2×10^{-6} per $\mu g/m^3$ (which is of the same order of magnitude as the IUR derived by Allen *et al.* (2014)). Notably, Ramboll Environ's value is 156 times lower than EPA's IUR. Consequently, Ramboll Environ's IUR would provide an ambient target concentration of 31.2 $\mu g/m^3$, 156 times higher than EPA's proffered value. Ramboll Environ's analysis confirms that the IUR in the 2010 IRIS Review is scientifically invalid and must be corrected and updated immediately.

C. EPA's IUR for Chloroprene is Drastically Higher Than IURs for Similar Chemicals

EPA's IUR for chloroprene is dramatically higher than IURs for similar chemicals. It is extremely important for EPA to use consistent scientific methodology for different chemicals, and it has not done so with chloroprene. Although the dramatic difference between the 2010 IUR for chloroprene and those for similar chemicals does not directly demonstrate that the 2010 chloroprene IUR is incorrect, it clearly provides a "reality check" and a basis for additional scrutiny of the 2010 IUR. And in the regulatory world of air pollution controls, the dramatic difference in the 2010 chloroprene IUR and those of similar chemicals translates into the difference between technologically feasible and infeasible emission control technologies.

Specifically, the IURs for several known carcinogenic compounds are 1 to 2 orders of magnitude lower than the chloroprene IUR, and are supported by stronger human epidemiological evidence (1,3-butadiene and benzene) or reflect the application of PBPK modeling to extrapolate results from animals to humans (vinyl chloride). One of the 2010 IRIS Review's stated reasons for characterizing chloroprene as a "likely" human carcinogen is the structural similarity between chloroprene and "known" carcinogens, like vinyl chloride and 1,3-butadiene.

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42 *See* Ramboll Environ Report at pp. 39-43.

43 *See* Ramboll Environ Report at pp. 44-50.

For vinyl chloride, and in contrast to chloroprene, the epidemiological evidence linking vinyl chloride with angiosarcomas of the liver, as well as primary hepatocellular cancers, is clear and consistent (Boffetta *et al.* 2003, Mundt *et al*. 2000, Mundt *et al.* 2017). EPA appropriately applied a PBPK model for vinyl chloride to account for differences between animals and humans, resulting in a cancer IUR that is approximately 57 times lower than the IUR for chloroprene.

Likewise, the IUR for 1,3-butadiene is based on sufficient and stronger epidemiological evidence. Further, there is a large body of evidence related to PBPK modeling of 1,3-butadiene that explains large differences in pharmacokinetics across species for 1,3-butadiene, much like the differences observed for chloroprene. This information is critical to informing the chloroprene IUR, particularly in light of insufficient epidemiological data. The 1,3-butadiene IUR based on human occupational studies is 17 times lower than the IUR for chloroprene.

Table 8.1 of the Ramboll Environ Report contains these comparisons and others (*e.g.*, the IUR for benzene is 64 to 227 times lower than the chloroprene IUR). The comparison of the chloroprene IUR with the IURs of known carcinogens – for which there is stronger evidence of human carcinogenicity – suggests that the chloroprene IUR from the 2010 IRIS Review is greatly at odds with the IURs for similar chemicals and should be viewed as suspect and deserving of further review.

D. EPA's Classification of Chloroprene as "Likely to be Carcinogenic to Humans" Should Be Reviewed

Additionally, EPA must reconsider the cancer classification for chloroprene. In the 2010 IRIS Review, EPA characterized chloroprene as "likely to be carcinogenic to humans" based on the following five criteria:

> (1) statistically significant and dose-related information from the NTP (1998) chronic inhalation bioassay data demonstrating the early appearance of tumors, development of malignant tumors, and the occurrence of multiple tumors within and across animal species;
> (2) evidence of an association between liver cancer risk and occupational exposure to chloroprene;
> (3) suggestive evidence of an association between lung cancer risk and occupational exposure;
> (4) a proposed mutagenic mode of action (MOA); and
> (5) structural similarities between chloroprene and known human carcinogens, 1,3-butadiene and vinyl chloride.

Ramboll Environ Report at p. 24. As noted above, however, three of the five criteria are based on EPA's misinterpretation of the underlying data. Further, the last criterion (structural similarities with known human carcinogens) is not informative because chloroprene has a different mode of action. In sum, based on the limited evidence remaining to support the

potential carcinogenicity of chloroprene, Ramboll Environ concludes that "a more appropriate classification of chloroprene is 'suggestive evidence of carcinogenic potential.'"[44]

In reaching that conclusion, Ramboll Environ observes that the epidemiological evidence, based on an appropriate weight of evidence approach, fails to demonstrate clearly increased risks among exposed occupational groups and the general population, and a weak difference between exposed and unexposed workers reflecting a deficit among the least exposed. This lack of evidence of the carcinogenicity in the human studies indicates that chloroprene should not be characterized as a "likely" human carcinogen.

Additionally, although chloroprene shares structural similarities with 1,3-butadiene and vinyl chloride, the toxicological evidence including possible modes of action (MOAs) demonstrate substantial differences between chloroprene, vinyl chloride, and 1,3-butadiene. As discussed above, the claim that chloroprene is mutagenic is not supported by the overall evidence from the available data.

Most importantly, EPA's narrative description does not include discussion of critical uncertainties in relying on the mouse data from the NTP (1998) to predict the potential for carcinogenic risk in the humans, given ample evidence of important pharmacokinetic differences between mice and other species. In fact, as noted above, the NTP study and other animal studies show that there is little evidence of consistent tumorgenicity across species other than the mouse and in particular the hamster. This difference can clearly be explained by evidence of differences in the pharmacokinetics of chloroprene across species.

Accordingly, EPA's classification of chloroprene as a "likely" human carcinogen is unwarranted. Instead, EPA should characterize the weight of evidence for chloroprene as only "suggestive" of human carcinogenicity.

E. EPA's Reference Concentration (RfC) for Chronic Inhalation Exposure Should Be Reviewed

Further, the 2010 IRIS Review establishes a Reference Concentration (RfC) for chronic inhalation exposure of 2×10^{-2} mg/m^3 for noncancer effects.[45] According to EPA, "the RfC is an estimate of a daily exposure to the human population (including susceptible subgroups) that is likely to be without an appreciable risk of health effects over a lifetime."[46] RfCs are derived for compounds for which inhalation is an important route of exposure, including gases such as chloroprene. However, EPA's RfC in the 2010 IRIS Review suffers from many of the same flaws as the IUR.

In particular, EPA did not employ a PBPK model to adjust the RfC to account for different species' differing sensitivity to chloroprene. The RfC is based on the National

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44 Ramboll Environ Report at p. 24.

45 2010 IRIS Review at p. 123.

46 2010 IRIS Review at p. 113.

Toxicology Program's two-year chronic inhalation study of rats and mice (NTP, 1998). EPA selected all noncancer endpoints that were statistically increased in mice and rats at low and mid-exposure levels compared with controls, and then employed benchmark dose modeling using its own software to estimate a Point of Departure (POD). As the Ramboll Environ Report explains, these noncancer endpoints suggest "significant cross-species and strain differences in the toxicological response to inhaled chloroprene" and underscore the need for adjusting the RfC value based on a PBPK model.[47] PBPK methods have been used to derive appropriate RfCs for other relevant chemicals, including vinyl chloride.

Additionally, as the Ramboll Environ Report shows, the RfC reflects the application of unwarranted conservative adjustments. For instance, EPA applied an uncertainty factor of 3 to account for database deficiencies related to the lack of a 2-generation reproductive study. This adjustment is not needed based on several lines of evidence, including evidence showing that a 1-generation study should adequately provide the potential for reproductive effects following exposure to chloroprene.[48]

Accordingly, EPA needs to review the RfC to correct these deficiencies.

IV. EPA's Corrections of the 2010 IRIS Review Would Benefit DPE, Which Has Been Harmed by the Errors

As shown in the attached letter from DPE to Administrator Pruitt, DPE has been harmed by the errors in the 2010 IRIS Review and its IUR, and it will continue to be harmed until EPA withdraws and corrects the 2010 IRIS Review and IUR.

As noted above, DPE acquired the Neoprene facility from DuPont on November 1, 2015. Shortly after the acquisition, on December 17, 2015, EPA publicly released its 2011 National Air Toxics Assessment (NATA), which identified DPE as creating the greatest offsite risk of cancer of any manufacturing facility in the United States. The NATA findings concerning DPE are based on the incorrect IUR in the 2010 IRIS Review and the emission profile of the Neoprene facility.

Following the public release of the NATA, EPA and the Louisiana Department of Environmental Quality (LDEQ) pressed DPE to reduce emissions to achieve an ambient air target of 0.2 $\mu g/m^3$ for chloroprene on an annual average basis. The 0.2 $\mu g/m^3$ target is based on the incorrect IUR in the 2010 IRIS Review, and represents more than a four thousand-fold reduction in the applicable standard. As DPE's letter explains, there is no agency rule or even proposed rule requiring the attainment of the 0.2 $\mu g/m^3$ target, yet EPA advised DPE, LDEQ, and the public that this is the appropriate value to achieve.

DPE is an environmentally proactive company, and it is fully committed to compliance with environmental requirements. Even though the 2010 IRIS Review and the IUR do not

[47] Ramboll Environ Report at p. 53.

[48] Ramboll Environ Report at pp. 53-54.

comply with the information quality standards, DPE is taking extraordinary steps to meet EPA's and LDEQ's demands. In January 2017, DPE entered into an agreement with LDEQ to reduce chloroprene emissions by approximately 85% as compared with the facility's 2014 emissions. As DPE notes in the attached letter, it estimates that the capital cost of these emission reduction devices is approximately $18 million, and the devices will cost hundreds of thousands of dollars per year to operate. Even though DPE is installing the most advanced air pollution controls available, DPE still will not be able to meet the stringent 0.2 $\mu g/m^3$ target.

Furthermore, because the 2010 IRIS Review and its IUR are flawed and incorrect, EPA's related public announcements have created unnecessary public alarm in LaPlace, Louisiana. For example, after issuing the NATA, EPA created a public webpage specifically addressing DPE's chloroprene emissions.[49] Additionally, environmental activists and plaintiffs' lawyers have had numerous meetings in the community about DPE, all based on the faulty assumption that 0.2 $\mu g/m^3$ is the "safe" level for chloroprene. Further, a local citizen's group has formed and has been handing out misleading flyers and protesting near DPE's facility.

In sum, the errors in the 2010 IRIS Review and the IUR and the related NATA findings have placed a substantial strain on DPE's limited resources, and have caused DPE severe reputational damage.

V. Other Required Information

The EPA Guidelines require requests for correction to include the name and contact information of the organization submitting the request, and to identify an individual to serve as a contact.

For this Request, the contact information is as follows:

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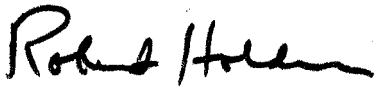
[49] *See* https://www.epa.gov/la/laplace-louisiana-background-information.

VI. Conclusion: 2010 IRIS Review Must Be Immediately Withdrawn and Revised

For the reasons set forth above and in the Ramboll Environ Report, DPE respectfully requests that: (1) this Request for Correction be granted; (2) the 2010 IRIS Review be suspended immediately, pending further review; and (3) EPA review and revise the 2010 IRIS Review to reflect the best available science and sound and objective scientific practices, as required by law.

Alternatively, as an interim measure, DPE requests that EPA immediately withdraw only the incorrect IUR and the RfC pending further review, and then correct those values based on the best available science and sound and objective scientific practices.

Very truly yours,



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REH:ddt
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Exhibit 1

Intended for

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BASIS FOR REQUESTING CORRECTION OF THE US EPA TOXICOLOGICAL REVIEW OF CHLOROPRENE

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RAMBOLL ENVIRON

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APPENDIX

ACRONYMS AND ABBREVIATIONS

ADAF	age-dependent adjustment factor
AIC	Akaike Information Criterion
BCME	bis(chloromethyl)ether
BMD	benchmark dose
BMD10	benchmark dose at the 10% extra risk level
BMDL	lower 95% confidence limit of the benchmark dose
BMDL10	lower 95% confidence limit of the benchmark dose at the 10% extra risk level
DAF	dosimetry adjustment factor
DPE	Denka Performance Elastomer, LLC
EDB:	ethylene dibromide
F1	first generation
IARC	International Agency for Research on Cancer
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
LOAEL	lowest-observed-adverse-effect level
µg/m^3	microgram(s) per cubic meter
MOA	mode of action
NATA	National Air Toxics Assessment
NDMA	nitrosodimethylamine
NOAEL	no-observed-adverse-effect level
NRC	National Research Council
NTP	National Toxicology Program
PBPK	physiologically based pharmacokinetic (model)
POD	point of departure
ppm	parts per million
Ramboll Environ	Ramboll Environ US Corporation
RR	relative risk
SIR	standardized incidence ratio
SMR	standardized mortality ratio
US EPA	United States Environmental Protection Agency
VCM	vinyl chloride monomer
WHO	World Health Organization
WOE	weight of evidence

EXECUTIVE SUMMARY

Background

In 2010, the United States Environmental Protection Agency (US EPA) Integrated Risk Information System (IRIS) program published a review of the epidemiology and toxicology literature on chloroprene to provide scientific support and rationale for hazard and dose-response assessment in IRIS, including deriving an inhalation unit risk (IUR) and other values for chronic exposure (www.epa.gov/iris).

In the "Toxicological Review of Chloroprene" (hereafter referred to as the "2010 Review") (US EPA 2010a), US EPA concluded that chloroprene was "likely to be carcinogenic to humans" based on (1) statistically significant and dose-related information from an National Toxicology Program (NTP 1998) chronic inhalation bioassay demonstrating the early appearance of tumors, development of malignant tumors, and the occurrence of multiple tumors within and across animal species; (2) evidence of an association between liver cancer risk and occupational exposure to chloroprene; (3) suggestive evidence of an association between lung cancer risk and occupational exposure; (4) the proposed mutagenic mode of action (MOA); and (5) structural similarities between chloroprene and known human carcinogens butadiene and vinyl chloride (US EPA 2010a).

The 2010 Review derived an IUR for lifetime exposure to chloroprene of 5×10^{-4} per microgram per cubic meter ($\mu g/m^3$). This is the 5th highest IUR generated by US EPA to date for any chemical (not including carcinogenic metals or coke oven emissions) classified by US EPA or the International Agency for Research on Cancer (IARC) as a known or likely/probable human carcinogen. As outlined in detail below, we have determined that US EPA's classification relied on questionable, non-transparent evaluation and interpretation of the toxicological and epidemiological evidence. Therefore, the IUR for chloroprene was not based on the best standard methods US EPA has used for other carcinogens.

The IRIS Process: Challenges, Recent Changes, and Recommendations for Improvement

The US EPA IRIS process has been subject to high-level constructive criticism. Most noteworthy, subsequent to the 2010 Review, the National Research Council (NRC) of the National Academies of Science (NAS) published a series of reports recommending important changes to improve the IRIS process (NRC 2011, 2014). The recommendations were well received by US EPA, but have not yet been fully implemented, and have not been applied to previously published reviews. In particular, NRC (2011, 2014) emphasized the importance of transparency and rigor in the review methods. NRC (2011) provided guidance on development of inclusion and exclusion criteria for studies, and on methods for evaluating and taking into account various forms of bias and other methodologic characteristics that could impact study findings.

While the 2010 Review meets some of these NRC recommendations, it does not meet other key standards such as the evaluation and synthesis of the epidemiological and mechanistic data, and would benefit from their consideration and application. A transparent evaluation and integration of the published

epidemiological and toxicological evidence on chloroprene carcinogenicity highlights the need to reconsider US EPA's classification of chloroprene as "likely to be carcinogenic to humans" to be in line with the weight of evidence and the International Agency for Research on Cancer's (IARC 1999) classification of chloroprene as "possibly carcinogenic."

Toxicological Evidence

US EPA should evaluate the animal toxicological data that form the basis of the estimated chloroprene inhalation unit risk (IUR) in accordance with the NRC recommendations and US EPA standard risk evaluation methodologies. US EPA relied on the animal studies conducted by the NTP that showed very little consistency across species in tumor incidence and sites. These results indicated substantial species differences and demonstrated a unique sensitivity in the female mouse, with lung tumors being the most sensitive endpoint. Thus, US EPA used the female mouse data to derive the IUR, but without fully accounting for important pharmacokinetic differences between the mouse and humans.

In addition to revisiting the reliance on the animal dataset for the estimation of the IUR, US EPA should critically re-evaluate and integrate the cytotoxic and genotoxic evidence for chloroprene. The evidence from these studies indicates that chloroprene acts through a different mode of action (MOA) than the structurally similar and known human carcinogen 1,3-butadiene. Based on an evaluation consistent with the NRC (2011, 2014) recommendations, chloroprene's genotoxicity profile lacks several attributes necessary to conclude that there is a mutagenic MOA. Instead, the evidence supports site-specific cytotoxicity as a more likely MOA, as opposed to US EPA's conclusion that chloroprene acts *via* a mutagenic MOA.

Epidemiological Evidence

It is also necessary to critically evaluate the available epidemiological evidence on occupational chloroprene exposure. US EPA evaluated the epidemiological evidence of chloroprene carcinogenicity based on several occupational cohorts from around the world. This evaluation, however, would have benefited from more transparency and rigor with regard to how individual study quality was assessed and weighted in the overall weight-of-the-evidence assessment. In particular, US EPA did not assign more weight to the most recent epidemiological study by Marsh *et al*. (2007a, b), which also is the largest and most robust study to date. This study has been rated by other scientists as the best quality study available in part because it has the most comprehensive characterization of chloroprene exposure (Bukowski *et al*. 2009). Instead, US EPA equally weighted this study with poorer quality Russian, Armenian, and Chinese studies.

Marsh *et al.* (2007a, b) reported no excess occurrence of lung or liver cancers among chloroprene exposed workers. In fact, overall and for all sub-cohorts defined by specific plant(s), standardized morality ratios (SMRs) based on local reference rates were all below 1.0, providing no indication of any excess of these cancers among chloroprene exposed workers. US EPA, however, discounted this primary finding, and instead interpreted a correlation between exposure level and risk relative to a comparison subgroup where the comparison group exhibited

anomalously fewer cancers than expected, creating the appearance of an increased risk in the higher exposure groups. Furthermore, US EPA overlooked that there were as few as two liver cancer deaths in the comparison subgroup, likely reflecting a random deficit among this group. The US EPA summary of this study indicates incomplete evaluation and misinterpretation of the published results. Properly interpreted, the evidence does not demonstrate an association between occupational chloroprene exposure and human cancer incidence.

US EPA's Derivation of the Chloroprene IUR

US EPA derived the current chloroprene IUR based on a number of assumptions that are not substantiated by the scientific evidence, contributing to overestimation of an already conservative risk estimate *(i.e.*, one based on the most sensitive species, gender, and endpoint). Specifically, US EPA based the chloroprene IUR on a composite estimate of risk based on multiple tumors observed primarily in mice, not just the lung tumors for which the data were more conclusive. US EPA then assumed that the female mouse-based IUR was representative of continuous human exposure, and that lung tumors were systemic rather than portal-of-entry effects; US EPA also rounded up at various stages of adjustment. Finally, US EPA applied an age-dependent adjustment factor (ADAF) based on insufficient data to support a mutagenic MOA.

A PBPK Model for Chloroprene

In calculating the IUR, US EPA should have used the available pharmacokinetic model for chloroprene. Himmelstein *et al*. (2004 a,b) developed a physiologically based pharmacokinetic (PBPK) model for chloroprene to help explain the divergent results observed across animal species. The model demonstrates why the mouse is the most sensitive species and why humans are likely to be comparatively much less sensitive to the effects of chloroprene exposure.

The hypothesis that differences in pharmacokinetics are determinants of the observed species differences has been demonstrated for other chemicals, including vinyl chloride. Thus, it is scientifically appropriate that US EPA employ PBPK models, which use the best available science to adjust for these differences, to derive IURs for all chemicals, such as chloroprene, for which data are available.

US EPA did not use the PBPK model developed by Himmelstein *et al*. (2004 a,b) to inform the chloroprene IUR because US EPA noted that the data required to validate the model had not been published. However, all of the quantitative data necessary to refine and verify the critical metabolic parameters for the existing peer-reviewed PBPK model for chloroprene were available at the time of the 2010 Review and could have been used. Since then, additional data have been published, and the findings validate the model (Thomas *et al.* 2013, Yang *et al*. 2012, Allen *et al*. 2014). In particular, Allen *et al.* (2014) derived an IUR based on PBPK results and the incidence of respiratory cancer that was 100 times lower than US EPA's value, using a method which integrates both the animal and human evidence. Importantly, the IUR reported by Allen *et al*. (2014) is consistent with IURs for similar compounds such as vinyl chloride and 1,3-butadiene, which have stronger and more consistent epidemiological evidence of human carcinogenicity than chloroprene.

Calculation of an Updated Chloroprene IUR

We conducted an updated analysis by applying the results from validated PBPK models to arrive at an IUR that includes an understanding of interspecies pharmacokinetics. We applied standard US EPA methodology and conservative assumptions to estimate of the potential cancer effects of chloroprene. Our estimated IUR is 1.1×10^{-2} per ppm or 3.2×10^{-6} per $\mu g/m^3$, which is of the same order of magnitude as the IUR derived by Allen *et al*. (2014), and which better reflects the scientific understanding of potential chloroprene cancer effects in humans. These results are also consistent with the results from validated PBPK models and comparisons with other structurally relevant compounds such as vinyl chloride and 1,3-butadiene, both recognized as known human carcinogens.

There is little scientific support for each of US EPA's conservative assumptions and subsequent adjustments. Combining a fuller understanding of interspecies pharmacokinetic differences and validated PBPK models with the results from the strongest epidemiological data provides the scientific grounds for updating the 2010 IUR and calls into question the strength of the evidence to support a "likely to be carcinogenic to humans" classification. Similar adjustments should also be considered in estimating the chloroprene inhalation reference concentrations (RfC), as species- and strain-specific differences are noted. This will assure that policies and decisions resting on these toxicity values meet the test of sound science, transparent methods, and reproducible findings.

Conclusions

The IUR published in the 2010 Review requires correction. An updated IUR should be based on the best available methodology as well as a valid interpretation of the body of published evidence. Correction is critical given that the IUR published in the 2010 Review is being used by US EPA for enforcement actions.

1 INTRODUCTION

In December, 2015, the United States Environmental Protection Agency (US EPA) published the 2011 National Air Toxics Assessment (NATA), indicating a high off-site air pollution cancer risk from emissions of chloroprene from the Neoprene production facility in LaPlace, Louisiana. The previous month, on November 1, 2015, Denka Performance Elastomer, LLC (DPE), had acquired the LaPlace Neoprene production facility. The underlying NATA risk calculations combined estimated ambient chloroprene concentrations from air modeling analyses with the cancer inhalation unit risk (IUR) value derived by the US EPA Integrated Risk Information System (IRIS) and documented in the Toxicological Review of Chloroprene (hereafter referred to as the "2010 Review") (US EPA 2010a).

On behalf of DPE, Ramboll Environ US Corporation (Ramboll Environ) prepared this summary review of the US EPA toxicity assessment for chloroprene, focusing on a detailed review of US EPA's derivation of the cancer IUR reported in the 2010 Review (US EPA 2010a). US EPA's chloroprene risk assessment calculations are based on and directly proportional to US EPA's IUR for lifetime exposure to chloroprene of 5×10^{-4} per micrograms per cubic meter ($\mu g/m^3$). The chloroprene IUR is the 5th highest IUR generated to date for any substance classified by US EPA or the International Agency for Research on Cancer (IARC) as a known or likely/probable human carcinogen (not including carcinogenic metals or coke oven emissions). The chloroprene IUR is orders of magnitude higher than IURs derived by US EPA for substances, such as vinyl chloride, 1,3-butadiene, and benzene, that have been classified by US EPA as known human carcinogens.[1] In contrast, chloroprene has been classified as "likely to be carcinogenic to humans" based on a weight-of-evidence (WOE) assessment that included an animal inhalation study conducted by the National Toxicology Program (NTP 1998) and four (of nine) epidemiological studies reportedly indicating increased risks for liver cancer (US EPA 2010a). It was noted that these data were insufficient to classify chloroprene as a known human carcinogen. On the other hand, IARC classified chloroprene as "possibly carcinogenic to humans," based on the same evidence from experimental animal studies and similar epidemiological evidence concluded that the human evidence was inadequate (IARC 1999).

Since the 2010 Review (US EPA 2010a), the National Academies of Sciences National Research Council (NRC 2011, 2014) has recommended substantive improvements to the IRIS evaluation process, calling for greater transparency including improved methods for and documentation of scientific study selection, critical review of study quality and limitations, and the synthesis of findings across studies. This has provided much of the impetus for changes to the IRIS process. Improvements in the critical evaluation of epidemiological study quality and bias were noted as especially important, as statistical associations in epidemiological studies are only meaningful if supported by rigorous study design and data quality control. In addition, NRC noted the need for improved approaches to integrating evidence across diverse lines of investigation—including evidence from animal

[1] https://www.epa.gov/fera/dose-response-assessment-assessing-health-risks-associated-exposure-hazardous-air-pollutants

experiments, mechanistic investigations and epidemiological studies—in drawing conclusions regarding carcinogenicity and in deriving unit risk factors for cancer. NRC recommended better evidence integration that considers and weighs the entire body of scientific evidence, and that does not rely on select and unrepresentative findings (NRC 2011, 2014). Similarly, using formaldehyde as an example, NRC recommended improved use of evidence in risk assessments. NRC (2011) recommended using physiologically based pharmacokinetic (PBPK) models to quantify demonstrated differences in pharmacokinetics across species, and further recognized PBPK models as a tool to support extrapolations between species, thereby reducing the uncertainty in quantitative risk assessments (NRC 2014). These NRC recommendations remain highly relevant to the evaluation of chloroprene. In **Section 2**, we highlight key recommendations made by the NRC for improvements to the IRIS process that potentially impact the chloroprene evaluation.

Consistent with the NRC recommendations to improve the scientific quality and validity of the 2010 Review, US EPA needs to address significant uncertainties associated with the derivation of the IUR. These uncertainties pertain to the human relevance of the animal evidence, and whether or not various cancer types observed in animal experiments should be combined in estimating potential cancer risk to humans. Studies available both at the time of the 2010 Review, and published since, demonstrate clear and significant pharmacokinetic differences between humans and animals (Himmelstein *et al.* 2004a, b; Yang *et al.* 2012; Thomas *et al.* 2013; Allen *et al.* 2014). These differences must be considered in order to derive a scientifically valid human cancer unit risk for chloroprene based on animal studies. In **Section 3**, we discuss the uncertainties associated with toxicological evidence; and in **Section 4** we propose that the available mechanistic evidence supports a cytotoxic, rather than mutagenic, MOA for chloroprene.

In **Section 5**, we discuss US EPA's evaluation of the epidemiological data. US EPA did not fully or accurately summarize the findings from the Marsh *et al*. (2007a, b) study, which represents the largest and most comprehensive epidemiological study of chloroprene to date. Marsh *et al*. (2007a, b) reported no evidence of increased risks of liver and lung cancer with occupational chloroprene exposure; however, US EPA drew contrary conclusions from small subsets of the Marsh *et al*. (2007a, b) data.

In **Section 6**, we discuss the uncertainty associated with the evidence presented by US EPA to support a classification of "likely to be carcinogenic to humans," noting that the weight of evidence narrative is incomplete and the evidence is weaker than US EPA reports, and is more consistent with a "suggestive" classification.

In **Section 7**, we summarize the uncertainties associated with the US EPA derivation of the IUR, and in **Section 8**, we compare the IUR for chloroprene to other chemicals that have been classified by US EPA and IARC as known or probably human carcinogens. This comparison shows that the IUR for chloroprene is substantially out of line with the US EPA risk evaluation of chemicals that are known carcinogens.

In **Section 9**, we summarize new evidence that indicates that a PBPK model is the most valid and appropriate means of quantifying the large differences between animal and human responses to chloroprene exposure and in **Section 10**, we use PBPK results and standard US EPA methods endorsed by NRC to calculate an IUR for chloroprene. In **Section 11**, we use exposure data from the Marsh *et al.* (2007a, b) study to calculate the expected incidence of cancer among workers using the 2010 US EPA IUR and using PBPK-adjusted IURs as a "reality check" to demonstrate that the PBPK-adjusted IUR, but not the US EPA-derived IUR, is consistent with the epidemiological findings.

In **Section 12** we discuss the need to apply pharmacokinetic modeling in the derivation of the RfC, which also suffers from application of default methodology that does not properly account for the known pharmacokinetic differences across species, and species- and strain-specific differences in response.

Lastly in **Section 13**, we conclude that an updated and corrected IRIS assessment, and especially an updated IUR, are warranted and urgently needed. The new assessment should combine the most up-to-date scientific evidence regarding chloroprene toxicity and carcinogenicity with improved and more transparent methods for conducting toxicological and epidemiological reviews, in accordance with the NRC recommendations and guidance (NRC 2011, 2014). We are confident that the substantive and procedural reasons for updating the IRIS assessment for chloroprene, as detailed in this report, will result in a valid and scientifically appropriate IUR for chloroprene that is also consistent with the assessments for other substances including several known human carcinogens.

2 THE IRIS PROCESS: CHALLENGES, RECENT CHANGES, AND NRC RECOMMENDATIONS FOR IMPROVEMENT

2.1 Purpose of the IRIS program

The IRIS program was developed to be the primary source of toxicological information for federal, state, and international regulatory agencies for setting risk-based regulatory standards. It was intended to provide consistency among toxicological assessments within US EPA. IRIS assessments contain hazard evaluations (determinations of whether substances are capable of causing disease) and dose-response assessments (determinations of the levels at which such effects occur) for various chemicals, including cancer and non-cancer outcomes.

2.2 Challenges in the IRIS process

While most of the IRIS assessments have been straightforward and well documented, others have proved to be more complex and challenging, sometimes lacking transparency of methods. These problems have led to significant variability and uncertainty regarding the calculated estimates of hazard or risk of health effects in humans. As a consequence, the NRC has been called on multiple times to review some of the more challenging or ambiguous assessments, including those for formaldehyde, dioxin, and tetrachloroethylene.

In perhaps the most critical evaluation, the NRC (2011) reviewed the draft "Toxicological Review of Formaldehyde- Inhalation Assessment" (US EPA 2010c) and outlined several general recommendations for the IRIS process, as well as some specific aspects needing improvement. Subsequently, Congress held several hearings regarding the IRIS program. A House Report (112-151) that accompanied the Consolidated Appropriations Act of 2012 (Public Law 112-74)[2] specified that as part of the IRIS process, US EPA had to incorporate the recommendations of NRC in its IRIS "Toxicological Review of Formaldehyde" where appropriate, based on chemical-specific information and biological effects. Congress requested that NRC oversee this process to ensure US EPA implemented the changes. Congress also directed that NRC should make additional recommendations as needed to further improve the program. In 2014, NRC released a report on the IRIS process, which largely described the findings in its 2011 formaldehyde review as they relate more broadly to the IRIS process (NRC 2014). The final Toxicological Review of Formaldehyde has not yet been released.

Subsequently, US EPA published a report entitled "Integrated Risk Information System (IRIS) Program: Progress Report and Report to Congress" (US EPA 2015) in which US EPA assured Congress that progress toward improving the IRIS process and addressing the NRC recommendations was continuing.

NRC (2011, 2014) also emphasized the importance of a detailed protocol, including making the methods and the process of the review transparent. Increased transparency provides not only the opportunity for meaningful peer review, but also

[2] Pub. No. 112-74, Consolidated Appropriations Act, 2012 available at https://www.gpo.gov/fdsys/pkg/PLAW-112publ74/pdf/PLAW-112publ74.pdf

for other investigators to verify the methods and replicate findings. The protocol should specify how studies will be evaluated and weighted according to quality rather than on the basis of findings; explicitly state the inclusion and exclusion criteria for studies; describe how study quality will be evaluated; and outline methods for evaluating and taking into account various forms of bias and other methodologic characteristics of the studies that could impact their respective conclusions. The 2010 Review did not follow such a protocol.

Another key criticism that the NRC (2011) made specific to the IRIS assessment of formaldehyde, and more generally to the IRIS program as a whole, was that the IRIS process lacked an appropriate framework for systematic review and integration of all applicable lines of evidence. NRC (2011) cited the systematic review standards adopted by the Institute of Medicine (2011) as being appropriate for such an analysis.

2.3 Recommendations for improvement of the IRIS process in updating the 2010 Review

Because the 2010 Review predates the NRC critique, it would benefit from application of many of their recommendations. For example, clearer descriptions of how the epidemiological evidence was evaluated would provide greater transparency. Similarly, epidemiological evidence should be evaluated for study quality and assessed for potential bias, as some of the strongest epidemiological evidence was misinterpreted (*i.e.*, from the Marsh *et al.*, 2007a, b studies), and results from some weaker studies (from Russia, Armenia, and China) were given equal weight.

US EPA's Guidelines for Carcinogen Risk Assessment (US EPA 2005) established study quality criteria for the WOE evaluation and for identifying and justifying the use of specific epidemiological studies in assessing evidence of carcinogenicity, as follows:

- Clear objectives
- Proper selection and characterization of comparison groups (cohort and reference)
- Adequate characterization of exposure
- Sufficient duration of follow-up
- Valid ascertainment of causes of cancer morbidity and mortality
- Proper consideration of bias and confounding
- Adequate sample size to detect an effect
- Clear, well-documented and appropriate methods for data collection and analysis
- Adequate response (minimal loss to follow-up)
- Complete and clear documentation of results

These points were similarly outlined in the NRC critique of the IRIS process (NRC 2014).

Based on a critical review of the animal toxicology evidence, important differences in chloroprene toxicity have been demonstrated across species that are explained by differences in pharmacokinetics. In such circumstances PBPK models are required to adjust for these differences and have been applied by US EPA for other chemicals. Although a chloroprene-specific PBPK model was available at the time of the 2010 Review, US EPA did not use it. Since the release of the 2010 Review, additional data and a fully validated PBPK model have been peer-reviewed and published. By incorporating the highest quality epidemiological studies and the most recently published data on the pharmacokinetics of chloroprene metabolism, deriving a scientifically sound IUR for chloroprene is straightforward. As demonstrated below, an IUR derived using methods applied by US EPA and the scientifically highest quality data publically available will produce an IUR that is over 150 times lower than the IUR published in the 2010 Review.

3 TOXICOLOGICAL WEIGHT OF EVIDENCE: ANIMAL STUDIES

3.1 Guidelines for evaluating toxicological studies

US EPA set forth criteria for the evaluation of toxicological data in the "Guidelines for Carcinogen Risk Assessment" (US EPA 2005). These guidelines are largely consistent with the NRC recommendations for IRIS (NRC 2014). However, US EPA did not apply these risk assessment guidelines in the 2010 Review in its evaluation and determination of the weight of evidence (WOE) available from the animal, mechanistic, and epidemiological studies of chloroprene. In this section, we discuss the toxicological evidence available to evaluate whether it supports carcinogenicity of chloroprene in humans.

3.2 Animal studies show important pharmacokinetic differences across species

US EPA based the 2010 IRIS IUR estimate for chloroprene primarily on the findings of a two-year inhalation study conducted by the NTP (1998). The NTP (1998) study found statistically significant increases in tumor incidence at multiple sites in the B6C3F1 mice, including: all organs (hemangiomas and hemangiosarcomas), lung (bronchiolar/alveolar adenomas and carcinomas), forestomach, Harderian gland (adenomas and carcinomas), kidney (adenomas), skin, liver, and mammary glands. With increasing exposures, the tumors generally appeared earlier, and statistically significant pair-wise comparisons were reported with increasing exposure level. F344/N rats were less sensitive to chloroprene exposures than B6C3F1 mice.

US EPA also considered results from another large study conducted by Trochimowicz *et al.* (1998) in Wistar rats and Syrian hamsters that showed a large variability in the tumor incidence and sites across species. Trochimowicz *et al*. (1998) found that although tumors appeared across multiple sites in both rats and hamsters, there were no statistically significant increases at any particular site, no significant trends observed with increasing concentration, and tumor incidence in less than 20% of hamsters. These results showed that the Wistar rat and the hamster are less sensitive to the toxicity of chloroprene than B6C3F1 mice or F344/N rats.

The results of the NTP (1998) and Trochimowicz *et al*. (1998) studies indicated that the mouse is the most sensitive species to chloroprene among the species tested, based on the concentrations at which statistically significant increases in tumor incidence were observed, as well as the number of tumor sites. In the NTP (1998) study, the incidence of lung tumors was observed to be statistically significantly elevated at the lowest exposure tested (12.8 parts per million [ppm]) in both female and male mice. Statistically significantly increased lung tumor incidence was not observed in any other animal species that was evaluated, including male and female rats administered chloroprene at concentrations up to 80 ppm. For other tumor sites, there were some statistically significantly elevated results in B6C3F1 mice and F344/N rats, but primarily limited to the highest exposure levels (80 ppm). For example, the incidence of liver tumors in mice were only statistically significantly increased in female mice at the highest exposure concentration tested

(80 ppm). For these reasons, the 2010 Review noted that the differences in response observed between the NTP (1998) and Trochimowicz *et al*. (1998) studies may be due to species and/or strain differences.

Thus, across all tested species, the data demonstrated that mice are the species most sensitive to chloroprene exposure and that the incidence of lung tumors is the most sensitive endpoint in mice. The findings therefore are specific to mice and not generalizable across animal species. Given the differences in response in the mouse as compared to other laboratory species following chloroprene exposure, it is particularly important to evaluate the potential for differences in pharmacokinetics to better characterize and explain the cross-species differences, particularly in developing an IUR intended to be predictive of human risk.

3.3 Conclusions

US EPA derived a chloroprene human IUR based not only on the highest IUR, which corresponded with the lung tumors (the most sensitive endpoint) and female mice (the most sensitive species and gender), but also, as discussed below, US EPA then calculated a human composite IUR that was based on multiple tumor sites in the female mouse. Rats were considerably less sensitive to the carcinogenic effects of chloroprene and thus were not considered further in the dose-response analysis; however, the observed lower incidence of tumors in rats than mice indicates significant species differences that cannot be disregarded in the human carcinogenicity evaluation.

4 MECHANISTIC EVIDENCE: CHLOROPRENE MODE OF ACTION

4.1 Guidelines for evaluating mechanistic studies

As with the evaluation of animal data, US EPA did not apply the guidelines for evaluation of mechanistic weight of evidence set forth in the "Guidelines for Carcinogen Risk Assessment" (US EPA 2005) and the NRC recommendations for IRIS (NRC 2014). In this section, we discuss the mechanistic evidence available to evaluate whether it supports a mutagenic mode of action (MOA) for chloroprene.

4.2 Mechanistic evidence for cancer effects from chloroprene do not support a mutagenic MOA

A key determinant of understanding whether an agent is carcinogenic is to establish an MOA. In the 2010 Review, US EPA hypothesized that chloroprene "acts via a mutagenic MOA involving reactive epoxide metabolites formed at target sites or distributed systemically throughout the body." US EPA noted that "this hypothesized MOA is presumed to apply to all tumor types" (US EPA 2010a), suggesting some non-independent events would be needed for the development of all of the tumors observed. In formulating this hypothesis of a mutagenic MOA, the 2010 Review did not present a description of whether or how the available evidence was critically evaluated, weighted and integrated. This is inconsistent with US EPA (2005) guidelines which indicated that the purpose of the hazard assessment is to "construct a total analysis examining what the biological data reveal as a whole about carcinogenic effects and MOA of the agent, and their implications for human hazard and dose-response evaluation." These 2005 guidelines are also consistent with the new NRC (2014) recommendations for the need for integration of the evidence to support scientific conclusions.

In providing supporting evidence for a mutagenic MOA, the 2010 Review focused on *in vitro* studies (using different exposure systems) in bacteria, with less weight placed on the results from *in vitro* studies in mammalian cells and *in vivo* studies.[3] In particular, in assessing whether chloroprene has a mutagenic MOA, the 2010 Review gave little weight to the studies conducted by the NTP and others (Tice 1988, Tice *et al*. 1988, NTP 1998, Shelby 1990, Shelby and Witt 1995). This also is contrary to the recommendations of NRC (2014) regarding evidence integration. The NTP (1998) study that served as the basis of the US EPA IUR for chloroprene states, "chloroprene was not mutagenic in any of the tests performed by the NTP."

Furthermore, the majority of the conventional genetic toxicology studies relied on in the 2010 Review did not report positive results following administration of chloroprene. In drawing conclusions concerning the chloroprene MOA, US EPA should have acknowledged the flaws and methodological limitations in the studies on which it relied. When these studies and their limitations are considered, along with the predominantly negative *in vitro* and *in vivo* genotoxicity tests, there is little evidence for concluding that chloroprene is mutagenic or genotoxic (NTP 1998, Pagan 2007). Therefore, this evidence should not be used to support a

[3] *In vitro* mammalian and *in vivo* studies are generally considered to be more relevant to effects that might be observed in humans (*e.g.*, Wetmore *et al.* 2013).

classification of chloroprene as a "likely" human carcinogen and should not influence the derivation of the chloroprene IUR.

In summary, the hypothesized MOA was based on four major assumptions by US EPA (2010a):

1. There are similarities in the MOA for the known human carcinogen 1,3-butadiene, which involves metabolism to a reactive epoxide intermediate
2. Chloroprene forms DNA adducts via its epoxide metabolite
3. Chloroprene is a point mutagen *in vitro*
4. Chloroprene is a point mutagen *in vivo*

However, the integration of the currently available evidence for chloroprene support none of these assumptions. A discussion of why the available science is inconsistent with these assumptions is provided in the following sections.

4.2.1 **The chloroprene mutagenic profile is distinct from that of 1,3-butadiene**

US EPA assumed that chloroprene has a similar MOA to that of 1,3-butadiene, which is metabolized to epoxide intermediates and is a rodent carcinogen. While both compounds may be carcinogenic in rodents, evidence is available that shows that the mutagenic and clastogenic profiles of 1,3-butadiene are considerably different from the profile of chloroprene (Tice 1988, Tice *et al.* 1988). Unlike 1,3-butadiene, chloroprene does not induce effects when tested in standard *in vivo* genotoxicity screening studies in mammals (Table 4.1). Although the reactive metabolite of chloroprene (1-chloroethenyl) oxirane does induce mutations *in vitro* in bacterial strains (Himmelstein *et al.* 2001a), neither the administration of chloroprene nor the reactive epoxide metabolite was genotoxic or mutagenic in *in vitro* mammalian cells, including Chinese hamster V79 cells (Himmelstein *et al.* 2001a, Drevon and Kuroki 1979). Also, unlike 1,3-butadiene, chloroprene was not genotoxic when tested *in vivo* (Tice 1988, Tice *et al*. 1988, NTP 1998, Shelby 1990, Shelby and Witt 1995).

Table 4.1. Comparison of the Mutagenic Profiles of Chloroprene and 1,3-Butadiene

Chemical	In Vitro Ames	In Vivo (B6C3F1 mouse)a		
		CA	SCE	Micronuclei
1,3-Butadiene	+	+	+	+
Chloroprene	+/-	-	-	-

a Exposure was 10-12 days (6 hr/day) inhalation (Tice 1988)

These findings indicate that the reactive metabolites formed from chloroprene are effectively detoxified *in vivo* in the concentration ranges studied. This is an important difference between chloroprene and 1,3-butadiene. In addition, 1,3-butadiene appears to be an effective somatic cell genotoxin in mice (Tice 1988), whereas chloroprene was not genotoxic in *in vivo* assays (Tice 1988, Tice *et al*.

1988, Shelby 1990, Shelby and Witt 1995, NTP 1998). The only published chloroprene-related study showing positive chromosomal aberrations *in vivo* was a study cited by Sanotskii (1976); but as acknowledged in the 2010 Review, this study was technically deficient and conflicted with stronger and more recent studies conducted by NTP in mice (Shelby 1990, NTP 1998).

Two other major differences between these chemicals are evident from the experimental data. First, the *ras* profile in lung tumors in treated animals is considerably different for chloroprene and 1,3-butadiene (Sills *et al.* 1999). Secondly, the toxic effects and histopathology observed in chloroprene-treated F344 rats and B6C3F1 mice are substantially different from those seen in 1,3-butadiene exposed animals (Melnick *et al*. 1996). These differences in toxic effects and histopathology suggest that the carcinogenic MOA for 1,3-butadiene also is different from that of chloroprene.

Furthermore, even if we disregard the assumption that chloroprene acts *via* a similar MOA as 1,3-butadiene, the chloroprene IUR is more than an order of magnitude greater than that of 1,3-butadiene. This is inconsistent with the assumption that these compounds have a similar MOA, and is also inconsistent with US EPA's underlying assumptions regarding the carcinogenicity and the potency of chloroprene relative to 1,3-butadiene.

4.2.2 **Evidence does not support the formation of DNA adducts by chloroprene metabolism to an epoxide intermediate in vitro**

The 2010 Review assumed that the chloroprene epoxide metabolite (1-chloroethenyl)oxirane forms DNA adducts. There is little evidence that this occurs *in vivo*. Although *in vitro* studies suggest an interaction between this metabolite and DNA adducts, this effect has not been confirmed *in vivo*. In addition, the lack of any observed genotoxicity *in vivo* as described above (Tice 1988, Tice *et al*. 1988, NTP 1998, Shelby 1990, Shelby and Witt 1995) does not support an interaction between chloroprene and DNA *in vivo*.

4.2.3 **Evidence does not support mutagenicity of chloroprene in vitro**

The 2010 Review also assumed that chloroprene is a point mutagen *in vitro*. However, the results of the bacterial mutagenicity studies are equivocal, at best, and the findings from the Ames tests question the classification of chloroprene as a mutagen (NTP 1998, Pagan 2007). The results from two studies indicated that chloroprene was mutagenic in *Salmonella typhimurium* TA100 and/or TA1535, particularly with the addition of S9 mix, which incorporates the metabolism of chloroprene (Bartsch *et al*. 1979, Willems 1980). Two other studies failed to show any increase in TA1535 or TA100 revertants, as shown in Table 4.2. Chloroprene was not mutagenic in *S. typhimurium* strains TA98 or TA1537 (Zeiger *et al*. 1987). Because toxicity to the Salmonella cells was reported for all of the studies, one can assume there was adequate exposure to chloroprene and its metabolites or oxidative degradation products, although concentrations and composition verification were not performed.

Table 4.2. Ames Test Results for Chloroprene with TA1535 and/or TA100

Study	Method	Exposure	Response	
			With S9 mix	Without S9 mix
Bartsch *et al*. 1979	Desiccator[a]	4 hours	++	+
Westphal *et al*. 1994	Pre-inc[b]	2 hours	-	-
NTP 1998	Pre-inc[b]	20 minutes	-	-
Willems 1980	Desiccator[a]	24-48 hours	++	+

[a] Plates sealed in desiccator at 37° C with tops removed.

[b] Chemical added to sealed tubes and mixed at 37° C.

Toxicity results further appear to be dependent on the exposure methods and the form of chloroprene tested *(e.g.*, newly distilled or aged). Westphal *et al*. (1994) confirmed the importance of both vehicle and decomposition products in assessing the mutagenicity of chloroprene. For example, they showed that freshly distilled chloroprene was not mutagenic, but chloroprene aged for as little as two to three days at room temperature was mutagenic in *S. typhimurium* TA100. The mutagenicity increased linearly with the age of the distillate, probably due to the presence of decomposition products such as cyclic dimers (Westphal *et al.* 1994). Therefore, it is not possible to conclude from published data that chloroprene is a point mutagen in bacteria.

Chloroprene also does not appear to be mutagenic in mammalian cells. Drevon and Kuroki (1979) were not able to induce point mutations when chloroprene was tested in Chinese hamster V79 cells. The results for mammalian cells should carry more weight than those in bacterial cells, because mammalian cells are more relevant for understanding any potential effects in humans. Himmelstein *et al*. (2001a) tested the primary metabolite of chloroprene, (1-chloroethenyl)oxirane, and found it to be mutagenic in the absence of S9, suggesting that this metabolite may be the reactive agent in the Ames test; however, this epoxide metabolite was not genotoxic in mammalian cells *in vitro* (Chinese hamster V79 cells) (Himmelstein *et al*. 2001a). Therefore, the results from the Ames test may not be an accurate predictor of carcinogenicity of chloroprene, because glutathione and other detoxification pathways that would mitigate or eliminate the production of potentially active metabolites are not present in S9 microsome preparations at levels present in intact cells. Westphal *et al.* (1994) also found that addition of glutathione to the chloroprene/metabolite Ames tests significantly diminished the reported mutagenic activity. The absence of genotoxicity in intact mammalian cells systems and *in vivo* studies suggests that the bacterial mutagenicity data have limited relevance to the genotoxicity of chloroprene in humans. Critically, and as discussed below, *in vitro* systems do not have the normal levels of detoxifying

pathways found in intact mammalian cells to further metabolize/detoxify this primary metabolite.

4.2.4 **Evidence does not support mutagenicity of chloroprene in vivo**

The 2010 Review assumed that chloroprene is a point mutagen *in vivo* (in carcinogenicity bioassays with mutations identified in proto-oncogenes). Investigators study mutations in tumors at target sites to identify "mutagen fingerprints" for specific chemicals. As such, Sills *et al*. (1999, 2001) produced a proto-oncogene mutation profile for some target tumors in the mouse. A comparison of chloroprene and 1,3 -butadiene indicated that the profile for chloroprene differed from that of 1,3-butadiene. In fact, the mutation rates in chloroprene-exposed animals were similar to mutation rates in control animals. Specific mutations were associated with chloroprene exposures across several different tumor types, but showed no dose-dependency. In contrast, the incidence of lung tumors increased with dose. This indicates that the lung tumors likely are independent of and unrelated to the mutations. These findings suggest that the underlying MOA is not the suspected K-*ras* mutation,[4] but rather a secondary MOA at target sites; for example, an MOA that follows a dose-dependent tumor response that is not associated with a corresponding dose-dependent increase in mutations, such as cytotoxicity-induced bronchiolar hyperplasia. If mutagenicity is the MOA, then mutation rates also should be dose-dependent. This is not the case for chloroprene, where mutations are not shown to be dose-dependent. Therefore, a different MOA is likely.

4.3 Evidence supports an alternative MOA for chloroprene based on cytotoxicity

Despite the inconsistencies in and questionable nature of the evidence for a mutagenic MOA, the 2010 Review never considered alternative MOAs for chloroprene. Considering alternative MOAs is recommended in US EPA's (2005) "Guidelines for Carcinogen Risk Assessment" and is consistent with recommendations by NRC (2011, 2014) for evidence integration and WOE analyses as specified in the Human Relevance Framework (Cohen *et al*. 2003, Meek *et al*. 2003, Cohen 2004, IPCS 2005, Boobis *et al.* 2006). US EPA (2005) guidelines noted that "where alternative approaches have significant biological support, and no scientific consensus favors a single approach, an assessment may present results using alternative approaches."

The likely alternative MOA for chloroprene is cytotoxicity, for which there are supportive experimental findings. At very high concentrations, chloroprene is toxic to animals, but does not demonstrate any genotoxicity (Shelby 1990), supporting an MOA based on target-site cytotoxicity. In mice, histopathology evaluations of chloroprene in target tissues are consistent with a non-genotoxic MOA. For example, the incidence of chloroprene-induced bronchiolar hyperplasia in the respiratory system follows the increased incidence of lung tumors, whereas the incidence of lung K-*ras* mutations (a precursor of many cancers) does not. Also, Melnick *et al*. (1996) reported that the toxicity and histopathology observed in

[4] Mutations of the k-*ras* gene are considered an essential step in the development of many cancers (*e.g.*, Jančík *et al.*, 2010).

chloroprene-treated F344 rats and B6C3F1 mice were substantially different from those seen in 1,3-butadiene exposed animals, suggesting an alternative MOA. In this case, a cytotoxicity-driven hyperplasia could be the cause, which can result from cell injury or death and subsequent tissue regeneration. Buzard *et al*. (1996) hypothesized that hyperplastic processes lead to selection of pre-existing oncogene and tumor suppressor gene mutations. Extrapolation from a target-site cytotoxic MOA involving cell proliferation and tumor promotion to other tumor sites is consistent with the attributes of chloroprene. It is important to note that the toxicity of chloroprene is observed at very high concentrations in mice and to a lesser extent in rats; however, it has been confirmed using a validated PBPK model that both species would be expected to be more sensitive to chloroprene exposure than humans. The differences in pharmacokinetics between mice, rats and humans helps to explain the lack of clear evidence of carcinogenicity in humans from epidemiology studies.

4.4 Conclusions

A critical evaluation of the cytotoxic and genotoxic profiles indicated that chloroprene acts through a MOA different from that of 1,3-butadiene, a known human carcinogen. Importantly, chloroprene's genotoxicity profile lacks several attributes necessary to conclude a mutagenic MOA:

- **Standard *in vivo* tests for genotoxicity are negative and unlike known carcinogens such as 1,3-butadiene**: Chloroprene, unlike 1,3-butadiene, is not genotoxic to somatic cells *in vivo.* The study results indicate that the epoxide metabolite of chloroprene is effectively detoxified under *in vivo* exposure conditions.
- **Consistent data are lacking for point mutation induction *in vitro* and *in vivo***: The evidence that chloroprene is able to produce point mutations *in vitro* (specifically in bacteria) is equivocal, and chloroprene did not induce mutations in cultured mammalian cells. There is a clear discordance between findings of *in vitro* point mutation, DNA adduct induction, and *in vivo ras* mutations in target site tumors, which indicate that the observation of these point mutations may not be relevant to the MOA for chloroprene-induced tumors.

Overall, unlike known carcinogens such as 1,3-butadiene, the evidence does not support a mutagenic MOA for chloroprene. Instead, the WOE supports an alternative MOA attributed to site-specific cytotoxicity. Thus, it is neither necessary nor appropriate to adjust the cancer unit risk based on a hypothesized mutagenic MOA, and deriving a new IUR based on an alternative MOA that can be scientifically substantiated is warranted.

5 EPIDEMIOLOGICAL EVIDENCE: OCCUPATIONAL STUDIES

5.1 Evaluation of the epidemiological studies

The 2010 Report classified chloroprene as “likely to be carcinogenic to humans” in part based on US EPA’s interpretation of “an association between liver cancer risk and occupational exposure to chloroprene” and “suggestive evidence of an association between lung cancer risk and occupational exposure.” As with the evaluation of the toxicological data, US EPA set forth criteria in the "Guidelines for Carcinogen Risk Assessment" (US EPA 2005) for the evaluation of epidemiological evidence, largely consistent with NRC recommendations (NRC 2014). While US EPA applied some of these criteria in the 2010 Review, US EPA did not present quality assessment and weighting of epidemiological evidence. Our application of these criteria led to largely opposite conclusions: appropriate weighing and synthesis of the epidemiological evidence demonstrated that chloroprene exposure is unlikely to cause lung or liver cancer at the occupational exposure levels encountered in the underlying studies. Furthermore, in contrast with US EPA’s interpretation, the lack of any clear cancer risk is consistent with the results from the animal studies demonstrating significant differences across species in the carcinogenic potential of chloroprene, and the mechanistic evidence that humans are far less sensitive to chloroprene.

Using an approach consistent with US EPA (2005) and NRC (2014), Bukowski (2009) evaluated the quality of eight mortality studies of seven chloroprene-exposed cohorts from six countries (Table 5.1). Studies were assigned to categories of high, medium or low quality for each of ten quality criteria and a WOE assessment was performed. The four-cohort Marsh *et al*. (2007a, b) pooled study is the most methodologically rigorous epidemiology study conducted to date. This study has the largest overall cohort size and the most rigorous follow-up. Based on the large cohort size, the Marsh study has the highest statistical power (see Table 5.2). Finally, the Marsh study has the most comprehensive exposure assessment, including assessment of exposure to potentially confounding agents such as vinyl chloride.

Table 5.1. Quality Rankings for Cohort Studies of Cancer Risks from Occupational Chloroprene Exposure

US EPA Criteria	Marsh et al. (2007 a,b) Study				Other Studies			
	Kentucky[1]	North Ireland[1]	Louisiana[1]	France-Mort*[1]	Armenia[2]	France-Incid**[3]	Russia[4]	China[5]
Clear objectives	H‡	H	H	H	H	H-M	H	M
Comparison groups	H	H-M	H-M	M	M	M	M-L	L
Exposure	H	H	H	H	M	M	L	L
Follow-up	H	H-M	H	H-M	M-L	M-L	M-L	M-L
Case ascertainment	H	H-M	H-M	H-M	M	M	M	H-M
Control of bias	H-M	H-M	H-M	M	M-L	M	M	M-L
Sample size	H	H	M	L	M-L	L	H-M	M-L
Data collection and evaluation	H	H	H	H	M	M	M-L	M-L
Adequate response	H	H	H	H	M	M	M	H-M
Documentation of results	H	H	H	H	M-L	M	M	L
Overall rank (1=best)	**1**	**2**	**3**	**4**	**5**	**5**	**5**	**6**

Source: Bukowski 2009 * Mort=Mortality ** Incid=Incidence ‡ Subjective estimate of study quality for each specific criterion H=high, M=medium, L=low; 1 – Marsh *et al*. 2007; 2 – Bulbulyan *et al.* 1999; 3 – Colonna and Laydevant 2001; 4 – Bulbulyan *et al*. 1998; 5 – Li *et al*. 1989

Table 5.2. Relative Size of Marsh *et al*. (2007a, b) Study Compared with Other Available Studies

Study	Subjects (Person-years)	Lung Cancer Deaths	Liver Cancer Deaths
Bulbulyan et al. 1998	5185 (70,328)	31	10
Bulbulyan et al. 1999	2314 (21,107)	3	3
Colonna and Laydevant 2001	717 (17,057)	9	1
Leet and Selevan 1982	Should not be included in the 2010 Review		
Li et al. 1989	1258 (20,105)[a.]	2	6
Total Other Studies	**9474 (128,597)**	**45**	**20**
Marsh et al. 2007a (L)	5507 (197,010)	266	17
Marsh et al. 2007a (M)	4849 (127,036)	48	1
Marsh et al. 2007a (P)	1357 (30,660)	12	0
Marsh et al. 2007a (G)	717 (17,057)	10	1
Total Marsh et al. (2007a, b)	**12,430 (372,672)**	**336**	**19**
Combined Studies	**21,904 (501,269)**	**381**	**39**
Marsh et al. (2007a,b) / Combined Studies	**57% (74%)**	**88%**	**49%**

Previously, Rice and Boffetta (2001) reviewed the published epidemiological studies of chloroprene-exposed cohorts. Their review included cohorts in the US (Pell 1978), China (Li *et al*. 1989), Russia (Bulbulyan *et al*. 1998), and Armenia

(Bulbulyan *et al*. 1999) and noted significant methodological limitations in these studies, including unclear documentation for cohort enumeration, inadequate reference rates for standardized ratios, a lack of detailed histopathology of liver cancer cases, and limited or no information on potential co-exposures. They also remarked that the occupational chloroprene exposure assessment was poor for all published studies, and the statistical power of the available studies was low due to the small number of observed cancers of interest. Notably, one of the co-authors of the critical review (Boffetta) was also a contributing author of the cohort studies in Russia and Armenia (Bulbulyan *et al*. 1998 and Bulbulyan *et al.* 1999, respectively).

To date, the identified limitations of the studies of Chinese, Russian, and Armenian cohorts remain unaddressed, and most have not been updated. Only the original studies of the US cohort from Louisville, Kentucky (Pell 1978, Leet and Selevan 1982) have been updated and improved. Substantial improvements included detailed descriptions of the cohorts, appropriate comparisons to local cancer rates, an improved exposure assessment both for chloroprene and associated co-exposures (such as vinyl chloride), appropriate follow-up times to capture all potential cancers, appropriate and valid determination of cancer cases, and well-documented methods and results (Marsh *et al.* 2007a, b). A comparison of the study limitations for key quality criteria across the different cohorts is summarized in Table 5.3, and discussed in detail in the next section.

Table 5.3. Comparison of Key Study Criteria across Epidemiological Studies

Key Criteria	US and Europe (Marsh et al. 2007a,b)	Armenia (Bulbulyan et al. 1999)	Russia (Bulbulyan et al. 1998)	China (Li et al. 1989)
Sample Size	French, Irish and US 12,430 (Kentucky ~200,000 person-years)	2,314	5,185	1,258
Follow-up	1949–2000	1979–1993	1979–1993	1969–1983
Exposure Assessment	Exposure modeling – 7 categories	Index (none, low, high)- before/after 1980	Index (none, med, high)- IH (inadequate) + job	High vs. low based on recall
Baseline rates	National, local plant area counties	Armenian rates	Moscow rates	From "local area" 1973–1975
	1960–1994	1980-1989	1979–1993 or	expected lung cancers: 0.4
			1992–1993 (liver)	
Confounding	Used local rate comparisons;	Alcohol use (high cirrhosis rates) and smoking prevalent	Alcohol use (high cirrhosis rates) and smoking;	Hepatitis B and aflatoxin;
	Low prevalence of other liver cancer risk factors		Co-exposure to VCM	Co-exposures to VCM

IH: Industrial hygiene
VCM: vinyl chloride monomer

5.2 Important limitations of the epidemiology literature

The 2010 Review considered lung and liver cancer mortality reported in studies of occupational cohorts from several countries published over 30 years: Pell (1978), Leet and Selevan (1982), Li *et al*. (1989), Bulbulyan *et al*. (1998, 1999), Colonna and Laydevant (2001), and Marsh *et al*. (2007a,b).

Cohort studies comprise a set of data distributed over time to address a hypothesized exposure-disease association (Checkoway *et al*. 2004). In synthesizing results of several cohort studies – or when conducting meta-analyses of such results – it is important to verify that each study cohort is an independent sample and that analytic results are independent, *i.e*., there should be no overlap (e.g., Greenland and O'Rourke 2008). Especially for outcomes with long latency periods and high case-fatality, such as lung and liver cancers, only the most recent and most complete (and non-overlapping) results from cohorts with multiple follow-up periods should be used. Updated results always have more observed person-years at risk and almost always include larger numbers of the health outcome of interest, increasing statistical stability and reducing the probability of chance findings.

The epidemiological literature on chloroprene consists of seven published reports based on nine distinct cohorts. In the 2010 Review, however, *each published epidemiological study* was included as if it were independent, including early results from overlapping or updated cohorts. Specifically, the early results from the Pell (1978) and Leet and Selevan (1982) were included in the most recent update (Marsh *et al*. 2007a, b). Therefore, the Pell (1978) and Leet and Selevan (1982) studies should not have been considered as independent evidence, since all of their cancer deaths were included in the Marsh (2007 a, b) update.

Additionally, the Chinese, Russian, and Armenian studies have serious limitations, as documented by several authors including Rice and Boffetta (2001), Acquavella and Leonard (2001), and Bukowski (2009). As noted above, these studies have not been updated and the noted limitations remain unaddressed. These studies therefore should be given less weight in the synthesis of evidence.

The study of Chinese workers (Li *et al*. 1989) suffered from small numbers of workers, inadequate reference population mortality rates for statistical comparisons, and a lack of adjustment for known causes of lung and liver cancers. The researchers ascertained mortality among 1,213 workers for a 14-year period from 1969 through 1983 and reported 6 deaths due to liver cancer and 2 deaths due to lung cancer. However, they used local mortality rates for only a three-year period (1973 to 1975) to estimate expected numbers of specific cancers. For rare events such as any specific cancer, estimates based on small numbers will be inherently imprecise. Li *et al*. (1989) reported 2.5 and 0.4 expected liver and lung cancer deaths, respectively, among all cohort members followed between 1969 and 1983. The limited number of observed liver and lung cancer deaths divided by the very small expected numbers produced highly imprecise standardized mortality ratios (SMRs) with very large confidence limits. Furthermore, estimates for liver and lung cancer incidence are higher among Chinese men (in 2002, liver cancer mortality was 38 per 100,000 persons per year, and lung cancer mortality was 42 per 100,000 persons per year) and women (liver cancer, 14 per 100,000 persons

per year, and lung cancer, 19 per 100,000 persons per year) (Parkin *et al*. 2005) compared to the rest of the world. In the most high-risk areas of China, 1 in 10 people died of liver cancer (Hsing *et al*. 1991). The major causes of liver cancer in China are chronic infection with hepatitis B virus and aflatoxin B1, in addition to the rising prevalence of alcohol consumption and tobacco smoking (Chen *et al*. 2003, Stuver and Trichopoulos 2008, Lee *et al*. 2009). In contrast, in the US in the years 2009–2013, there were an estimated 9 liver cancer deaths per 100,000 men and 4 liver cancer deaths per 100,000 women per year (SEER 2017). Therefore, observational studies of liver cancer mortality within this Chinese population should control for known causes of these cancers as potential confounding factors. However, the authors of the Chinese study did not control for these confounding factors, and US EPA did not consider the lack of control for confounders when evaluating the quality and weight of the evidence from this study.

Similar to the Li *et al*. (1989) study, Bulbulyan and colleagues (1998) calculated expected numbers of liver cancers using mortality and incidence rates for Moscow for only two years (1992 to 1993), resulting in imprecise reference rates and unstable results. Cancer mortality data from 36 European countries, including the Russian Federation, showed that liver cancer mortality rates among women increased from 1960, peaked during the late 1970s, and declined to their lowest levels during the early 1990s, the period chosen for the study's reference mortality rates (Levi *et al*. 2004). In addition, the Armenian cancer registry is incomplete and may have misclassified the histopathology of reported liver cancers for the general population. Using a reference population with incomplete numbers and mortality rates representative of only a small time period would underestimate the expected incidence and mortality of liver cancer, resulting in over-estimates of the risk estimates. In light of the small numbers and the likelihood that chance may be an explanation for these estimates, the imprecise numbers reported in Bulbulyan *et al*. (1999) and repeated in Zaridze *et al*. (2001) should be viewed skeptically and given little, if any, weight.

The Russian and Armenian cohorts also suffered from inadequate consideration of other major causes of liver cancer. In the populations represented in these cohorts, there is a high incidence of alcoholic cirrhosis, a well-known precursor for liver cancer (London and McGlynn 2006). There were 11 deaths from cirrhosis of the liver (3 in males and 8 in females) recorded for the Russian cohort. In the Armenian cohort, 32 cases of cirrhosis of the liver were reported (27 in males and 5 in females). Alcohol consumption and smoking are well known risks factors for liver cancer, and these factors were not adjusted for in the eastern European cohort studies (Keller 1977, Makimoto and Higuchi 1999, Lee *et al*. 2009). A report by the World Health Organization (WHO 2009) reported a prevalence of 70% and 27% for current tobacco use among Russian men and women, respectively, and noted high levels of alcohol consumption for the general population. The prevalence of current tobacco use among Armenian men is also very high at 55% (WHO 2009). Proper control for these causes was not possible, increasing the likelihood of confounding and thus rendering the results unreliable.

Previous reviews have critiqued the Chinese, Russian, and Armenian studies for inadequate descriptions of the source population rates used to calculate SMRs and standardized incidence ratios (SIRs) (Rice and Boffetta 2001). Another important

methodological concern for the interpretation of SMR and SIR estimates is that when they are based on very small expected values (*i.e.*, less than two), they indicate small population size and/or short follow-up, contributing to unstable estimates (Checkoway, 2004). As such, findings from these studies are not reliable and should carry little if any weight in evaluating cancer causation.

Taken together, the epidemiological studies evaluated in the 2010 Review do not establish a clear causal connection between occupational chloroprene exposure and liver and lung cancers. Consequently, the US EPA's interpretation of the epidemiological evidence as justifying a classification of chloroprene as "likely to be carcinogenic to humans" is questionable. In particular, US EPA's giving the same weight to the large and more robust Marsh *et al*. (2007a, b) epidemiological studies as it gave to the lower quality, lower power studies is inappropriate. Although the Marsh *et al*. (2007a, b) studies have limitations typical of all historical cohort studies, they are the largest studies of potential cancer outcomes with the most complete documentation of exposure. These studies also were designed and conducted specifically to address the limitations previously noted, making the evidence from the Marsh *et al*. (2007a, b) studies far more valid and informative than that from the other studies evaluated by US EPA. The review by Bukowski (2009) (represented in Table 5.1) ranked the study by Marsh *et al.* (2007a, b) as having the highest relative strength based on the same criteria for evaluation listed in the US EPA's "Guidelines for Carcinogen Risk Assessment" (US EPA 2005) and consistent with NRC recommendations (NRC 2011, 2014), and it therefore should be given the greatest weight.

5.3 The Marsh *et a*l. (2007a, b) studies do not show a causal link between occupational exposure to chloroprene and increased cancer risks

The Marsh *et al*. (2007 a, b) studies, the most robust epidemiological studies of occupational chloroprene exposure, found no excess of lung or liver cancers (Marsh *et al*. 2007a, b). The 2010 Review, however, stated, "The study involving four plants (including the Louisville Works plant included in the Leet and Selevan (1982) study by Marsh *et al*. (2007a, 2007b), which had the largest sample size and most extensive exposure assessment, also observed increased relative risk estimates for liver cancer in relation to cumulative exposure in the plant with the highest exposure levels (trend p value = 0.09, relative risks [RRs] 1.0, 1.90, 5.10, and 3.33 across quartiles of exposure)." However, the interpretation of these relative risks is more complex than US EPA stated, as the rate of liver cancer deaths among workers was not different from that in the general population.

As shown in Table 5.4, Marsh *et al*. (2007a) computed standardized mortality ratios (SMRs) using national and regional standard populations for the overall cohorts, for selected demographics (males, females, blue-collar workers), and for work histories and exposure factors. The authors concluded that occupational exposures to chloroprene at the levels encountered by each of the cohorts did not show evidence of elevated risk of cancer, including liver cancer.

In a separate publication, Marsh *et al.* (2007b) reported exposure-response data for chloroprene exposure and cancer. In Table 5.5 and Figure 5.1, results for the Louisville plant are shown, including both the internal analyses (relative risks or RRs) and external analyses (SMRs) which are based on comparisons with county

populations. The RRs are the values that US EPA focuses on in their assessment of potential liver cancer risks. However, as noted by Marsh *et al*., "The elevated RRs result mainly from the exceedingly low death rates associated with the baseline categories of each measure, as reflected by the correspondingly low SMRs (*i.e*., the RR for a given non-baseline category is roughly related to the ratio of the corresponding SMR for that category to the SMR for the baseline category)."

Table 5.4. Reported Observed Liver Cancer Cases, Expected Counts, and Standardized Mortality Estimates for the Marsh *et al*. 2007a Study

Study Cohort	Observed	Expected*	SMR or SIR	95% Confidence Limits		p-value
				Lower	Upper	
Louisville	17	16.35	1.04	0.61		
Maydown	1	4.17	0.24	0.01		
Pontchartrain	0	--	--	--	--	--
Grenoble	1	1.79	0.56	0.01		
Louisville Subcohorts (local reference)						
Full Cohort	17	18.89	0.9	0.53	1.44	0.78
White race	16	15.69	1.02	0.58	1.65	0.99
Non-White race	1	3.13	0.32	0.01	1.77	0.36
Males	16	17.98	0.89	0.51	1.45	0.75
Females	1	0.94	1.06	0.03	5.93	0.99
Blue collar	17	18.28	0.93	0.54	1.49	0.89
Short-term worker	4	8.16	0.49	0.13	1.26	0.18
Long-term worker	13	10.74	1.21	0.64	2.07	0.57
Duration of employment						
< 5years	4	8.16	0.49	0.13	1.25	0.18
5-19 years	6	3.57	1.68	0.62	3.66	0.30
20+ years	7	7.14	0.98	0.4	2.03	0.99
Time since 1st employment						
< 20 years	1	1.79	0.56	0.01	3.11	0.93
20-29 years	3	3.3	0.91	0.19	2.66	0.99
30 + years	13	13.68	0.95	0.5	1.62	0.99
CD exposure status						
Exposed	17	18.89	0.9	0.53	1.44	0.78

From Marsh *et al.* 2007a

Table 5.5. Exposure-Response Analysis for Chloroprene and Liver Cancers, Based on Internal (Relative Risks) and External (Standardized Mortality Ratio) Estimates, Louisville Plant

Liver cancer	Deaths	Internal Analysis			External Analysis	
		# cases	RR (95% CI)	p-value	Person-years	SMR (95% CI)
Exposure Duration (years)						
<10	6	1500	1.00	Global=0.24	131276	0.61 (0.22-1.32)
10-19	4	216	3.85 (0.75-17.09)	Trend=0.36	30404	2.08 (0.57-5.33)
20+	7	965	1.75 (0.49-6.44)		36239	0.99 (0.40-2.04)
Average Intensity of Exposure (ppm)						
<3.62	3	714	1.00	Global=0.22	69274	0.62 (0.13-1.80)
3.62 - 8.12	7	568	3.81 (0.77-25.76)	Trend=0.84	27933	1.73 (0.70-3.56)
8.12-15.99	3	388	1.84 (0.22-15.74)		28689	0.94 (0.19-2.74)
16.0+	4	1011	1.31 (0.20-10.07)		72023	0.59 (0.16-1.52)
Cumulative exposure (ppm-years)						
<4.75	2	744	1.00	Global=0.17	68918	0.43 (0.05-1.55)
4.75-55.19	3	725	1.9 (0.21-23.81)	Trend=0.09	56737	0.59 (0.12-1.74)
55.91-164.0	7	653	5.1 (0.88-54.64)		39840	1.62 (0.65-3.33)
164.0+	5	559	3.33 (0.48-39.26)		32424	1.00 (0.33-2.34)

From Marsh et al. 2007b; Table 4
CI: confidence interval
ppm: parts per million

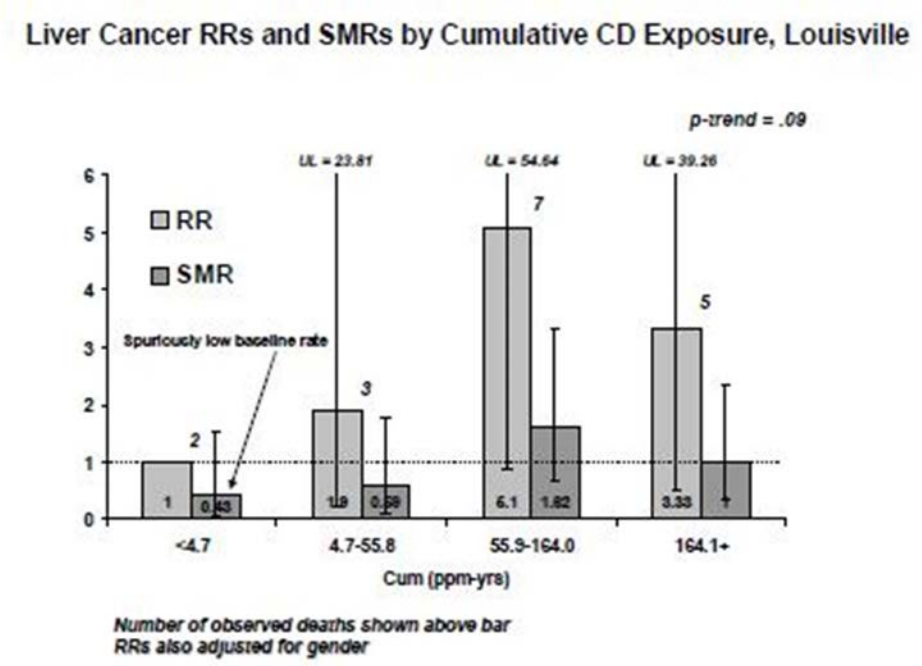


Figure 5.1 Liver Cancer RRs and SMRs by Cumulative Chloroprene Exposure, Louisville

US EPA noted that 3 of the 15 subgroups in Table 5.5 had SMRs greater than 1.00, and inferred from these a likely causal relationship between chloroprene exposure and cancer. However, none of these three SMRs reached statistical significance *(i.e.*, the findings may have been due to chance). In fact, the 95% confidence intervals in Table 5.5 show up to a 10-fold margin of error around the estimated SMRs, underscoring the statistical instability and uncertainty of the risk estimates for these subgroups. In addition, as noted by Marsh *et al*. (2007b), the risk estimates were derived comparing risk from higher exposure groups to risk in the group with the lowest exposure, which had only two liver cancer deaths. The occurrence of only two liver cancer deaths in the lowest exposure group represented a clear deficit in the expected rate of liver cancer, as demonstrated by the SMR (Table 5.5). Comparison to a group with a deficit (most likely due to chance given the small numbers) led to the spurious appearance of an increased risk among the more highly exposed groups. Overall, the chloroprene exposed workers had only about 90% of the expected mortality rate (17 observed with about 19 expected), based on a non-exposed population reference rate (Table 5.4).

Taken as a whole, the epidemiological evidence on chloroprene and cancer is insufficient to conclude that chloroprene is a human carcinogen. The study by Marsh *et al*. (2007a, b) is the largest and methodologically the strongest and, therefore, should carry the greatest weight in integrating the epidemiological evidence for chloroprene. This epidemiological evidence is consistent with the toxicological hypothesis that humans are less sensitive than animals to the possible carcinogenic effects of chloroprene, and also supports the conclusion by Allen *et al*. (2014) that a modified cancer unit risk that accounts for animal-to-human extrapolations is needed.

6 CANCER CLASSIFICATION FOR CHLOROPRENE

The 2010 Review determined that chloroprene was "likely to be carcinogenic to humans" based on EPA's conclusions of (1) statistically significant and dose-related information from the NTP (1998) chronic inhalation bioassay data demonstrating the early appearance of tumors, development of malignant tumors, and the occurrence of multiple tumors within and across animal species; (2) evidence of an association between liver cancer risk and occupational exposure to chloroprene; (3) suggestive evidence of an association between lung cancer risk and occupational exposure; (4) a proposed mutagenic mode of action (MOA); and (5) structural similarities between chloroprene and known human carcinogens, 1,3-butadiene and vinyl chloride. As has been demonstrated in this report, three of the five EPA conclusions are not supported by the weight of evidence, and the fourth—structural similarities—has been shown not to be informative, as the chemicals demonstrate different modes of action. Based on the limited evidence remaining to support the potential carcinogenicity of chloroprene, we conclude that a more appropriate classification of chloroprene is "suggestive evidence of carcinogenic potential."

To classify a chemical as "likely to be carcinogenic to humans," US EPA notes that "this descriptor is appropriate when the weight of the evidence is adequate to demonstrate carcinogenic potential to humans but does not reach the weight of evidence for the descriptor "carcinogenic to humans (US EPA, 2005)." Adequate evidence consistent with this descriptor covers a broad spectrum and as noted by US EPA (2005), "choosing a descriptor is a matter of judgment and cannot be reduced to a formula. Each descriptor may be applicable to a wide variety of potential data sets and weights of evidence." Strong evidence for carcinogenicity in humans is not needed; however, the weight of evidence is still required to support the classification descriptor.

In the 2010 Review, the weight of evidence narrative provided for chloroprene to support the descriptor of "likely to be carcinogenic to humans" was limited to a check-list provided above (US EPA, 2010a, pg. 96 and Table 4-39). However, in reviewing the underlying data for the evidence presented in this checklist, we note that only two of the five can be substantiated: (1) statistically significant and dose-related information from the NTP (1998) chronic inhalation bioassay data, and (5) structural similarities between chloroprene and known human carcinogens, 1,3-butadiene and vinyl chloride.

We have demonstrated considerable misinterpretation in the 2010 Review of the available science to support other items on the checklist. For example, the epidemiological evidence, based on an appropriate weight of evidence approach, fails to demonstrate clearly increased risks among exposed occupational groups and the general population, and a weak difference between exposed and unexposed workers reflecting a deficit among the least exposed (see Section 5). The claim that chloroprene is mutagenic is not supported by the overall evidence from the available data, as discussed in Section 4. Although there are structural similarities of chloroprene and 1,3-butadiene and vinyl chloride, the toxicological evidence including possible modes of action (MOAs) demonstrate substantial differences between chloroprene, vinyl chloride, and 1,3-butadiene.

Most importantly, the narrative does not include discussion of critical uncertainties in relying on the mouse data from NTP (1998) to predict the potential for carcinogenic risk in the humans, given ample evidence of important pharmacokinetic differences between mice and other species. In fact, the NTP study and other animal studies show that there is little evidence of consistent tumorgenicity across species other than the mouse and in particular the hamster (see Section 3). This difference can clearly be explained by evidence of differences in the pharmacokinetics of chloroprene across species. In addition, consideration of the lack of evidence of the carcinogenicity of chloroprene from human studies and the risks that would be predicted relying on the results from human studies (see Section 11) further indicate that a classification of "likely" carcinogen is inappropriate.

The weight of evidence supports a reclassification. According to US EPA (2015) the updated classification narrative should address the following:

- The weight of the evidence should be presented as a narrative laying out the complexity of information that is essential to understanding the hazard and its dependence on the quality, quantity, and type(s) of data available, as well as the circumstances of exposure or the traits of an exposed population that may be required for expression of cancer.
- In borderline cases, the narrative explains the case for choosing one descriptor and discusses the arguments for considering but not choosing another.
- The descriptors can be used as an introduction to the weight of evidence narrative. The complete weight of evidence narrative, rather than the descriptor alone, provides the conclusions and the basis for them.

A complete and accurate narrative also should capture and interpret all documented major uncertainties in the evidence as it relates to the classification of chloroprene. Transparent documentation of methods, data and assumptions, coupled with an accurate and informative classification of the weight of evidence is needed. Considering the misinterpretation of some data and the uncertainty in relying on responses in the mouse to be predictive of the potential for carcinogenicity in humans, the current classification of "likely to be carcinogenic to humans" unduly raises public health concerns. We conclude that a descriptor of "suggestive to be carcinogenic to humans" is more representative of the weight of evidence and uncertainties associated with relying significantly on results from a species for which there is evidence of differences that explain the observed sensitivity compared to the human.

7 US EPA DERIVATION OF THE CHLOROPRENE IUR

As described in Section 3, US EPA relied primarily on the findings of a two-year inhalation study conducted by the NTP (1998) in B6C3F1 mice and F344/N rats. Trochimowicz *et al*. (1998) also conducted studies in Wistar rats and Syrian hamsters. The results of the NTP (1998) and Trochimowicz *et al*. (1998) studies showed that the mouse is the most sensitive species to chloroprene among the species tested. US EPA selected the results from the female mouse to be the basis for deriving the chloroprene IUR. However, given the differences in response in the mouse compared to other laboratory species, US EPA should have considered the potential for differences in pharmacokinetics to better characterize and explain the cross-species differences. Although this source of bias is likely the largest and most significant, US EPA applied a number of additional assumptions in deriving the chloroprene IUR that lead to conservative bias and unsupported uncertainty in the IUR. The following sections highlight these key sources of uncertainty.

7.1 US EPA's dose-response modeling applied overly conservative methodology

US EPA determined the point of departure (POD)[5] using dose-response modeling to derive the IUR. Specifically, US EPA estimated the effective dose at a specified level of response (a benchmark dose concentration associated with a 10% risk level [BMD_{10}]) and its lower-bound based on the lower 95% confidence interval of the BMD_{10} ($BMDL_{10}$) for each chloroprene-induced tumor type in the mouse. Having determined that chloroprene was more potent in inducing tumors in mice than in rats, US EPA did not consider the rat data further in developing the IUR. US EPA further noted that the observed differences may be due to species differences in metabolism.

US EPA modeled each mouse tumor endpoint reported in NTP (1998) separately using the US EPA multistage Weibull time-to-tumor model. The multistage Weibull model has the following form:

$$P(d,t) = 1 - \exp[-(b_0 + b_1 d + b_2 d^2 + \ldots + b_k d^k) \times (t - t_0)^c]$$

where P(d,t) represents the lifetime risk (probability) of cancer at dose d (the human equivalent exposure in this case) at time t (a human lifetime in this case); parameters $b_i \geq 0$, for I = 0, 1, ..., k; t is the time at which the animal's tumor status, either no tumor, tumor, or unknown (missing or autolyzed) was observed; t_0 is the latency of response; and c is a parameter which characterizes the change in response with age. For the analysis performed in the 2010 Review, the latency (t_0) was set to zero for all models. The power term parameter c is normally a parameter that is estimated by the BMD software. For some tumors, the model software was unable to calculate this parameter and US EPA had to estimate this value (*e.g*., for forestomach tumors).

In the modeling, US EPA conservatively considered all tumor types, both benign and malignant. US EPA also assumed that the dose-response was linear in the low

[5] A POD is defined as the point on a dose-response curve that marks the beginning of a low-dose extrapolation. This point is typically a lower bound, expressed in human-equivalent terms, near the lower end of the observed range. This POD is used to extrapolate to lower exposures to the extent necessary.

dose range, based on the assumption that chloroprene has a mutagenic MOA. This approach is not justified by the available scientific evidence; therefore, the assumption of linearity inappropriately adds another level of uncertainty to the IUR.

7.2 Extrapolation from animals to humans should have included use of a PBPK model

In the 2010 Review, US EPA did not use a PBPK model for chloroprene to adjust for differences across species, even though a model was available. At the time, US EPA stated that it did not have sufficient data to validate the model. However, all of the quantitative data necessary to refine and verify the critical metabolic parameters for the existing peer-reviewed model for chloroprene (*i.e.*, Himmelstein *et al*. 2004b) were available and could have been applied to adjust the IUR. Further, since the release of the 2010 Review, additional peer-reviewed studies have been published, demonstrating consistent results and validating the use of the model for dose-response modeling and determination of an appropriate human equivalent concentration for the human IUR (Yang *et al*. 2012, Thomas *et al*. 2013, Allen *et al*. 2014).

Instead of using a PBPK model to account for differences between humans and animals, US EPA used a default approach that entails applying a dosimetry adjustment factor (DAF) that accounts for some differences in the blood:air partitioning in animals compared to humans. US EPA used a DAF of 1.0 (essentially assuming equivalence), based on the unsubstantiated assumption that all the lung tumors observed were the result of systemic effects from chloroprene exposures. US EPA provided no evidence to support the assumption that tumors in the lungs of mice are the result of systemic effects, rather than the more plausible portal-of-entry effects that would result from direct contact of chloroprene with lung tissue.[6] As noted by US EPA (2010a), "treating lung tumors as systemic effects returns the highest composite unit risk (approximately 60% greater than if lung tumors are treated as portal-of-entry effects)."

7.3 Deriving a composite IUR based on multiple tumors is not scientifically supported

Another source of overly-conservative bias in the derivation of the IUR is the use of a composite value of multiple tumor types instead of the standard approach of using the most sensitive species, gender, and endpoint(s). The use of the composite value for chloroprene is not valid. While US EPA assumed statistical independence of different tumor types based on a hypothesized MOA for chloroprene involving the production of epoxide metabolites, the underlying data do not demonstrate mechanistic or biological independence. The mechanism of action in multiple tissues could also be due to dependent events; for example, a liver tumor could be dependent on the generation of the same metabolite as that needed for the development of a lung tumor. Figure 7.1 illustrates how US EPA's assumption of adding risk across multiple tumor sites overestimates the potential overall cancer risk. Figure 7.1 also shows the considerable non-random distribution

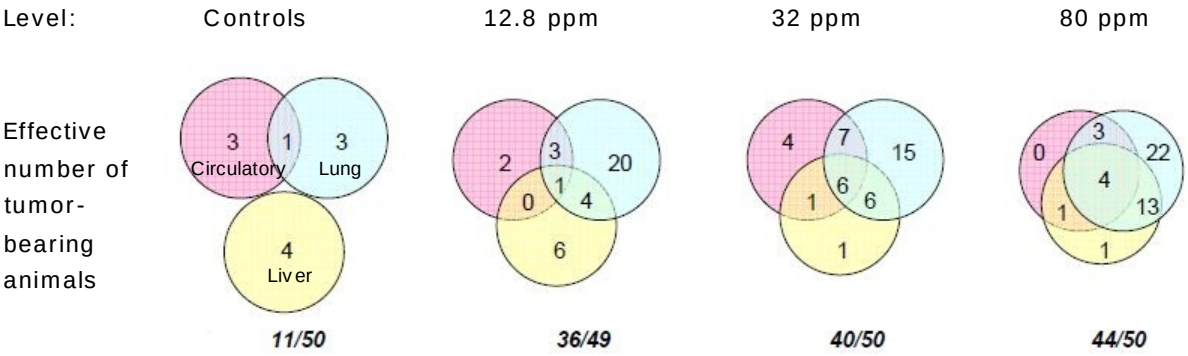
[6] A portal-of-entry effect is a localized effect that occurs at the point at which a substance enters the body (*e.g.*, via inhalation there would be effects on the respiratory system). Systemic effects, on the other hand, are effects that occur in other organs of the body distant from the portal-of-entry (*e.g.*, effects on the liver following inhalation of the substance).

of tumors in the animals bearing multiple tumors. Therefore, when US EPA assumed independence based on an unknown MOA, this inflated the effective number of animals developing tumors and overstated the carcinogenicity of chloroprene. US EPA recognized that the assumption of independence could not be verified, and that if this assumption did not hold, it indeed would overestimate risk (US EPA 2010a), in this case by another 50%.

In calculating the composite estimated IUR, US EPA also assumed that the IURs were normally distributed around the mean with a 95% upper confidence limit that represents the composite estimate. However, there is no evidence to support a normality assumption either in the benchmark dose (BMD) or the IUR, which adds to the uncertainty in the risk estimate.

Based on the US EPA approach of summing IURs for individual tumor types, the estimated composite inhalation IUR for female mice (which were more sensitive to chloroprene than male mice) was increased by approximately 50%, from 1.8×10^{-4} for the most sensitive endpoint (lung tumors in female mice) to 2.7×10^{-4} per $\mu g/m^3$ for all tumors combined. US EPA rounded this to a single significant figure, resulting in an even more conservative IUR for continuous lifetime exposures to adult humans of 3×10^{-4} per $\mu g/m^3$.

NTP Data



US EPA Approach

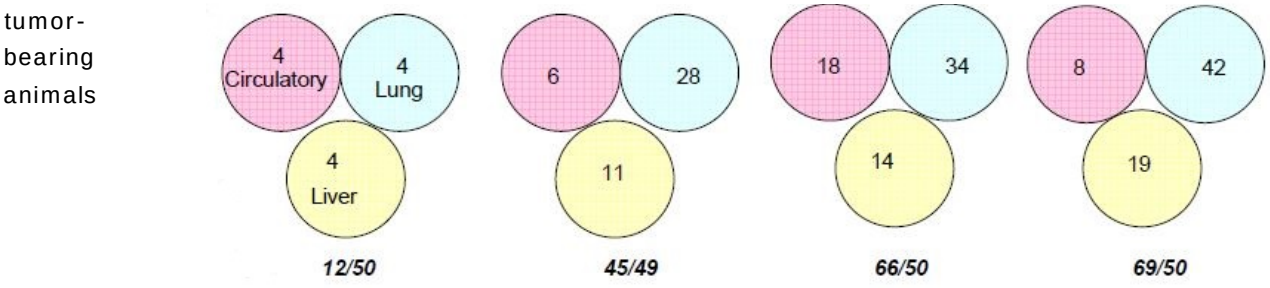


Figure 7.1. Illustration of How US EPA's Approach of Summing Individual Tumor Potencies Overestimates Total Tumor Potency in Female Mice by Assuming Independence.

7.4 IUR adjustment for early life susceptibility is not appropriate

In the final step, US EPA applied an age-dependent adjustment factor (ADAF) to account for early-life susceptibility, because of a hypothesized mutagenic MOA. This yielded a final adjusted unit cancer risk of 5×10^{-4} per $\mu g/m^3$. This adjustment reflects the use of several sensitivity adjustments for different life-stages, which are applied for presumed mutagenic compounds as specified in US EPA's "Supplemental Guidance for Assessing Susceptibility From Early-Life Exposure to Carcinogens" (US EPA 2005). Specifically, as described in the US EPA (2005b) guidance, US EPA applied the default ADAFs and their age groupings of 10 for <2 years, 3 for 2 to <16 years, and 1 for 16 years and above. The calculations are shown below.

Risk for birth through <2 yr $= 3 \times 10^{-4}$ per $\mu g/m^3 \times 10 \times 2$ yr/70 yr $= 8.6 \times 10^{-5}$ per $\mu g/m^3$

Risk for ages 2 through <16 $= 3 \times 10^{-4}$ per $\mu g/m^3 \times 3 \times 14$ yr/70 yr $= 1.8 \times 10^{-4}$ per $\mu g/m^3$

Risk for ages 16 until 70 $= 3 \times 10^{-4}$ per $\mu g/m^3 \times 1 \times 54$ yr/70 yr $= 2.3 \times 10^{-4}$ per $\mu g/m^3$

The individual risk estimates were then summed to obtain the final lifetime (70 years) IUR for chloroprene:

$$\text{Risk} = 8.6 \times 10^{-5} + 1.8 \times 10^{-4} + 2.3 \times 10^{-4} = 5.0 \times 10^{-4} \text{ per } \mu g/m^3$$

As with the calculation of a composite IUR (which was increased by 67% based on the combination of tumors), US EPA's assumption of a mutagenic MOA increased the calculated IUR by another 67%. Taken together, these assumptions increased the IUR calculation to 178% of the IUR calculated based on the most sensitive species at the most sensitive site. As discussed in detail in Section 4, the ADAF adjustment is not applicable to chloroprene because there is insufficient evidence of a mutagenic MOA for chloroprene.

7.5 Summary of US EPA's derivation of the chloroprene IUR

The chloroprene IUR derived in the 2010 Review was based on the following assumptions, some of which are not scientifically substantiated:

1. US EPA selected the most sensitive species, female B6C3F1 mice, based on the results from the NTP (1998) study;
2. US EPA assumed lung tumors in mice to be a systemic lesion and not a portal-of-entry effect, resulting in a minimal dosimetric adjustment for extrapolating from animals to humans (i.e., application of a DAF =1);
3. US EPA calculated a composite risk estimate based on multiple tumor sites, although multi-tumor data were inconsistent and relatively weak for most tumor sites;
4. US EPA rounded the IUR prior to applying the ADAF, increasing the IUR further; and
5. US EPA applied an ADAF based on the assumption of a mutagenic MOA.

Table 7.1. Conservative Assumptions in the Calculation of the Chloroprene IUR

Step	IUR per $\mu g/m^3$	Basis	Amount of overestimate	Cumulative overestimate
Most sensitive endpoint/species (portal-of-entry DAF=1.7)	1.06×10^{-4}	Lung tumors in female mice as a portal-of-entry effect		
Most sensitive endpoint/species (systemic lesion DAF=1)	1.8×10^{-4}	Lung tumors in female mice as a systemic effect	1.7	
Multiple tumor adjustment	2.7×10^{-4}	Multiple tumors	1.5	
Rounding	3×10^{-4}	Rounding	1.1	2.8
Application of ADAF	4.5×10^{-4}	Adjustment (without rounding)	1.5	4.2
Application of ADAF	**5×10^{-4}**	**Adjustment (with rounding)**	**1.7**	**4.8**

Combined, these assumptions contribute to a risk estimate that is over-estimated by about a factor of 5 (Table 7.1). However, these assumptions contribute only to a small overestimate compared to consideration of the documented differences across species, which was reported by Allen *et al*. (2014) and confirmed by our own calculations of an updated IUR. Consideration of pharmacokinetic differences across species indicate that the chloroprene IUR is likely overestimated by two orders of magnitude.

7.6 Replication of US EPA's dose-response modeling

The 2010 Review used the results from the NTP (1998) study in mice to calculate multiple PODs for derivation of the composite IUR (see previous section). US EPA focused specifically on the female mouse as this was the most sensitive species and gender, but assumed that this animal model was directly applicable to humans. Further, US EPA assumed a default linear dose-response and applied the multistage Weibull model, which accounts for the influence of competing risks (such as early death) and for the occurrence of multiple tumors, some of which are incidental (benign or not fatal), and others which are carcinogenic (*i.e.*, fatal).

Ramboll Environ attempted to re-create the dose-response modeling for the female mouse endpoints using the same time-to-tumor model provided in the current version of the US EPA BMD software. However, we could not completely replicate US EPA numbers. In attempting to do so, we identified several inconsistencies in the US EPA method and other issues that prevented full replication of US EPA's estimates. Furthermore, we were unable to identify adequate documentation supporting US EPA's calculations. The need for transparency highlighted by the NRC (2014), and as underscored by our inability to replicate the 2010 IUR, demonstrate the need to review and revise the IUR for chloroprene.

Examples of the inconsistencies encountered in our independent modeling of the NTP (1998) data included the following:

1. We were unable to confirm which version of the US EPA Benchmark Dose Modeling Software was used to conduct the modeling presented in the 2010 Review. This is significant because it appears that US EPA used a version of the model (from 2009) that may have contained important errors that were later corrected (personal communication with John Fox, US EPA, June 16, 2016). This could also explain some of the discrepancies in our results compared to those presented in the 2010 Review.
2. US EPA did not provide the complete input files for the model, but only a summary; therefore, we could not verify the data needed for conducting the time-to-tumor model (time of death of the animals, tumor status: censored (C) for no tumor, incidental (I) or fatal (F) tumors, or unknown (U) when there is no tissue or tissue was unusable). The lack of transparency made it difficult to verify whether US EPA conducted the modeling appropriately.
3. For the analysis of the incidence of forestomach tumors, US EPA calculated a power parameter (c), as described above, outside of the modeling program and entered it as a specific variable in the analysis. This parameter necessarily was calculated outside of the program because the program was unable to calculate it. It was unclear how US EPA calculated this parameter and whether this value is larger or smaller than what would be predicted by the program. This could impact the results and introduced additional uncertainty.
4. US EPA did not apply a consistent methodology across all the endpoints and time points that were examined. For example, in some cases animals that had no tumors or evidence that tumors were naturally "digested" by the animal (autolyzed tumors) were simply removed from the analysis (*e.g.*, for the forestomach analysis) and in other cases these were treated as "unknown" tumors (*e.g.*, in the mammary analysis). This approach would result in an overestimate of risk and there was no clear reason why US EPA took this approach.
5. There were also inconsistencies in the number of animals that were reported in each endpoint and time-point group. For example, the number of animals considered in Table C-1 of the 2010 Review (data from NTP 1998) did not match the numbers in Table 5-4 (US EPA 2010a). The major differences were identified in the total number of animals examined for tumors of the skin, mammary gland, forestomach, Harderian gland, and Zymbal's gland, and for the dose levels up to 32 ppm, depending on the endpoint. US EPA reported that tissue from 50 animals was examined, whereas NTP (1998) reported that tissue from only 49 animals was examined. Although this may not have impacted the results significantly, it indicated that US EPA allowed errors in their reporting of the results and possibly made errors inputting the results into the model, some of which might be consequential. Without full transparency and availability of model inputs, this could not be verified.

Ramboll Environ analyzed each endpoint independently, as was done by US EPA, but did not combine the estimates to obtain a composite IUR. We did not agree that US EPA's approach was standard or scientifically justified given that independence could not be confirmed and the MOA across tumor types was unknown. In addition, we corrected the issues associated with the appropriate counts and, following US EPA guidance, removed any unknowns when using an incidence-only analysis (assuming all tumors observed were incidental and were not fatal to the animals). A comparison of our independent results and those generated by US EPA is presented in Table 7.2.

Table 7.2. Comparison of Dose-Response Modeling for Female Mice at a Benchmark Response of 0.01

Site	US EPA Results from Tables C-3 and C-4							Ramboll Environ Results							
	Stage	LL	χ2	AIC	Model Selection	BMD ppm	BMDL ppm	Stage	LL	χ2	p-value	AIC	Model Selection	BMD ppm	BMDL ppm
Lung					One-stage model			3	-83.0	-0.11	0.74	176.04			
								2	-82.96	0.00	1.00	173.93			
	1	-83.02	—	172.0		0.11	0.09	1	-82.96			171.93	Lowest AIC	0.11	0.08
Hemangiomas,hemangio-sarcomas, (fatal) (highest dose group dropped)	3							3	FAILED			279.74			
	2	-135.85	5.34	279.7	χ2, lowest AIC	3.12	0.64	2	-135.87	5.34	0.02	279.74	Lowest AIC	3.04	0.47
	1	-138.52	—	283.0				1	-138.54			283.08			
Hemangiomas,hemangio-sarcomas, (all incidental) (highest dose group dropped)	3							3	FAILED						
	2	-65.81	2.28	139.6	Lowest AIC	4.61	2.02	2	-65.74	2.22	0.14	139.48	Lowest AIC	4.60	1.92
	1	-66.95	—	139.9				1	-66.85			139.70			
Harderian gland	3	-58.26	0.02	126.5				3	-58.22	0.02	0.89	126.45			
	2	-8.27	0	124.5				2	-58.23	0.00	0.98	124.47			
	1	-58.27	—	122.5	Lowest AIC	2.58	1.20	1	-58.23			122.47	Lowest AIC	2.50	1.14
Mammary gland carcinomas, adenoacanthomas	3				One-stage model			3	-84.21	0.00	1.00	178.42			
	2							2	-84.21	0.00	0.99	176.42			
	1	-87.96	—	181.9		1.95	1.34	1	-84.21			174.42	Lowest AIC	2.03	1.38
Forestomach	3	-19.17	0.84	48.35				3	-19.18	0.84	0.36	46.36			
	2	19.60	2.35	45.19	Lowest AIC	20.94	5.69	2	-19.60	2.35	0.13	45.20	Lowest AIC	20.54	5.48
	1	-20.77	—	45.54				1	-20.78			45.55			
Hepatocellular adenomas, carcinomas	3				One-stage model			3	-119.94	0.00	1.00	249.87			
	2							2	-119.94	0.00	1.00	247.87			
	1	-119.2	—	245		0.40	0.23	1	-119.94			245.87	Lowest AIC	0.39	0.23
Skin	3				One-stage model			3	-87.395	0.00	1.00	184.79			
	2							2	-87.395	0.00	0.99	182.79			
	1	-87.463	—	180.9		0.91	0.67	1	-87.395			180.79	Lowest AIC	0.89	0.67
Zymbal's gland	3	-11.402	0.65	32.8				3	-11.406	0.66	0.42	32.81			
	2	-11.726	1.77	31.45				2	-11.734	1.76	0.19	31.47			
	1	-12.611	—	31.22	Lowest AIC	15.78	5.76	1	-12.612			31.22	Lowest AIC	29.9	8.23

AIC: Akaike Information Criterion; BMD: benchmark dose; BMDL: lower 95% confidence limit of the benchmark dose; LL: log likelihood

7.7 Conclusions

US EPA applied a number of scientifically unsupported conservative assumptions in deriving the IUR for chloroprene that resulted in substantial overestimation of the IUR and added uncertainty to the toxicity estimate. Consistent with the majority of available IRIS profiles on other chemicals, the IUR should be based on the most sensitive endpoint in the most sensitive species, as this will be protective for other effects. Not assuming a systemic lesion for lung cancers yields an initial IUR of 1.06×10^{-4} based on the female mouse as the most sensitive species. In recommending a final IUR based on the mouse data, US EPA should have considered the significant pharmacokinetic differences between species and applied the PBPK model for extrapolating from animals to humans (Himmelstein *et al*. 2004), as demonstrated in Section 10.

8 THE CHLOROPRENE IUR COMPARED TO KNOWN CHEMICAL CARCINOGENS

The chloroprene IUR reported in the 2010 Review is much higher than those of similar chemicals, including known carcinogens. We compared (and summarize below) the IURs for all compounds classified by IARC as Group 1 (carcinogenic) or 2A (probably carcinogenic), which generally correspond with US EPA's classification for known or likely/probable human carcinogens. We used IARC classifications because IARC generally applied consistent methods and criteria for evaluating human carcinogens.

We also obtained the US EPA WOE classification and basis of the IUR for carcinogens for which US EPA has calculated and reported an IUR. These compounds are summarized in a table developed and updated by US EPA to be used in dose-response assessments of hazardous air pollutants.[7] In the US EPA table, all hazardous air pollutants are listed with available toxicity values based on source.

We excluded metallic compounds, which tend to be associated with particulate exposures, and mixtures, such as coke oven emissions. We sorted the remaining compounds by the IUR calculated by US EPA, from highest to lowest (Table 8.1). In addition, the table shows the WOE conclusions by IARC, the dates of each evaluation, and the relative strength of the epidemiological evidence. More detailed information on the toxicity evaluations and epidemiological evidence can be found in Appendices A and B, respectively.

[7] See Table 1 available at https://www.epa.gov/fera/prioritization-data-sources-chronic-exposure

Table 8.1. Summary of Potentially Carcinogenic Compounds by IUR Listed in IRIS

Chemical Name	US EPA WOE	Year	IARC WOE	Year	IUR per µg/m3	MOA	Basis of IUR/ Endpoint	Strength of Epidemiology Evidence
Benzidine	A	1987	1	2012	0.067	M*	Human/ bladder	Moderate
Bis(chloromethyl) Ether (BCME)	A	1988	1	2012	0.062		Rat/lung	Moderate
Nitrosodimethyl-amine (NDMA)	B2	1987	2A	1987	0.014	M*	Rat/liver	Limited
Ethylene dibromide	LH	2004	2A	1999	0.0006		Mouse/ nasal	Limited
Chloroprene	LH	2010	2B	1999	0.0005	M*	Mouse/ multiple	Limited
Acrylamide	LH	2010	2A	1994	0.0001	M*	Rat/ thyroid	Limited
Polychlorinated biphenyls	B2	1996	2A	2013	0.0001		Rat/liver	Very limited
1,3-Butadiene	CH	2002	1	2012	0.00003		Human/ leukemia	Strong (high exposures)
Formaldehyde	B1		1		0.000013		Human/nasal	Moderate (high exposures)
Vinyl chloride	CH	2010 Draft	1	2012	0.0000088		Rat/liver	Moderate (high exposures)
Benzene	CH	2003	1	2012	0.0000022 to 0.0000078		Human/ leukemia	Strong (high exposures)
Trichloroethylene	CH	2011	2A	2014	0.0000041	M*	Human/ kidney	Moderate
Epichlorohydrin	B2	1988	2A	1999	0.0000012		Rat/ kidney	Very limited
Tetrachloroethene	LH	2012	2A	2014	0.00000026		Mouse/ liver	Limited for bladder/NHL/ MM

US EPA WOE (2005 Guidelines) = CH - carcinogenic to humans; LH - likely to be carcinogenic; US EPA WOE (1986 Guidelines): A - human carcinogen; B1 - probable carcinogen, limited human evidence; B2 - probable carcinogen, sufficient evidence in animals; IARC WOE for carcinogenicity in humans (1 - carcinogenic; 2A - probably carcinogenic; 2B - possibly carcinogenic).; US EPA MOA (2005 Guidelines) M* - mutagenic and early life data lacking. NHL- non-Hodgkin lymphoma; MM – multiple myeloma

Despite being classified by IARC as a 2B carcinogen, chloroprene has the 5th highest IUR (see Table 8.1), which is orders of magnitude greater than the IURs for the known carcinogens vinyl chloride, 1,3-butadiene, and benzene. Three of the compounds with IURs higher than chloroprene (benzidine, bis(chloromethyl)ether [BCME], and N-Nitrosodimethylamine [NDMA]) have IURs that are based on reviews from the 1980s, performed before new methods were developed for integration of evidence, and likely would be different using current methods. Although there may be more recent data available to update the estimates for these compounds, two of these compounds are no longer of concern for human exposures: benzidine is no longer produced in the US (US EPA 1987a); additionally, there is very limited production of BCME, and what is produced or used is highly regulated (Bruske-Hohfeld 2009).

The only other compound with a higher IUR than chloroprene is ethylene dibromide (EDB)(US EPA 2004). US EPA (2004) described a single epidemiological study of occupational exposures to EDB, which was determined to be inadequate due to lack of exposure information and potential co-exposures to other carcinogens. Therefore, the IUR for ethylene dibromide was based on animal study results. Like

chloroprene, however, there were several important areas of uncertainty, including the extrapolation to low doses from high doses in rats, the application of the dose for respiratory tumors, portal of entry vs. systemic effects, and the need to account for metabolic differences between mice and humans. At the time of the assessment, a pharmacokinetic model was available (Hissink *et al*. 2000, Ploemen *et al*. 1995) but, as in the case of chloroprene, it was not deemed adequate for use by US EPA due to limited validation of the model. Therefore, updating the IUR for EDB also may be warranted.[8]

In contrast, there are several examples of carcinogenic compounds that have IURs that are *1 to 2 orders of magnitude lower* than chloroprene and for which US EPA has based the WOE evaluation and IUR development on much stronger positive human epidemiological evidence (1,3-butadiene and benzene) or for which US EPA appropriately used PBPK modeling to extrapolate results from animals to humans (vinyl chloride). In fact, one of the reasons US EPA classified chloroprene as a likely human carcinogen was structural similarities with 1,3-butadiene and vinyl chloride (US EPA 2010a), and it is particularly relevant to recognize how much higher the 2010 chloroprene IUR is compared to vinyl chloride and 1,3-butadiene. Both of these compounds were classified as known human carcinogens based on both stronger epidemiological evidence and supporting animal evidence than that available for cholorprene.

Vinyl chloride presents a relevant comparison to chloroprene based on its structural similarity to chloroprene and has been classified by IARC (2012) and US EPA (2000) as a known human carcinogen. Unlike chloroprene, however, the epidemiological evidence linking vinyl chloride with angiosarcomas of the liver, as well as primary hepatocellular cancers, is clear and consistent (Mundt *et al*. 2000, Boffetta *et al*. 2003, Mundt *et al*. 2017). US EPA appropriately applied a PBPK model for vinyl chloride to account for differences between animals and humans, resulting in a cancer IUR that is approximately 57 times lower than the IUR for chloroprene. When accounting for metabolic differences between animals and humans using a PBPK model, the cancer IUR for vinyl chloride was found to be consistent with risk estimates based on human epidemiological data and were lower than those based on external dose concentrations by a factor of 80 (Clewell *et al.* 2001).

1,3-butadiene has an extensive literature that describes its pharmacokinetics (US EPA 2002). Like chloroprene, the carcinogenetic mode of action of 1,3-butadiene is proposed to be related to its reactive metabolites, and results from PBPK models have demonstrated that there are important species differences in the rates of formation and detoxification of these reactive metabolites. In fact, the model results showed that, like chloroprene, pharmacokinetics can explain why mice are considerably more sensitive to the carcinogenic effects of 1,3-butadiene than other species, including humans. In comparing chloroprene with 1,3-butadiene, US EPA should have considered the differences observed across species that were also related to pharmacokinetics of 1,3-butadiene in deriving a chloroprene IUR, as similar differences across species have been observed for 1,3-butadiene.

[8] This is presented as a comparison for chloroprene, and is outside of the scope of our analysis.

There are other examples of recent assessments, such as that for trichloroethylene, for which US EPA appropriately applied a PBPK model to develop the IUR and for which epidemiological evidence is more robust than for chloroprene.

In summary, the comparison of the chloroprene IUR with the IURs of similar chemicals suggests that the chloroprene IUR from the 2010 Review is high even by IRIS standards, and that the chloroprene IUR should be reviewed and corrected.

9 A PBPK MODEL FOR CHLOROPRENE

9.1 PBPK modeling should be used to quantify the pharmacokinetic differences between species

PBPK modeling is used to predict the absorption, distribution, metabolism and excretion of chemical substances in humans and other animal species. These models are based on the integration of the available science for a specific compound. PBPK modeling is particularly important for use in extrapolating results from animal studies to develop toxicity values for humans, especially when there are significant differences across species. The "Guidelines for Carcinogenic Risk Assessment" (US EPA 2005) and the NRC review of the IRIS process (NRC 2014) recommend that if sufficient and relevant quantitative information is available (such as blood/tissue partition coefficients and pertinent physiological parameters for the species of interest), PBPK models should be constructed to assist in the determination of tissue dosimetry, species-to-species extrapolation of dose, and route-to-route extrapolation.

In the 2010 Review, US EPA acknowledged the shortcomings in their derivation of the chloroprene IUR, noting that: "Ideally, a PBPK model for the internal dose(s) of the reactive metabolite(s) would decrease some of the quantitative uncertainty in interspecies extrapolation; however, current PBPK models are inadequate for this purpose" (US EPA, 2010a). Although the PBPK models have been validated since the release of the 2010 Review, a PBPK model for chloroprene was available at the time US EPA prepared the 2010 Review. Despite uncertainties in the application of this model at the time of the development of the IUR, the results from these PBPK models would have explained the large observed inconsistencies in the data between mice, rats and humans. Additionally, there was substantial evidence at that time showing that external exposure concentrations from mouse chamber experiments were not representative of human health risks.

The 2010 Review noted that pharmacokinetic information on the absorption, distribution, and *in vivo* metabolism and excretion of chloroprene and/or its metabolites was available primarily for animals, but not humans. Several *in vitro* studies focused on chloroprene metabolism in lung and liver tissue fractions from rat, mouse, hamster, and humans (Cottrell *et al*. 2001; Himmelstein *et al*. 2001a, b; Himmelstein *et al*. 2004a, b; Hurst and Ali 2007; Munter *et al.* 2003; Munter *et al*. 2007; Summer and Greim 1980). These studies indicated that chloroprene is metabolized via the CYP450 enzyme system to active metabolites that are thought to be associated with the carcinogenic MOA for chloroprene. As noted in the 2010 Review, although the metabolic profile for chloroprene is qualitatively similar across species, *in vitro* kinetic studies using tissues from rodents and humans suggest significant interspecies and tissue-specific differences that, if operative *in vivo*, could account for the species, strain, and sex differences observed in chloroprene-induced *in vivo* effects.

The available *in vitro* information on the metabolism of chloroprene (Cottrell *et al.* 2001, Himmelstein *et al*. 2001b, Himmelstein *et al*. 2004a) demonstrates significant quantitative differences across species in the production of the major metabolites of chloroprene, and in particular, in the production of the epoxide likely to be the

carcinogenic constituent. The results from the *in vitro* studies indicate that greater amounts of these metabolites are produced in mice, followed by rats, and lastly in hamsters and humans. The 2010 Review discussed these differences, but did not incorporate this information when calculating the human equivalent dose for dose-response modeling. Himmelstein *et al*. (2004a) also noted species differences in the detoxification of epoxide metabolites, most notably the epoxide hydrolase, which serves to eliminate any epoxide formed. For example, the cross-species ranking of intrinsic clearance in the liver for enzymatic hydrolysis of the chloroprene metabolite was human ~ hamster > rat > mouse. In the lung, the order was human ~ hamster > rat ~ mouse. Therefore, the mouse not only had the highest capability for the generation of epoxide metabolites, but also the slowest capacity for clearance.

Overall, the balance of reactive metabolite formation and detoxification across species indicates that the mouse would be the most sensitive species, based on higher rates of epoxide formation, slower hydrolysis, and more enzyme activity. The mouse-specific pharmacokinetics all contribute to potentially increased formation and sustained concentrations of potentially toxic metabolites at lower exposures to chloroprene, explaining the increased sensitivity of this species.

The 2010 Review relied on the animal chamber air concentrations for the mouse exposure data to calculate the human IUR. Himmelstein *et al*. (2004b) demonstrated that there was no dose-response relationship when air concentrations from animal chambers (the administered dose) were used, whereas when the internal dose[9] was used (obtained from the PBPK model) a dose-response was clearly observed with relation to lung tumors. This is shown in Table 9.1, where the lung tumor incidence risk is assessed based on the internal dose. This table not only illustrates the dose-response based on internal dose, but clearly highlights the differences across species, showing that the mouse is the most sensitive species. When evaluating internal dose, which accounts for metabolic differences between mice, rats and hamsters, the differences in the lung tumor response across these species can be explained.

[9] In an experimental setting the administered dose is the concentration of the chemical that is given to the animal (measured in air, water, etc.), whereas the internal dose is the concentration of the chemical that is actually absorbed by the animal (measured inside the animal's body) and delivered to the target tissue.

Table 9.1. Exposure-Dose-Response for Rodent Lung Tumors

	Exposure concentration (ppm)	PBPK internal dose [a]	Lung tumor incidence	Number of animals	Extra risk (%)[b]
Hamster	0	0	0	100	0
	10	0.18	0	97	0
	50	0.88	0	97	0
Wistar rat	0	0	0	97	0
	10	0.18	0	13	0
	50	0.89	0	100	0
Fischer rat	0	0	3	50	0
	12.8	0.22	3	50	0.3
	32	0.55	6	49	7.7
	80	1.37	9	50	14.0
B6C3F1 mouse[d]	0	0	15	50	0
	12.8	3.46	32	50	48.3
	32	5.30	40	50	70.4
	80	7.18	46	50	89.9

(a) Internal dose - average daily mg Chloroprene metabolized/g lung tissue (AMPLU).
(b) The incidence data were corrected for extra risk equal to (Pi – Po)/(1 –Po), where P is the probability of tumor incidence in "i" exposed and "o" control animals (Himmelstein *et al*. 2004b).
(c) Male Syrian hamster and Wistar rat data from Trochimowicz *et al.* (1998).
(d) Male Fischer rat and B6C3F1 mouse data from Melnick *et al*. (1996).

9.2 US EPA calculation of the human equivalent concentration for chloroprene in the 2010 Review

All of the quantitative data necessary to refine and verify the critical metabolic parameters for the existing peer-reviewed PBPK model for chloroprene (Himmelstein *et al*. 2004b) were available at the time the 2010 Review was published and could have been applied to adjust the cancer unit risk to account for species-specific target-tissue dosimetry. Instead, the 2010 Review used the default approach and limited default assumptions described in the US EPA (1994) "Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry."

The 2010 Review assumptions included the following:

1. Lung tumors result primarily from systemic distribution, and
2. Chloroprene is a Category 3 gas according to US EPA (1994) guidelines.

Based on these assumptions, US EPA calculated the human equivalent concentration for chloroprene using the default DAF for Category 3 gases. As described by US EPA (1994), DAFs are ratios of animal to human physiologic parameters, and are based on the nature of the contaminant (particle or gas) and the target site (*e.g.*, respiratory tract) (US EPA 1994). For Category 3 gases with

systemic effects, the DAF is expressed as the ratio between the animal and human blood:air partition coefficients:

DAF = (Hb/g)A/(Hb/g)H

where:

(Hb/g)A = the animal blood:air partition coefficient

(Hb/g)H = the human blood:air partition coefficient

DAF = 7.8/4.5

DAF = 1.7

Furthermore, following US EPA guidelines (1994), US EPA used a default DAF of 1 because, as US EPA noted, "In cases where the animal blood:air partition coefficient is higher than the human value, resulting in a DAF>1, a default value of 1 is substituted (US EPA, 1994)." This was a conservative assumption, as it is noted in the guidelines that the available data for rats indicated that (Hb/g)A is greater than (Hb/g)H for most chemicals. This restricted the evaluation to equivalence between the mouse and the human and did not address the important pharmacokinetic differences in chloroprene metabolism in the mouse compared to the human.

9.3 The Allen et al. (2014) study shows that a validated PBPK model should be used to update the 2010 chloroprene IUR

Allen *et al.* (2014) combined the results from the most recent PBPK models for chloroprene (Yang *et al.* 2012) with a statistical maximum likelihood approach to test commonality of low-dose risk across species. Using this method, Allen *et al*. (2014) evaluated the difference between risk estimates obtained using external (chamber air concentrations) and internal dose (calculated with the PBPK model) metrics. The PBPK model for chloroprene incorporates data regarding species differences in metabolism of chloroprene, and allows species-specific estimation of internal exposure metrics, specifically the amount of chloroprene metabolized per gram of lung tissue. By using this model, IURs can then be compared across species based on equivalent internal exposure metrics rather than external air concentrations measured outside of the body. This is an important consideration when the toxicity of a compound is related to how the compound is metabolized in animals vs. humans.

Allen *et al*. (2014) found that for chloroprene, external concentration-based estimates were not appropriate for calculating and comparing cancer risks across species. As discussed in Section 5, epidemiological studies related to occupational exposures to chloroprene must also be considered in evaluating the unit risk estimate. These epidemiological studies provide little or no scientific support for the hypothesis that human and animal low-dose risks were equivalent when expressed as a function of air concentrations. In contrast, by accounting for the daily amount of chloroprene that is metabolized per gram of tissue at the target site for different species, the PBPK results provided a substantially better fit of the models to the data. Importantly, the differences in internal dose across species explained the greater sensitivity in mice (Himmelstein *et al*. 2004b), as well as the lower sensitivity of humans.

Allen *et al*. (2014) derived cancer unit risks for respiratory system cancer using the PBPK model results from both animal and human data that ranged from 2.9 x 10^{-5} to 1.4 x 10^{-2} per ppm (8.1 x 10^{-9} to 3.9 x 10^{-6} per µg/m^3), with a maximum-likelihood estimate of 6.7 x 10^{-3} per ppm (1.86 x 10^{-6} per µg/m^3). This estimate is about 100 times lower than the 2010 Review estimate of 6.5 x 10^{-1} per ppm (1.81 x 10^{-4} per µg/m^3) based on the incidence of lung tumors in female mice. It is also important to note that the Allen *et al*. (2014) assessment is highly conservative in that it does not account for species-to-species differences in detoxification and pharmacodynamics, which is justified and would lead to an even lower IUR.

It is difficult to apply the method used by US EPA for multi-tumor adjustment using the data provided in the Allen *et al*. (2014) publication, because the Allen *et al*. data were limited to lung tumors. However, this method likely would generate an estimate that is 100 times lower than the US EPA estimate. A similar rationale can be used for the application of the ADAF, yielding an IUR of approximately 5 x 10^{-6} per µg/m^3. However, because there is limited evidence for mutagenicity, we concluded that the 2010 IUR should be closer to the estimate calculated by Allen *et al*. (2014) of 1.86 x 10^{-6} per µg, and that this value is appropriately protective.

Overall, the evidence indicates that humans are far less sensitive to chloroprene exposures than mice, which is also consistent with the lack of clear or consistent epidemiological evidence of carcinogenicity as discussed in Section 5.

10 CALCULATION OF AN UPDATED CHLOROPRENE IUR

Ramboll Environ recalculated the IUR for chloroprene using the same standard methodologies that US EPA has employed in IRIS assessments for several known carcinogens, but did not employ in the 2010 Review of chloroprene. Ramboll Environ employed this methodology to reduce the significant uncertainty associated with extrapolating results from animal experiments to humans (and from one route of exposure to another), and in consideration of the substantial body of evidence demonstrating large differences in sensitivity to chloroprene across species. These differences reflect underlying pharmacokinetic differences that, if not taken into account, result in a highly inflated IUR value such as that derived in the 2010 Review.

The Allen *et al*. (2014) analysis provided a rigorous approach for integrating the available epidemiological and toxicological evidence to estimate a chloroprene IUR. However, it incorporated a maximum likelihood statistical method different from the traditional PBPK models used by US EPA in estimating IURs and other toxicity values, such as reference concentrations (RfC) or reference doses (RfD). In deriving an IUR, US EPA typically applies a PBPK model to estimate an internal dose at the target organ of interest (*e.g.*, the lung), based on the mode of action.

As discussed above, it is hypothesized that chloroprene itself does not exert a carcinogenic effect, but rather a metabolite of chloroprene exerts the effect. Therefore, carcinogenicity depends on the internal concentration of the metabolite, and not the internal (or external) concentration of chloroprene. The internal concentration of the metabolite is determined by how rapidly it is produced and eliminated from the body, and metabolite production and elimination rates vary considerably across species. Therefore, accounting for species-specific pharmacokinetic differences using PBPK modeling is critical. The US EPA (2005) Guidelines for Carcinogen Risk Assessment states that PBPK models

> *"…generally describe the relationship between exposure and measures of internal dose over time. More complex models can reflect sources of intrinsic variation, such as polymorphisms in metabolism and clearance rates. When a robust model is not available, or when the purpose of the assessment does not warrant developing a model, simpler approaches may be used."*

The preferred approach to PBPK modelling has been documented in the US EPA (2005) "Guidelines for Carcinogen Risk Assessment." Furthermore, US EPA has applied these PBPK models in estimating toxicity values for several compounds; for example, dichloromethane, vinyl chloride, tetrachloroethylene, carbon tetrachloride, and acrylamide, specifically to reduce uncertainty associated with animal-to-human extrapolation or route-to-route extrapolation. Although there may be no "perfect" model, toxicity values derived from models that best reduce uncertainty are more scientifically supportable and therefore preferred to those obtained using default adjustment factors (DeWoskin *et al*. 2007).

When an IUR is based on animal data, an animal PBPK model is required to estimate the internal dose corresponding to each of the administered

concentrations (*i.e.*, ppm in the chamber air), following the same pattern of exposure of the animals in the study (*e.g.*, days/week). This internal dose estimate is then used (instead of the air concentration) for dose-response modeling and estimating a Point of Departure (POD). This POD corresponds to the internal dose in the animal. The human PBPK model then is applied to account for known physiological and metabolic differences between the animal and human. This is accomplished by estimating the equivalent external concentration that results in the internal dose equal to the POD derived from the animal data. The IUR is estimated by dividing the risk level (benchmark risk or BMR associated with the POD) by the POD. The IUR is interpreted as the risk per unit (ppm or $\mu g/m^3$) intake.

Chloroprene PBPK modeling results for mice, rats, and humans are reported in Yang *et al*. (2012). Specifically, the internal dose estimates associated with the concentrations administered to both mice and rats in the NTP (1998) study are provided, including gender-specific internal tissues doses, *i.e*., the average amount of chloroprene metabolized per day per gram of lung (AMPLU) based on the PBPK model. These internal doses represent the concentration of the toxic moiety (*i.e*., the chloroprene metabolite) identified by US EPA as the key carcinogenic metabolite (US EPA, 2010a). The Yang *et al*. (2012) analysis showed that mice had the greatest amount of chloroprene metabolized per gram of lung, followed by rats and then humans. The human and rat showed linear dose-responses over the range of NTP bioassay concentrations of 12.8, 32 and 80 ppm. Based on this, the following was established as the relationship between the internal dose and the external exposure (ppm) in the human: 1 ppm of constant external exposure in the human results in 0.008 µmole of chloroprene metabolized per gram of lung tissue per day.

We relied on the internal dose results from the PBPK modeling conducted and reported by Yang *et al*. (2012), consistent with the PBPK modeling approach that US EPA has used in other IRIS assessments (dichloromethane, vinyl chloride, tetrachloroethylene, carbon tetrachloride). In addition, also consistent with the conclusions in the US EPA (2010) chloroprene review regarding the most sensitive endpoint in the most sensitive species, we estimated the chloroprene IUR using the results for the combined incidence of alveolar/bronchiolar adenomas and carcinomas (the most sensitive endpoint) in female mice (the most sensitive species and gender).

Using the internal doses for female mice as provided in Table 5 of Yang *et al.* (2012) (see Table 10.1), time-to-tumor modeling of the lung alveolar/bronchiolar adenomas and carcinomas was performed using the Multistage-Weibull model provided with the US EPA BMDS software (February 25, 2010 version). Time-to-tumor dose-response modeling is preferred and was used in the US EPA (2010) chloroprene assessment to model the incidence of tumors from the NTP (1998) bioassay. This type of dose-response model was necessary, as the survival of the female mice exposed to chloroprene was "significantly less than that of the chamber control" (NTP 1998). Time-to-tumor models adjust for early death of the animal, and thus the probability that the animal, if it had lived longer, may have developed the tumor of interest.

The female mouse data that we used in our analyses are presented in Table 10.2, with each animal's time of death and the observation of C, I, F or U to indicate: C=censored or the animal did not have the tumor of interest; I = incidental or the animal had the tumor of interest but it was not indicated as the cause of death; F=fatal or the animal had the tumor of interest and it was indicated as the cause of death; or U=unknown or the presence of the tumor could not be determined as the organ was autolyzed or missing in the animal. The alveolar/bronchiolar adenomas or carcinomas were all considered to be incident tumors, consistent with the time-to-tumor dose-response models and approaches used in US EPA (2010). One tumor was classified as unknown in one animal in the 12.8 ppm group, so modeling was conducted both including and excluding that animal to determine if there was any major impact on the outcome of the dose-response modeling.

Consistent with the US EPA (2010) approach, we selected a benchmark risk (BMR) of 1% (see Table 10.3 and Appendix C for the complete Multistage-Weibull modeling results). Note that models including or excluding the animal with the unknown tumor (Animal #320)[10] generated the same estimated IUR. We calculated the external human dose (in ppm) by dividing the POD or lower bound on the benchmark dose (BMDL) by the factor of 0.008 to obtain the external concentration for continuous exposure in the human in ppm associated with the internal POD. We then calculated the IUR by dividing the BMR by the human equivalent POD/BMDL in either ppm or µg/m^3:

$$IUR = BMR/POD$$

The final results are presented in Table 10.4. Using the standard methods applied in other IRIS assessment by US EPA and publically available published data, the recalculated IUR for chloroprene was 1.1x 10^{-2} per ppm or 3.2 x 10^{-6} per µg/m^3. This result, which incorporates appropriate PBPK models and adjustments necessary to extrapolate the findings from animal studies to relevant human exposure considering the differences in pharmacokinetics, is consistent with methods used in other IRIS assessments by US EPA. However, the IUR value is very different from that recommended in the 2010 Review and underscores the scientific importance of correcting and updating it.

[10] When it cannot be determined if an animal had the tumor of interest due to the organ being missing or deteriorated too much to examine, the animal will get an observation of "unknown". This data can be used in a time-to-tumor model (*e.g.* Multistage Weibull) as a time of death is available for that animal. In this case, including the animal with an observation of unknown or excluding the animal from the modeling did not result in a detectable difference in the results.

Table 10.1. Internal and External Doses from Yang et al. (2012)

External Dose (ppm)	PBPK Internal Dose Metric[11] (µmole CD metabolized /gram lung tissue/day)		Linear Relationship between ppm and PBPK metric in humans
	Mouse	Human	
12.8	0.74	0.1	0.008
32	1.19	0.25	0.008
80	1.58	0.64	0.008

[11] Data from Yang *et al*. (2012) Table 5.

Table 10.2. NTP (1998) Study – Female B6C3F$_1$ Mice Lung Alveolar/bronchiolar adenoma or carcinoma

Control = 0 ppm			Dose = 12.8 ppm			Dose=32 ppm			Dose = 80 ppm		
0 µmole/g tissue/day			0.74 µmole/g tissue/day			1.19 µmole/g tissue/day			1.58 µmole/g tissue/day		
Animal #	Time (wks)	Obs.[12]	Animal #	Time (wks)	Obs.	Animal #	Time (wks)	Obs.	Animal #	Time (wks)	Obs.
141	5	C	318	41	C	505	31	C	738	1	C
110	69	C	330	46	C	532	50	I	711	36	C
138	70	C	350	46	U	545	54	C	725	47	I
107	71	C	311	63	C	535	56	C	734	48	C
130	76	C	321	64	I	540	57	C	729	55	C
135	78	C	342	69	C	530	61	C	721	64	C
126	88	C	303	75	I	502	63	I	705	65	I
105	91	C	327	76	C	548	65	I	741	66	I
146	91	C	344	78	C	510	67	C	701	67	C
124	95	C	315	79	C	529	68	C	716	67	I
133	97	C	316	79	C	521	70	C	735	70	I
103	98	C	328	79	C	506	72	I	709	75	I
127	101	C	301	87	C	512	72	I	717	75	I
132	101	I	324	89	I	524	73	C	722	75	I
101	105	C	347	89	I	523	74	I	749	75	I
102	105	C	304	90	C	531	75	I	715	76	I
104	105	C	325	91	I	547	75	C	726	76	I
106	105	C	343	91	I	518	76	I	745	77	C
108	105	C	349	91	C	519	76	I	740	79	I
109	105	C	313	97	C	503	77	C	710	81	I
111	105	C	314	97	I	504	77	I	702	83	I
112	105	C	329	97	I	511	78	C	704	83	I
113	105	C	310	98	I	528	79	I	746	83	I
114	105	C	308	99	C	546	79	I	714	84	I
115	105	C	319	99	I	533	82	I	730	86	I
116	105	C	323	99	I	520	84	I	703	87	C
117	105	C	332	99	I	522	84	C	713	88	I
118	105	C	340	99	I	536	86	I	728	88	I
119	105	C	345	100	C	507	87	I	712	90	I
120	105	C	306	101	I	525	87	C	737	90	I

[12] Observations are coded as C=censored, the animal did not have the tumor of interest
I = Incidental, the animal had the tumor of interest but it did not cause death
F = fatal, the animal had the tumor of interest and it was the cause of death (none in this dataset)
U = Unknown, it is not known if the animal had the tumor or not due to organ being autolyzed or missing

Control = 0 ppm			Dose = 12.8 ppm			Dose=32 ppm			Dose = 80 ppm		
0 µmole/g tissue/day			0.74 µmole/g tissue/day			1.19 µmole/g tissue/day			1.58 µmole/g tissue/day		
Animal #	Time (wks)	Obs.[12]	Animal #	Time (wks)	Obs.	Animal #	Time (wks)	Obs.	Animal #	Time (wks)	Obs.
121	105	C	334	102	I	526	87	I	718	91	I
122	105	C	346	102	I	527	89	I	727	91	I
123	105	I	331	103	C	539	89	I	732	91	I
125	105	C	341	103	I	541	90	I	733	91	I
128	105	C	302	105	I	542	90	I	736	91	I
129	105	C	305	105	I	544	90	I	747	91	I
131	105	I	307	105	I	501	91	I	750	91	I
134	105	I	309	105	C	509	91	I	724	92	I
136	105	C	312	105	C	516	91	I	742	93	I
137	105	C	317	105	I	537	92	I	748	93	I
139	105	C	320	105	I	508	93	I	707	94	I
140	105	C	322	105	I	517	94	I	708	95	I
142	105	C	326	105	C	538	94	I	739	95	I
143	105	C	333	105	C	550	94	I	744	96	I
144	105	C	335	105	I	534	96	I	723	97	I
145	105	C	336	105	I	549	96	C	731	97	I
147	105	C	337	105	I	513	97	I	743	98	I
148	105	C	338	105	C	515	99	C	706	105	I
149	105	C	339	105	I	543	103	I	719	105	I
150	105	C	348	105	I	514	105	I	720	105	I

Table 10.3. Multistage-Weibull Time-to-Tumor Modeling Results for a Benchmark Risk of 1%

Site	Stages	Log-Likelihood	AIC	Model Selection	BMD (µmole/gram lung tissue/day)	BMDL (µmole/gram lung tissue/day)	BMDU (µmole/gram lung tissue/day)
Female Mouse Lung – incidental. Animal with unknown status excluded	3	-82.607	175.21		0.0098	0.0052	0.0783
	2	-82.669	173.34	Lowest AIC	0.0677	0.0069	0.0770
	1	-85.722	177.44		0.0049	0.0039	0.0060
Female Mouse Lung – incidental. Animal with unknown status included	3	-82.674	175.35		0.0099	0.0053	0.0791
	2	-82.739	173.48	Lowest AIC	0.0676	0.0070	0.0768
	1	-85.882	177.77		0.0048	0.0037	0.0060

Table 10.4. Calculation of IURs using Human Equivalent Concentrations

Results from 2-stage Multistage Weibull Time-to-tumor model	BMR = 0.01				
	BMDL (µmole/gram lung tissue/day)	External Concentration (ppm) [13]	IUR (per ppm)	External Concentration (µg/m^3)	IUR (per µg/m3)
Female Mouse Lung – incidental. Animal with unknown status excluded	0.0069	0.863	0.012	3122	3.2E-06
Female Mouse Lung – incidental. Animal with unknown status included	0.0070	0.875	0.011	3168	3.2E-06

[13] Human doses in ppm are obtained by dividing the BMDL by the conversion factor derived from Yang et al. (2012) Table 5 of 1 ppm = 0.008 µmole/gram lung tissue/day

11 CANCER RISK ASSESSMENT: VALIDATION OF THE CHLOROPRENE IUR

As a validity check, we calculated the excess cancers that would be expected based on application of the US EPA IUR at the chloroprene exposure concentrations reported by Marsh *et al*. (2007b). Marsh *et al*. (2007b) modeled the chloroprene exposures for all unique job title classes using six exposure classes for each plant over the entire period of chloroprene production in each plant. Job title classes and time-specific chloroprene exposure estimates were linked to each worker's job history to construct a profile. These subject-specific profiles were then used to compute the statistical estimates of worker exposures used in the risk calculations presented in Table 11.1.

As shown in Table 11.1, we calculated risk estimates (excess cancers) for each of the unit risk estimates that US EPA derived for chloroprene in the 2010 Review. These included an IUR based on lung tumors, an IUR based on multiple tumors, and an IUR adjusted for lifetime exposures (with application of the ADAF). In addition, we calculated cancer risk estimates based on the IUR derived by Allen *et al*. (2014), as well as the IUR provided in this report, both of which account for pharmacokinetic differences between animals and humans. We derived risk estimates using exposure estimates from the Louisville plant (Marsh 2007a, b), as these exposures were much higher (at least an order of magnitude or more) than the exposures at other plants. In Table 11.1, we compared calculated excess cancer risk estimates with the excess liver cancers observed at the Louisville plant (observed cases minus expected cases, based on both US and local county rates).

The risk assessment summarized in Table 11.1 illustrates that cancer risk estimates calculated based on the IUR in the 2010 Review overestimated actual liver cancer risks. Marsh *et al*. (2007a) reported less than one excess liver cancer death when compared to US rates, and a deficit of about two liver cancer deaths when compared to the more appropriate local country rates. In contrast, using the 2010 Review IUR and mean reported chloroprene exposures, approximately 15 excess liver cancer deaths should have been observed. Repeating this exercise using the risk estimate derived by Allen *et al*. (2014), as well as the Ramboll Environ estimated IUR in this report, we showed that the estimated excess cancer risk estimates were consistent with the observed cases reported by Marsh *et al*. (2007a).

Table 11.1. Cancer Risk Estimates Based on US EPA and Allen et al. (2014) IURs for Chloroprene Compared with Excess Cancers Observed in the Louisville Plant

Source	Unit risk (per ppm)	Exposure (ppm)[a]			Excess Cancers (Risk Estimate)[b]			Excess Liver Cancers (Observed-Expected)[c]	
								Comparison Group	
		Median	Mean	Max	Median	Mean	Max	US	Local County
US EPA (2010)									
lung tumor	0.65	5.23	8.42	71	3.40	5.5	46		
multi tumor	1.08	5.23	8.42	71	5.65	9.1	77		
w/ADAF	1.80	5.23	8.42	71	9.41	15.2	128	0.65	-1.89
Allen et al. (2014)									
lung tumor	0.0067	5.23	8.42	71	0.04	0.1	0.5		
Ramboll Environ									
lung tumor	0.011	5.23	8.42	71	0.06	0.1	0.8		

a Data from Marsh *et al*. 2007b (Table 3)
b Excess cancer risk calculated by multiplying the unit risk (per ppm) by the exposure level (in ppm)
c Data obtained from Marsh *et al*. 2007a (Table 3). Expected cancers = Observed/SMR

This analysis demonstrates that the 2010 Review IUR overestimates risk, and that a PBPK adjustment provides a better fit to the best available human data.

12 THE CHLOROPRENE RFC

A reference concentration (RfC) is a health risk value that is intended to be protective of non-cancer risks from inhalation in humans. The RfC reported in the 2010 Review for chloroprene is 2×10^{-2} mg/m^3. The RfC is an estimate of the daily exposure to human populations, including susceptible groups such as children and the elderly, which is considered to be without an appreciable risk for non-cancer health effects over a lifetime. The value is calculated by first determining the point of departure, traditionally using a no-observed-adverse-effect level or lowest-observed-adverse-effect level (NOAEL or LOAEL, respectively) and more recently using dose-response modeling.

Like the calculation of the cancer IUR, US EPA relied upon the results from the 2-year chronic inhalation study conducted in rats and mice by the National Toxicology Program (NTP 1998) as the basis for the RfC, but focusing on the non-cancer effects. US EPA also considered a second study conducted in a different strain of rats and in hamsters (Trochimowicz *et al*., 1998), but did not rely on this study because it reported a high mortality rate in animals in the lowest exposure group due to failure in the exposure chamber. However, though significant histopathological lesions were reported in the NTP (1998) study in the lungs and spleen in the lowest exposure group (12.8 ppm) in B6C3F1 mice, comparatively few histopathological lesions were observed even in the highest exposure groups in Wistar rats and Syrian hamsters (Trochimowicz *et al*., 1998).

From the NTP (1998) study, US EPA selected all the non-cancer endpoints that were statistically significantly increased in mice and rats at the low and mid-exposure levels (12.8 and 32 ppm) compared with controls. These endpoints included both portal of entry and systematic lesions observed in the nose, lung, kidney, forestomach, and spleen in mice and in the nose, lung and kidney of the rats (see Table 5-1 in US EPA 2010a). US EPA used their own benchmark dose modeling software (BMDS) to estimate a Point of Departure (POD). As with the cancer endpoints, these results suggested significant cross-species and strain differences in the toxicological response to inhaled chloroprene. In addition, for some of the endpoints, no model provided an adequate fit to the data, suggesting external concentrations may not correspond to the observed incidences. These results also underscore the importance of understanding the difference in pharmacokinetics across species to derive the most biologically relevant human equivalent RfC. PBPK methods have been used to derive appropriate RfCs for other relevant chemicals, including vinyl chloride (Clewell 2001, US EPA 2000).

The last source of uncertainty that US EPA should have considered in the derivation of the RfC is the application of uncertainty factors to the POD. US EPA applied a total uncertainty factor of 100 to the POD of 2 mg/m^3. A standard uncertainty factor of 10 was applied to account for variation in the susceptibility among members of the human population. An uncertainty of 3 was applied to account for extrapolation of animals to humans; however, this uncertainty can be removed if a validated PBPK model is used to derive a human equivalent exposure to chloroprene that accounts for pharmacokinetic differences between animals and humans. Lastly, an uncertainty factor of 3 was applied to account for database

deficiencies related to reproductive toxicity. This adjustment is also not needed based on several lines of evidence. First, chloroprene is not expected to accumulate in tissues such that in a multigenerational study, exposures to the second generation (F2) would be greater than experienced by the first generation (F1). Second, the results of a single generation reproductive toxicity study for a structurally similar chemical, 2,3-dichloro-1,3-butadiene (Mylchreest *et al*. 2006) indicate that effects at the point of contact (nasal effects) in parental animals are more sensitive than reproductive/developmental effects. Specifically, this study reported a NOAEL of 10 ppm for nasal effects in rats, and a NOAEL of 50 ppm for reproductive toxicity (changes in maternal and fetal body weights). Similarly, an unpublished one-generation reproductive toxicity study of chloroprene in rats reported a NOAEL of 100 ppm for reproductive toxicity (Appelman and Dreef van der Meulan 1979). All of these NOAELs are considerably higher than any other non-cancer effect and suggest that the application of an uncertainty factor for database deficiencies for the lack of a two-generation reproductive study is not necessary.

13 CONCLUSIONS

The IUR derived in the 2010 Report did not address the large recognized differences in cancer susceptibility across animal species, and especially between female mice and humans. Failure to apply well-accepted and now specifically validated methods for accounting for these differences led to an invalid (and implausible) IUR for chloroprene.

Our critical review and synthesis of the available evidence from toxicological, mechanistic, and epidemiological studies, as well as an integration of the evidence across these lines of scientific inquiry, determined that the approach US EPA used to derive an IUR for chloroprene relied on several unsubstantiated assumptions and failed to take into account the large inter-species cancer susceptibilities. We demonstrated that an IUR derived today would be considerably different from the one recommended in the 2010 Review. Our approach comported with US EPA methods and guidance, as well as the recommendations made by multiple NRC Committees evaluating the US EPA IRIS evaluation methods.

Although animal studies provided a positive response for carcinogenicity, the current science for chloroprene demonstrates major differences in species-specific cancer response to chloroprene exposure. Quantitative differences in pharmacokinetics across species, specifically related to differences in metabolism and detoxification of potentially active metabolites, can and should be incorporated into a corrected IUR or other risk number. In the 2010 Review, the available chloroprene pharmacokinetic findings were not incorporated to quantitatively account for differences between the mouse, rat, and human. When genotoxicity/genomics, MOA, and pharmacokinetic data are considered in an appropriately integrated manner, the data strongly suggest that the cancer responses from chloroprene are largely confined to—and possibly unique to—the female mouse. Because of these strong interspecies differences, use of the female mouse data for risk evaluation, in the absence of affirmative epidemiological data that can be used quantitatively, must incorporate tissue-specific dosimetry and metabolic differences. Additionally, because the available evidence does not support a mutagenic MOA for chloroprene, the cancer unit risk should not be adjusted to account for potential risks from early-life exposures with the application of the ADAF. While appropriate PBPK models were available to US EPA at the time of the 2010 Review, US EPA stated that published data were unavailable to validate the model. Data have now been published, have validated the PBPK model, and should be used to correct the IUR.

Our critical review and synthesis of all epidemiological studies of chloroprene-exposed workers, using standard methods that consider study quality and potential sources of bias, indicated no clear or consistent association between occupational chloroprene exposure and mortality from lung or liver cancers. The strongest study, in fact, demonstrated small deficits in lung and liver cancer mortality among chloroprene-exposed workers (Marsh 2007a, b). Nevertheless, in the 2010 Review, this study is cited as providing support for a causal association, directly contradicting our conclusions as well as the study authors' own conclusions. In fact, the epidemiology was consistent with the application of a PBPK model to

adjust the animal experimental evidence and account for the large differences in interspecies cancer susceptibilities. There is a substantial body of evidence supporting the conclusion that humans are far less susceptible to the potential carcinogenicity of chloroprene than mice primarily because the way humans metabolize chloroprene does not lead to the production of significant concentrations of the carcinogenic metabolite. The epidemiological study results also support this conclusion.

Using standard methods consistent with the NRC recommendations and EPA Guidelines, and the most current scientific evidence, we derived an IUR for chloroprene that is 156 times lower than that derived by US EPA. Following methods used in other IRIS assessments, we derived an IUR of 3.2×10^{-6} per $\mu g/m^3$. We request that US EPA re-evaluate and correct the IUR, which is based on the most sensitive species and endpoint (lung tumors in female mice) and apply a PBPK model to more appropriately account for the large differences between mice and humans. We recommend no further adjustment for multiple tumor sites, and no adjustment for a mutagenic MOA. Similarly, the chloroprene RfC will need to be updated to incorporate the same pharmacokinetic differences across species.

Based on a comprehensive evaluation and integration of the published epidemiological, toxicological and mechanistic evidence, we consider the US EPA 2010 Review of chloroprene to be outdated and invalid. Accordingly, US EPA should also revisit the cancer classification for chloroprene and provide a transparent and accurate narrative that reflects a weight of evidence approach. Most importantly, however, the IUR derived in the 2010 Report is not scientifically defensible and needs to be corrected.

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APPENDIX A
TOXICOLOGICAL SUMMARY OF CARCINOGENIC COMPOUNDS

Toxicological Summary of Carcinogenic Compounds

Chemical	IUR (per µg/m³)	US EPA WOE/ Year	Human Data	Animal Data	Geno-toxicity	Extrapolation Method	Species	Endpoint	Model Used	PBPK Model
Benzidine**	0.067	A/1987	Sufficient	Limited *via* inhalation	Yes	One-hit with time factor, extra risk	Human Occupational (Inhalation)	Bladder tumors	--	No
Bis(chloromethyl)ether (BCME)**	0.062	A/1988	Sufficient	Sufficient	Yes	Linearized multistage, extra risk	Rat	Respiratory tract tumors	--	No
N-Nitrosodimethylamine (NDMA**)	0.014	B2/1987	Limited due to exposure to mixtures	Limited evidence *via* inhalation	Yes	Weibull, extra risk	Rat	Liver tumors	--	No
Ethylene Dibromide	0.0006	B2/2004	Inadequate	Sufficient	Yes	Multistage	Rat	Nasal cavity tumors	Multistage-Weibull time-to-tumor	No
Chloroprene	0.0005	B1/2010	--	Clear evidence	Yes - Metabolites	Linear low-dose extrapolation	Mice	All tumor sites reported	Multistage-Weibull time-to-tumor	No
Acrylamide	0.000147	B2/2010	Inadequate	Sufficient	Yes	Route-to-route extrapolation of the oral POD	Rat	Thyroid tumors	Multistage-Weibull Time-to-tumor	No
Polychlorinated biphenyls (under reassessment)#	0.0001	B2/1996	Inadequate	Sufficient	--	Linear extrapolation below LED10s	Rat	Liver tumors	--	No
1,3-Butadiene	0.00003	A/2002	Sufficient	Sufficient	Yes - Metabolites	Linear extrapolation	Human	Leukemia	Relative Rate Model	No

Chemical	IUR (per $\mu g/m^3$)	US EPA WOE/ Year	Human Data	Animal Data	Geno-toxicity	Extrapolation Method	Species	Endpoint	Model Used	PBPK Model
Formaldehyde	0.00066	Supports carcino-genicity/ 2010 (Draft)	Supportive, but alone not sufficient	Strong support	Data suggests genotoxicity	Linear extrapolation from the POD	Human	Naso-pharyngeal cancer, Hodgkin lymphoma and leukemia	--	Yes
Vinyl Chloride	0.0000088	A/2000	Sufficient	Sufficient	Yes - Metabolites	Linearized multistage method	Rat	Liver tumors	Linearized Multistage Model	Yes
Benzene	0.000002 – 0.0000078	A/2003	Strong evidence	Limited evidence	Suggestive but not conclusive	Low-dose linear; maximum likelihood	Human	Leukemia	--	No
Trichloroethylene (TCE)	0.0000041	CH/2011	Modest	Clear evidence	Data suggests potential for genotoxicity	Linear low dose-extrapolation	Human	Kidney cancer; Non-Hodgkin's lymphoma ; Liver cancer	Weighted linear regression model	No
Epichlorohydrin	0.0000012	B2/1988	Inadequate	Sufficient	Suggestive	Linearized multistage procedure, extra risk	Rat	Kidney lesions	--	No
Tetrachloroethene	0.00000026	LH/2012	Evidence of association	Evidence of association	Insufficient	Linear extrapolation	Mouse	Liver tumors	Multistage model	Yes

US EPA WOE (2005 Guidelines) = CH - carcinogenic to humans; LH - likely to be carcinogenic; US EPA WOE (1986 Guidelines): A - human carcinogen; B1 - probable carcinogen, limited human evidence; B2 - probable carcinogen, sufficient evidence in animals

* Draft version available – currently under public comment

** Only an IRIS Summary was available, not a full ToxProfile

The draft reassessment is currently in the scoping and problem formulation portion. Therefore, no updated assessment has been performed.

PBPK: physiologically based pharmacokinetic (model)

IUR: inhalation unit risk

APPENDIX B
SUMMARY OF EPIDEMIOLOGICAL EVIDENCE OF KNOWN OR LIKELY CARCINOGENIC COMPOUNDS CLASSIFIED BY US EPA

Summary of the Epidemiological Evidence of Chemical Carcinogens Classified as Known or Likely Human Carcinogens by IARC and/or US EPA

Compound	Sources	Outcomes with strong evidence	Types of studies	Quantification (if possible)	Conclusion
Benzidine	US EPA 1987a; Meigs et al. 1986; Tomioka et al. 2016; Golka et al. 2004; IARC 2012	Bladder and lung cancer	Several occupational epidemiology studies from the 1980s to 2000s for bladder cancer; 23 retrospective cohort studies from 1970s-2010s for lung cancer	SIR (bladder cancer) = 3.43,95% CI: 1.48-6.76; (Meigs et al. 1986, cited in US EPA) Pooled risk estimate (lung cancer)= 2.33, 95% CI 1.31-4.14 (Tomioka et al. 2016) based on meta-analysis of 23 cohort studies of highly exposed workers 30-fold to 75-fold higher risk of bladder cancer based on occupational cohort studies in China 1980s–2000s (Golka et al. 2004)	US EPA: Category A; IARC 2012: Group 1, "Benzidine causes cancer of the urinary bladder." Risk of lung cancer is statistically significantly elevated; but confounding by co-exposure with beta-naphthylamine cannot be ruled out. (Tomioka et al. 2016) "Toxicologically, benzidine has been the most important carcinogenic aromatic amine directed towards the human bladder." (Golka et al. 2004)
Bis (chloromethyl) ether (BCME)	US EPA 1988a; IARC 2012; Bruske-Hohfeld 2009	Lung cancer	Occupational epidemiology studies from the 1970s-1990s	"Among heavily exposed workers, the RRs are tenfold or more." (Bruske-Hohfeld 2009)	US EPA: Category A; IARC: Group 1
Nitrosodimethylamine (also N-Nitrosodimethylamine)	US EPA 1987b; ATSDR 1989; IARC 1978	None specified in humans Numerous multisite tumors in various animal species (inhalation and oral exposures)	Animal studies of oral exposure from 1970s-1980s; two studies of inhalation exposure in animals from 1967 No studies of inhalation and cancer in humans; confounding by co-exposure cannot be ruled out	No risk estimates in humans available	US EPA – Category B2; IARC – Group 2A

Compound	Sources	Outcomes with strong evidence	Types of studies	Quantification (if possible)	Conclusion
Ethylene dibromide (also 1,2-Dibromoethane)	US EPA 2004; IARC 1999	None in humans. In animals, inhalation (long term) is associated multi-site tumors	Three occupational epidemiological studies evaluated by US EPA deemed to be inadequate	No risk estimates in humans available	US EPA - Category LH ; IARC - Category 2A "*inadequate evidence* in humans" but "*sufficient evidence"* in experimental animals
Acrylamide	US EPA 2010b; Pelucchi et al. 2011; IARC 1994	Little evidence in humans In animals, oral exposure associated with multi-site tumors	5 retrospective and prospective cohort studies of occupational exposure (inhalation/dermal) from the 1980s to the 2000s – no strong associations. Meta-analysis of occupational (inhalation/dermal) exposure found positive, but no statistically significant associations (Pelucchi et al. 2011)	Select SMRs (95% CI) of meta-analysis (Pelucchi et al. 2011): Pancreas, high exposure: 1.67 (0.83-2.99) Kidney, high exposure: 2.22 (0.81-4.84)	US EPA: Group B2; IARC: Group 2A (Inadequate evidence in humans; sufficient evidence in animals).
Polychlorinated biphenyls (PCBs)	US EPA 1996; ATSDR 2000; Zani et al. 2013; IARC 2016	Melanoma Inconsistent findings for non-Hodgkin lymphoma, breast cancer	Many occupational cohort studies of PCB exposure, 1980s-2010s; limitations include small sample sizes, confounding exposures, and short follow-up.	Occupational exposures SMR for melanoma = 2.4, 95% CI: 1.1-4.6 (Ruder 2006, as reported by Zani et al. 2013) RR = 4.8, 95% CI: 1.5-15.1 for high exposures (Loomis et al. 1997)	US EPA – Category B2 IARC - Group 1 Sufficient evidence for melanoma. For occupational exposures, "weak evidence of a major role of PCBs as human carcinogens" (Zani et al. 2013)
1,3-Butadiene	US EPA 2002; IARC 2008	Lymphatic and hematopoietic cancers	Many occupational cohort studies; stronger evidence of leukemia; suggestive link with non-Hodgkin lymphoma.	US EPA: 43% to 336% increase in leukemia in styrene-butadiene rubber workers, adjusting for styrene and benzene. IARC: Most recent update of the styrene-butadiene rubber worker cohort show no significant risk (IARC 2008).	US EPA: Group A; IARC: Group 1

Compound	Sources	Outcomes with strong evidence	Types of studies	Quantification (if possible)	Conclusion
Formaldehyde	US EPA 2010c; DRAFT IARC 2012; Checkoway et al. 2015	Nasal cancer Leukemia	Numerous cohort studies of occupationally exposed formaldehyde workers.	Nasopharyngeal cancer: RR = 4.14 for highest exposure (Hauptmann et al. 2004, as reported by US EPA 2010) All leukemia: RR=2.49, 95% CI: 1.13-5.49 for highest exposure) Chronic myeloid leukemia: RR=3.81, 95% CI:0.36-40.44 for highest exposure (Checkoway et al. 2015)	US EPA - Category B1 (DRAFT); IARC - Group 1 - "Formaldehyde causes cancer of the nasopharynx and leukemia."
Vinyl chloride	US EPA 2000; IARC 2012; Ward et al. 2001; Mundt et al. 2000	Liver cancer	At least 14 cohort studies from the 1970s to 1990s of liver cancer in occupational workers, including 2 multicenter cohort studies (US and Europe)	RR=28.3, 95% CI: 12.8-62.3 for very high exposures (Ward et al. 2001) HR=6.0, 95% CI: 2.5-14.4 for exposures ≥ 20 years of exposure (Mundt et al. 2000)	US EPA: Category A ; IARC: Group 1 Mundt: "deaths from liver cancers have occurred in excess, due to the well documented association between VCM and angiosarcoma of the liver." Ward: "A strong relation is observed between cumulative VC exposure and occurrence of liver cancer."
Benzene	US EPA 2003; IARC 2012; Khalade et al. 2010	Leukemia	Numerous occupational benzene-exposed workers in the chemical industry, shoemaking, and oil refineries. Consistent excess risk of leukemia across studies	Pooled estimate (leukemia) 2.62 (95%CI, 1.57-4.39) for high exposures based on meta-analysis (Khalade et al. 2010)	US EPA - Category A; IARC - Group 1 "sufficient evidence" in humans for leukemia.
Trichloroethylene	US EPA 2011; IARC 2014	Kidney cancer	Numerous cohort and case-control studies with consistent evidence.	Pooled estimate (RR) = 1.58, 95% CI: 1.28, 1.96 based on meta-analysis of highest exposure group (US EPA 2011)	US EPA- Category CH; IARC- Group 2A

Compound	Sources	Outcomes with strong evidence	Types of studies	Quantification (if possible)	Conclusion
Epichlorohydrin	US EPA 1988b; IARC 1999	Inadequate data in humans. In animals, stomach and oral cavity cancers via oral and nasal tumors via inhalation exposure	4 cohort studies (including 3 nested case-control studies) found weak and inconsistent associations with lung cancer and central nervous system tumors with no dose-response (IARC 1999)	No risk estimates in humans available	US EPA- Category B2, IARC - Group 2A, "probably carcinogenic to humans," based on animal studies, the "known chemical reactivity of epichlorohydrin and its direct activity in a wide range of genetic tests."
Tetrachloroethene (Also tetrachloroethylene)	US EPA 2012; IARC 2014 Pesch et al. 2000 Radican et al. 2008 Seidler et al. 2007	Bladder cancer, non-Hodgkin lymphoma, multiple myeloma	**Bladder cancer: 10-14% increased risk** Five of the six occupational high quality studies (dry cleaner or laundry workers) **Non-Hodgkin lymphoma:** Five cohort high quality occupational studies **Multiple myeloma:** Little evidence from lower quality but larger cohort studies Some evidence with higher quality cohort and case control studies	**Bladder cancer:** RR = 1.8, 95% CI: 1.2, 2.7 high exposure (Pesch et al. 2000) **NHL:** RR = 3.4, 95% CI: 0.7, 17.3 for the highest exposure (Seidler et al. 2007) **Multiple myeloma:** Aircraft maintenance workers cohort RR men: 1.71, 95% CI: 0.42, 6.91 RR women: 7.84, 95% CI: 1.43, 43.1 (Radican et al. 2008)	US EPA - Category LH, IARC - Category 2A

CI: confidence interval
HR: hazard ratio
IARC: International Agency for Research on Cancer
NHL: Non-Hodgkin lymphoma
RR: relative risk
SIR: standardized incidence ratio
SMR: standardized mortality ratio
US EPA: United States Environmental Protection agency
VC: vinyl chloride
VCM: vinyl chloride monomer

APPENDIX C
MULTISTAGE WEIBULL MODELING OUTPUT

```
================================================================
          Multistage Weibull Model. (Version: 1.6.1;  Date: 11/24/2009)
          Solutions are obtained using donlp2-intv, (c) by P. Spellucci
          Input Data File: FMLAd1In.(d)
          Tue May 02 10:15:41 2017
 ================================================================
 Female Mouse Lung C+I Grouped Incidental Risk 1-stage MSW model
 ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
    The form of the probability function is:
   P[response] = 1-EXP{-(t - t_0)^c *
                 (beta_0+beta_1*dose^1)}
   The parameter betas are restricted to be positive
   Dependent variable = CLASS
   Independent variables = DOSE, TIME
 Total number of observations = 199
 Total number of records with missing values = 0
 Total number of parameters in model = 4
 Total number of specified parameters = 1
 Degree of polynomial = 1
   User specifies the following parameters:
          t_0    =          0
 Maximum number of iterations = 16
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008
                  Default Initial Parameter Values
                        c      =      2.65306
                        t_0    =            0   Specified
                        beta_0 = 3.87553e-007
                        beta_1 = 8.74531e-006
           Asymptotic Correlation Matrix of Parameter Estimates
           ( *** The model parameter(s)  -t_0
                 have been estimated at a boundary point, or have been specified by the user,
                 and do not appear in the correlation matrix )
                 c            beta_0       beta_1
    c                 1        -0.99           -1
    beta_0        -0.99            1         0.98
    beta_1           -1         0.98            1
Parameter Estimates
                                                        95.0% Wald Confidence Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
         c                2.7855         0.871309             1.07777             4.49324
         beta_0     2.09796e-007     8.59988e-007       -1.47575e-006        1.89534e-006
         beta_1     4.84999e-006     1.88357e-005       -3.20673e-005        4.17673e-005
                Log(likelihood)   # Param             AIC
   Fitted Model        -85.7218         3         177.444
```

Data Summary

DOSE	CLASS C	F	I	U	Total
0	46	0	4	0	50
0.74	21	0	28	0	49
1.2	16	0	34	0	50
1.6	8	0	42	0	50

Benchmark Dose Computation

Risk Response	=	Incidental
Risk Type	=	Extra
Specified effect	=	0.01
Confidence level	=	0.9
Time	=	105
BMD	=	0.00485752
BMDL	=	0.00394674
BMDU	=	0.00604099

```
================================================================
         Multistage Weibull Model. (Version: 1.6.1;  Date: 11/24/2009)
         Solutions are obtained using donlp2-intv, (c) by P. Spellucci
         Input Data File: FMLAd1Io.(d)
         Tue May 02 09:56:18 2017
================================================================
Female Mouse Lung C+I+U Grouped Incidental Risk 1-stage MSW model
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   The form of the probability function is:
  P[response] = 1-EXP{-(t - t_0)^c *
                (beta_0+beta_1*dose^1)}
  The parameter betas are restricted to be positive
  Dependent variable = CLASS
  Independent variables = DOSE, TIME
Total number of observations = 200
Total number of records with missing values = 0
Total number of parameters in model = 4
Total number of specified parameters = 1
Degree of polynomial = 1
  User specifies the following parameters:
        t_0    =          0
Maximum number of iterations = 16
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008
                 Default Initial Parameter Values
                        c      =      2.70833
                        t_0    =            0   Specified
                        beta_0 = 2.99752e-007
                        beta_1 = 6.82409e-006
          Asymptotic Correlation Matrix of Parameter Estimates
          ( *** The model parameter(s)  -t_0
                have been estimated at a boundary point, or have been specified by the user,
                and do not appear in the correlation matrix )
                c            beta_0       beta_1
   c                 1        -0.98           -1
   beta_0        -0.98            1         0.98
   beta_1           -1         0.98            1
                                Parameter Estimates
                                                        95.0% Wald Confidence Interval
      Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
        c               2.82393          0.86564             1.12731             4.52055
        beta_0     1.75446e-007     7.14572e-007       -1.22509e-006        1.57598e-006
        beta_1     4.07913e-006     1.57386e-005        -2.6768e-005        3.49262e-005
               Log(likelihood)   # Param             AIC
  Fitted Model        -85.8823         3         177.765
```

Data Summary

DOSE	CLASS C	F	I	U	Total
0	46	0	4	0	50
0.74	21	0	28	1	50
1.2	16	0	34	0	50
1.6	8	0	42	0	50

Benchmark Dose Computation

Risk Response	=	Incidental
Risk Type	=	Extra
Specified effect	=	0.01
Confidence level	=	0.9
Time	=	105
BMD	=	0.00482968
BMDL	=	0.00372838
BMDU	=	0.00600798

```
================================================================
         Multistage Weibull Model. (Version: 1.6.1;  Date: 11/24/2009)
         Solutions are obtained using donlp2-intv, (c) by P. Spellucci
         Input Data File: FMLAd2In.(d)
         Tue May 02 09:56:30 2017
================================================================
Female Mouse Lung C+I Grouped Incidental Risk 2-stage MSW model
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
   The form of the probability function is:
  P[response] = 1-EXP{-(t - t_0)^c *
                (beta_0+beta_1*dose^1+beta_2*dose^2)}
  The parameter betas are restricted to be positive
  Dependent variable = CLASS
  Independent variables = DOSE, TIME
Total number of observations = 199
Total number of records with missing values = 0
Total number of parameters in model = 5
Total number of specified parameters = 1
Degree of polynomial = 2
  User specifies the following parameters:
        t_0    =          0
Maximum number of iterations = 16
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008
                 Default Initial Parameter Values
                       c      =      3.71429
                       t_0    =            0   Specified
                       beta_0 = 2.99856e-009
                       beta_1 =            0
                       beta_2 = 7.10296e-008
          Asymptotic Correlation Matrix of Parameter Estimates
          ( *** The model parameter(s)  -t_0       -beta_1
                have been estimated at a boundary point, or have been specified by the user,
                and do not appear in the correlation matrix )
                c            beta_0       beta_2
   c                 1        -0.99           -1
   beta_0        -0.99            1         0.99
   beta_2           -1         0.99            1
                                Parameter Estimates
                                                        95.0% Wald Confidence Interval
      Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf. Limit
        c               3.51729         0.955751             1.64405             5.39052
        beta_0     7.51777e-009     3.39426e-008       -5.90086e-008        7.40441e-008
        beta_1                0               NA
        beta_2     1.70594e-007     7.25361e-007       -1.25109e-006        1.59228e-006
```

NA - Indicates that this parameter has hit a
bound implied by some inequality constraint
and thus has no standard error.

	Log(likelihood)	# Param	AIC
Fitted Model	-82.6686	4	173.337

Data Summary

	CLASS				
DOSE	C	F	I	U	Total
0	46	0	4	0	50
0.74	21	0	28	0	49
1.2	16	0	34	0	50
1.6	8	0	42	0	50

Benchmark Dose Computation

Risk Response = Incidental
Risk Type = Extra
Specified effect = 0.01
Confidence level = 0.9

Time = 105

BMD = 0.0676952
BMDL = 0.00685005
BMDU = 0.0770164

```
 ================================================================
          Multistage Weibull Model. (Version: 1.6.1;  Date: 11/24/2009)
          Solutions are obtained using donlp2-intv, (c) by P. Spellucci
          Input Data File: FMLAd2Io.(d)
          Tue May 02 09:56:48 2017
 ================================================================

 Female Mouse Lung C+I+U Grouped Incidental Risk 2-stage MSW model

~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:
   P[response] = 1-EXP{-(t - t_0)^c *
                 (beta_0+beta_1*dose^1+beta_2*dose^2)}

   The parameter betas are restricted to be positive

   Dependent variable = CLASS
   Independent variables = DOSE, TIME

 Total number of observations = 200
 Total number of records with missing values = 0
 Total number of parameters in model = 5
 Total number of specified parameters = 1
 Degree of polynomial = 2



   User specifies the following parameters:
          t_0    =          0

 Maximum number of iterations = 16
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008


                  Default Initial Parameter Values
                        c      =      3.33333
                        t_0    =            0   Specified
                        beta_0 = 1.77269e-008
                        beta_1 =            0
                        beta_2 = 3.85864e-007


            Asymptotic Correlation Matrix of Parameter Estimates
            ( *** The model parameter(s)  -t_0       -beta_1
```

have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	c	beta_0	beta_2
c	1	-0.99	-1
beta_0	-0.99	1	0.99
beta_2	-1	0.99	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
c	3.53767	0.951903	1.67197	5.40336
beta_0	6.83164e-009	3.07193e-008	-5.33771e-008	6.70404e-008
beta_1	0	NA		
beta_2	1.55674e-007	6.59259e-007	-1.13645e-006	1.4478e-006

NA - Indicates that this parameter has hit a
bound implied by some inequality constraint
and thus has no standard error.

	Log(likelihood)	# Param	AIC
Fitted Model	-82.7393	4	173.479

Data Summary

	CLASS				
DOSE	C	F	I	U	Total
0	46	0	4	0	50
0.74	21	0	28	1	50
1.2	16	0	34	0	50
1.6	8	0	42	0	50

Benchmark Dose Computation

Risk Response = Incidental
Risk Type = Extra
Specified effect = 0.01
Confidence level = 0.9
Time = 105
BMD = 0.0675827
BMDL = 0.00695368
BMDU = 0.0767564

```
 ================================================================
          Multistage Weibull Model. (Version: 1.6.1;  Date: 11/24/2009)
          Solutions are obtained using donlp2-intv, (c) by P. Spellucci
          Input Data File: FMLAd3In.(d)
          Tue May 02 09:57:04 2017

 ================================================================

 Female Mouse Lung C+I Grouped Incidental Risk 3-stage MSW model

~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:
   P[response] = 1-EXP{-(t - t_0)^c *
                 (beta_0+beta_1*dose^1+beta_2*dose^2+beta_3*dose^3)}

   The parameter betas are restricted to be positive

   Dependent variable = CLASS
   Independent variables = DOSE, TIME

 Total number of observations = 199
 Total number of records with missing values = 0
 Total number of parameters in model = 6
 Total number of specified parameters = 1
 Degree of polynomial = 3



   User specifies the following parameters:
          t_0    =          0

 Maximum number of iterations = 16
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008


                  Default Initial Parameter Values
                        c      =      3.51351
                        t_0    =            0   Specified
                        beta_0 = 7.69524e-009
                        beta_1 = 8.17936e-008
                        beta_2 =            0
                        beta_3 =  8.3075e-008
```

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -t_0 -beta_2
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	c	beta_0	beta_1	beta_3
c	1	-0.99	-0.99	-0.99
beta_0	-0.99	1	0.98	0.98
beta_1	-0.99	0.98	1	0.97
beta_3	-0.99	0.98	0.97	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
c	3.565	1.09332	1.42214	5.70787
beta_0	6.06284e-009	3.09921e-008	-5.46806e-008	6.68063e-008
beta_1	6.3958e-008	3.37242e-007	-5.97025e-007	7.24941e-007
beta_2	0	NA		
beta_3	6.69836e-008	3.08585e-007	-5.37832e-007	6.718e-007

NA - Indicates that this parameter has hit a
bound implied by some inequality constraint
and thus has no standard error.

	Log(likelihood)	# Param	AIC
Fitted Model	-82.6066	5	175.213

Data Summary

DOSE	CLASS C	F	I	U	Total
0	46	0	4	0	50
0.74	21	0	28	0	49
1.2	16	0	34	0	50
1.6	8	0	42	0	50

Benchmark Dose Computation

Risk Response = Incidental
Risk Type = Extra
Specified effect = 0.01
Confidence level = 0.9

Time = 105

BMD = 0.00978798
BMDL = 0.0052444
BMDU > 0.0783038

```
 ================================================================
          Multistage Weibull Model. (Version: 1.6.1;  Date: 11/24/2009)
          Solutions are obtained using donlp2-intv, (c) by P. Spellucci
          Input Data File: FMLAd3Io.(d)
          Tue May 02 09:58:50 2017
 ================================================================

 Female Mouse Lung C+I+U Grouped Incidental Risk 3-stage MSW model

~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:
   P[response] = 1-EXP{-(t - t_0)^c *
                 (beta_0+beta_1*dose^1+beta_2*dose^2+beta_3*dose^3)}

   The parameter betas are restricted to be positive

   Dependent variable = CLASS
   Independent variables = DOSE, TIME

 Total number of observations = 200
 Total number of records with missing values = 0
 Total number of parameters in model = 6
 Total number of specified parameters = 1
 Degree of polynomial = 3



   User specifies the following parameters:
          t_0    =          0

 Maximum number of iterations = 16
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008


                  Default Initial Parameter Values
                        c      =      3.02326
                        t_0    =            0   Specified
                        beta_0 =  7.4445e-008
                        beta_1 = 8.31425e-007
                        beta_2 =            0
                        beta_3 = 6.42289e-007


            Asymptotic Correlation Matrix of Parameter Estimates
```

(*** The model parameter(s) -t_0 -beta_2
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	c	beta_0	beta_1	beta_3
c	1	-0.99	-0.99	-0.99
beta_0	-0.99	1	0.98	0.98
beta_1	-0.99	0.98	1	0.97
beta_3	-0.99	0.98	0.97	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
c	3.59456	1.08684	1.4644	5.72473
beta_0	5.28712e-009	2.68702e-008	-4.73775e-008	5.79518e-008
beta_1	5.52071e-008	2.89531e-007	-5.12264e-007	6.22678e-007
beta_2	0	NA		
beta_3	5.93591e-008	2.72143e-007	-4.74031e-007	5.92749e-007

NA - Indicates that this parameter has hit a
bound implied by some inequality constraint
and thus has no standard error.

	Log(likelihood)	# Param	AIC
Fitted Model	-82.6739	5	175.348

Data Summary

	CLASS				
DOSE	C	F	I	U	Total
0	46	0	4	0	50
0.74	21	0	28	1	50
1.2	16	0	34	0	50
1.6	8	0	42	0	50

Benchmark Dose Computation

Risk Response = Incidental
Risk Type = Extra
Specified effect = 0.01
Confidence level = 0.9
Time = 105
BMD = 0.00988202
BMDL = 0.0052649
BMDU > 0.0790561

APPENDIX D
ABOUT RAMBOLL ENVIRON

ABOUT RAMBOLL ENVIRON

A premier global consultancy, Ramboll Environ is trusted by clients to manage their most challenging environmental, health and social issues. We have earned a reputation for technical and scientific excellence, innovation and client service. Our independent science-first approach ensures that our strategic advice is objective and defensible. We apply integrated multidisciplinary services and tailor each solution to our client's specific needs and challenges.

At the end of 2014, ENVIRON joined forces with Ramboll, Northern Europe's leading engineering, design and management consultancy, to create a global practice called Ramboll Environment and Health. Together we provide an even higher level of service to our clients and address some of the most important issues facing our global community, including the environmental and health implications of urbanization, climate change and resource scarcity.

Ramboll Environ's network of experts includes more than 2,100 employees across 130 offices in 28 countries around the world. Clients will continue to benefit from our unique ability to bring clarity to issues at the intersection of science, business and policy.

APPENDIX E
EXPERT BIOGRAPHIES

RAMBOLL ENVIRON

ENVIRONMENT & HEALTH

P ROBINAN GENTRY

Principal / Operations Director – Gulf Coast

Dr. Robinan Gentry is a toxicologist with over 25 years of experience in toxicological issues relevant in the determination of the potential safety or risk associated with exposure to chemicals. Over her career, she has been a principal investigator or contributing author for numerous safety and risk assessments for both government and industry. She has worked as a government subcontractor in which she developed toxicological profiles for the US EPA IRIS program, ATSDR and FDA. Many assessments in which she has been involved has been to incorporate innovative quantitative approaches at that time (e.g., benchmark dose modelling, probabilistic assessments, PBPK modelling, in vitro to in vivo extrapolation, genomics data). She is a published author in the development of risk assessment methods, including Physiologically Based Pharmacokinetic (PBPK) models, and their application into both the cancer and non-cancer risk assessment process.

EXPERIENCE HIGHLIGHTS

Quantitative Risk Assessments

Managed numerous human health risk assessments and projects related to the development of criteria and other health effects documents, including application of benchmark modelling; conducted detailed analyses of guidance used in the determination of acute toxicity exposure levels and comparison of USEPA's and California's Proposition 65's risk assessment methods for multiple chemicals; quantified margin of exposures and cancer slope factor using existing kinetic and mechanism of action for multiple compounds.

Toxicological Reviews

Prepared toxicological reviews for USEPA's Office of Pesticide Programs and Program for Toxic Substances (OPPTS), FDA's Center for Food Safety and Nutrition, the Agency of Toxic Substances and Disease Registry (ATSDR), contributing author for development of Drinking Water Criteria Documents for several radionuclides and chloroform; development of weight-of-evidence evaluations and systemic reviews for multiple chemicals including formaldehyde, methyl salicylate and arsenic.

Pharmacokinetics and PBPK Modelling

Served as principal investigator or co-investigator for several PBPK modelling projects, including the development of models in multiple species for constituents such as coumarin, arsenic, acrylic acid and isopropanol.

CONTACT INFORMATION

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3107 Armand Street
Monroe, LA 71201
United States of America

CREDENTIALS

PhD, Toxicology, Utrecht University, The Netherlands

Diplomate. American Board of Toxicology, 2002; recertified, 2007, 2011

MS, Pharmacology & Toxicology, Northeast Louisiana University

BS, Toxicology, Northeast Louisiana University

RAMBOLL ENVIRON

ENVIRONMENT & HEALTH

KENNETH A MUNDT

Principal

Dr. Kenneth Mundt is Health Sciences Practice Network Leader. He brings 30 years of experience in applying epidemiological concepts and methods to understand human health risks from environmental, occupational and consumer product exposures.

Dr. Mundt specializes in the pragmatic interpretation of epidemiological evidence in evaluating disease causation and supporting science-based regulation and decision-making.

Previously, Dr. Mundt served 11 years on the Graduate Faculty of the School of Public Health and Health Sciences, University of Massachusetts at Amherst. He received his PhD in Epidemiology at the University of North Carolina at Chapel Hill, and is a Fellow in the American College of Epidemiology.

EXPERIENCE HIGHLIGHTS

Epidemiological Studies
Managed multidisciplinary teams in designing, conducting and interpreting occupational epidemiological studies of workers involved in rubber, porcelain, chemical and steel industries, as well as military and other professionals.

Health Risks Evaluation and Communication
Responded to observed and perceived health problems related to occupational, environmental and consumer product exposures.

Teaching and Scholarship
Frequent participant in scientific meetings, training courses, and litigation proceedings. Consistent publication record.

Scientific Regulatory Support
Provided scientific evaluation and support to various regulatory and policy processes, including oral and written comments, statistical re-analysis of data from key studies, preparation of commentaries and technical communications, identification of new research opportunities, critical review and meta-analyses of epidemiological evidence, integration of scientific evidence from diverse lines of inquiry, organize and manage expert panels and topical symposia.

Critical Reviews and Syntheses
Comprehensively identified, systematically critically reviewed and synthesized the epidemiological literature on human health risks associated with numerous occupational, environmental and consumer product exposures.

CONTACT INFORMATION

Kenneth A Mundt

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28 Amity Street
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Amherst, 01002
United States of America

CREDENTIALS

PhD, Epidemiology
University of North Carolina

MS, Epidemiology
University of Massachusetts

MA, English
University of Virginia

AB, English
Dartmouth College

RAMBOLL ENVIRON

ENVIRONMENT & HEALTH

SONJA SAX

Senior Environmental Health Scientist

Dr. Sonja Sax is an environmental health scientist with over 15 years of exposure and health risk assessment experience. She has particular expertise in airborne gases and particles, and has performed indoor and outdoor air quality investigations, managed several large environmental projects, conducted critical evaluations of toxicology and epidemiology studies, and helped prepare technical and expert reports. Sonja has authored and co-authored several publications, presented her research and consulting work at various conferences and testified before scientific panels. Sonja earned an MS and doctorate in environmental health from the Harvard T.H. Chan School of Public Health, where she also served as a postdoctoral fellow.

EXPERIENCE HIGHLIGHTS

Critical Reviews and Syntheses
Conducted an extensive literature search on the toxicity and health effects of different chemical compounds including cobalt alloys found in dental materials, diesel exhaust, carbon black, welding fumes, particulate matter and sulfur dioxide.

Systematic Reviews
Conducted weight-of-evidence evaluation of cardiovascular and respiratory effects from exposures to ozone. Results were published in several peer-reviewed manuscripts.

Litigation Support
Contributed to the preparation of expert reports in litigation projects involving different chemical exposures (e.g., vinyl chloride, asbestos, carbon black, particulate matter, sulfur dioxide, and pesticides).

Exposure and Risk Assessment
For numerous projects prepared technical analyses on exposures and potential health effects associated with various pollutants (e.g., particulate matter, sulfur dioxide, nitrogen dioxide, arsenic, and pesticides). Exposure assessments included air dispersion modeling.

Regulatory Comments
Provided written and oral comments to the Clean Air Scientific Advisory Committee on exposure and health effects data and their bearing on US EPA's National Ambient Air Quality Standards for particulate matter and ozone.

Indoor Exposure and Risk Assessment
Conducted analyses of residential exposures to chemicals (e.g., formaldehyde from wood products, vapor intrusion of tetrachloroethylene, mercury from wallboard, and flame retardants from various indoor sources).

CONTACT INFORMATION

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28 Amity Street
Suite 2A
Amherst, 01002
United States of America

CREDENTIALS

ScD, Environmental Health Sciences
Harvard School of Public Health

MS, Environmental Health Management
Harvard School of Public Health

BA, Biological Chemistry
Wellesley College

Exhibit 2

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
NATIONAL CENTER FOR ENVIRONMENTAL ASSESSMENT

OFFICE OF
RESEARCH AND DEVELOPMENT

May 25, 2016

MEMORANDUM

SUBJECT: EPA's Integrated Risk Information System (IRIS) Assessment of Chloroprene

FROM: John Vandenberg, Director /s/
Research Triangle Park Division
National Center for Environmental Assessment
Office of Research and Development

TO: Wren Stenger, Division Director
Multimedia Planning and Permitting Division
EPA Region 6

The purpose of this memo is to provide to you information regarding the EPA's 2010 Integrated Risk Information System's (IRIS) assessment of the air pollutant chloroprene. The information below summarizes key aspects of that assessment. As such, this memo is neither binding on any party nor establishes any obligations.

EPA completed the most recent IRIS assessment of chloroprene in 2010. In that assessment, the agency concluded that chloroprene is "likely to be carcinogenic to humans" through a mutagenic mode of action and that the primary exposure route of concern is the inhalation pathway. Accordingly, the assessment included an inhalation unit risk (IUR), which is an estimate of the increased cancer risk from inhalation exposure to a concentration of 1 µg/m^3 of chloroprene for a lifetime. The IUR is multiplied by a chloroprene exposure concentration (in µg/m^3) to estimate the cancer risk that would be expected in a population exposed to that concentration of chloroprene in the air every day over a lifetime. The composite IUR for chloroprene, which was based on numerous tumors observed in female mice (see some of the tumor types below), is 3 x 10^{-4} per ug/m^3. The adjustment made for a mutagenic mode of action results in a value of 5 x 10^{-4} per ug/m^3. Based on this value, the concentrations associated with the 100-in-1 million and the 1-in-1 million cancer risk-based comparison levels for chloroprene are 0.2 ug/m^3 and 0.002 ug/m^3, respectively.[1]

The conclusion in the 2010 IRIS assessment that chloroprene is "likely to be carcinogenic" to humans was based on a comprehensive review of the available evidence on chloroprene toxicity.

[1] Under EPA's air toxics risk management framework, a cancer risk of 100-in-1 million is generally described as the upper limit of acceptability for purposes of risk-based decisions. Cancer risks at or below 1-in-1 million indicate little potential for cancer risks in the air toxics program.

This included human epidemiological data, animal toxicology data, and evidence that chloroprene is mutagenic. More specifically, in studies of occupational workers, there is evidence that chloroprene causes an increased risk of liver cancer, while other studies in humans show the possibility of an increased lung cancer risk. In animal studies, chloroprene has been shown to cause many different types of tumors, including tumors in the lung, circulatory system, liver, skin, and mammary gland, among others. Additionally, chloroprene's chemical structure is very similar to the known human carcinogens butadiene and vinyl chloride. The IRIS assessment explains that all of this evidence taken together supports the assessment conclusion that chloroprene is "likely to be carcinogenic to humans." The findings of the IRIS assessment are also similar to those of other highly respected, internationally recognized cancer agencies:

- The National Toxicology Program's (NTP) Report on Carcinogens evaluated chloroprene in 2005 and classified it as "reasonably anticipated to be a human carcinogen." This was based on evidence of tumors at multiple tissue sites in multiple species of animals including malignant tumors. The Report on Carcinogens is a congressionally mandated, science-based, public health document. The report identifies agents, substances, mixtures, and exposure circumstances that are known or reasonably anticipated to cause cancer in humans.
- The International Agency for Research on Cancer (IARC) evaluated chloroprene in 1999 and classified it as "possibly carcinogenic to humans." IARC is the specialized cancer agency of the World Health Organization.

The chloroprene IRIS assessment, including the IUR, was also subject to a rigorous review process that included review within EPA, by other Federal agencies and White House offices (e.g., NIEHS, OMB, CEQ, DOD, ATSDR), and the public. The chloroprene IRIS assessment was also reviewed by an independent external peer review panel, which unanimously concluded that chloroprene is a likely human carcinogen that acts via a mutagenic mode of action.

The chloroprene IRIS assessment was developed using a robust, transparent, and public process and represents the Agency's top tier source of toxicity information on chloroprene. We are confident that the chloroprene IRIS assessment and the IUR within are scientifically sound. If you have any questions please do not hesitate to contact me.

cc: Vincent Cogliano, ORD/NCEA
Allen Davis, ORD/NCEA
Kelly Rimer, OAQPS/HEID
Mary Ross, ORD/NCEA
Erika Sasser, OAQPS/HEID
John Stanek, ORD/NCEA
Debra Walsh, ORD/NCEA

Chloroprene Background Information

EPA's Integrated Risk Information System (IRIS) Program

- Through the Integrated Risk Information System (IRIS) Program, EPA provides high quality, publicly available information on the toxicity of chemicals to which the public might be exposed. IRIS is the top tier source of toxicity information used by EPA to support environmental chemical risk management decisions– decisions that protect the public from cancer and other diseases.
- The IRIS assessment of chloroprene (2010) was developed following a very rigorous process.
    - The process began with the development of the assessment by a technically skilled, interdisciplinary scientific team comprised of Masters- and PhD-level biologists, toxicologists, epidemiologists, and statisticians within EPA. The team utilized EPA's long-standing risk assessment guidance to develop a complex hazard and dose-response assessment of chloroprene.
    - The process was completed following multiple reviews of the draft assessment including review by other scientists in EPA's program and regional offices, and by other Federal agencies and White House offices (e.g., NIEHS, OMB, CEQ, DOD, ATSDR). Subsequently, the draft assessment was made available for review and comment by the public and underwent independent, external peer review by a panel of scientific experts. Finally, the draft assessment was reviewed once again by EPA's program and regional offices, other Federal agencies, and White House offices.
- The IRIS assessment evaluated the published scientific evidence to develop both qualitative conclusions and quantitative analyses as part of the noncancer and cancer assessment for the inhalation route of exposure. The chloroprene assessment is a comprehensive, independent analysis that involved evaluation and integration of the

available, relevant and reliable human, animal, and mechanistic evidence associated with chloroprene exposure.

- The EPA toxicity assessment for chloroprene identifies 9 epidemiological studies with 8 cohorts (group of people that share a common characteristic or experience, e.g., work in the same area of an industry). Some studies may use the same cohorts but can be considered independently because they consider different parameters, e.g., cohorts may be followed for different amounts of time during the people's life.

- There are many studies in animals, one of them being the National Toxicology Program (NTP) 2 year bioassay which is considered the gold standard of toxicity testing for noncancer and cancer effects. The NTP study includes noncancer and cancer toxicity data, and a battery of genotoxicity tests that provide information on how a compound may cause cancer at the gene level.

- The IRIS assessment concludes that chloroprene is "likely to be carcinogenic to humans." This finding is based on consideration of the entire range of information which includes: some evidence of cancer in humans, strong evidence of multiple tumor types in multiple animals, and strong evidence that chloroprene interacts with DNA and causes cancer.

  - The IRIS assessment for chloroprene provides a cancer narrative with compelling lines of evidence of a chemical likely to be carcinogenic to humans based on: 1) statistically significant and dose-related information from the chronic NTP bioassay showing the early appearance of tumors, development of malignant tumors, and the occurrence of multiple tumors within and across animal species; 2) evidence in humans of an association between liver cancer risk and occupational exposure to chloroprene; 3) suggestive evidence in humans of an association between lung cancer risk and occupational exposure; 4) proposed mutagenic action of chloroprene; and 5) structural similarities

between chloroprene and the known human carcinogens, butadiene and vinyl chloride.

- Specifically, in rats, increased incidences of neoplastic lesions primarily occurred in the oral cavity (both sexes), lung (males only), kidney (both sexes), and mammary gland (females). In mice, increased incidences in neoplasms occurred in the lungs (both sexes), circulatory system (all organs, both sexes), Harderian gland (both sexes), forestomach (both sexes), liver (females only), skin (females only), mammary gland (females only), and kidney (males only).

- The inhalation unit risk of 3 x 10^{-4} per µg/m^3 is based on the ***incidence of tumors in multiple organ systems in mice***, and represents a 95% upper confidence limit. The calculation of a composite cancer inhalation unit risk (IUR) is consistent with recommendations from the NRC (1994) for when multiple tumor types are identified, as is the case with chloroprene. The chloroprene toxicity assessment also concludes that there is strong evidence that chloroprene works via a mutagenic mode of action (i.e., works by damaging DNA directly) based on the following: 1) chloroprene is metabolized to an epoxide intermediate; 2) interaction with epoxide has been shown to cause DNA adducts (binds to DNA and this process could be the start of a cancerous cell); 3) chloroprene has been shown to cause mutations in bacterial cells; 4) similarities exist in tumor profile and sensitive species between chloroprene and butadiene, which is a known carcinogen; and 5) evidence of genetic alterations in chloroprene-induced lung tumors in rodents exists. **Because chloroprene was concluded to be mutagenic, EPA's 2005 Cancer Guidelines Supplemental document recommends the application of age-dependent adjustment factors. Thus, the adjusted IUR for chloroprene is 5 x 10^{-4} per ug/m^3.**

Exhibit 3

Denka Performance Elastomer LLC
560 Highway 44
LaPlace, LA 70068

June 26, 2017

The Honorable Scott Pruitt
Administrator
U.S. Environmental Protection Agency Headquarters
William Jefferson Clinton Building
1200 Pennsylvania Avenue, N.W.
Mail Code: 1101A
Washington, D.C. 20460

Re: Request to Withdraw and Correct the 2010 IRIS Review of Chloroprene

Dear Administrator Pruitt:

I write on behalf of Denka Performance Elastomer LLC (DPE) in support of the request that the U.S. Environmental Protection Agency (EPA) withdraw and correct its Integrated Risk Information System (IRIS) Toxicological Review of Chloroprene (EPA/635/R-09/010F, 2010) (the 2010 IRIS Review). The errors in the 2010 IRIS Review threaten the very survival of DPE's Neoprene production facility in LaPlace, Louisiana (Facility). In particular, based on those errors and EPA's subsequent flawed determinations concerning the risks caused by Facility emissions, EPA is making stringent air pollution control demands concerning the Facility that are technologically impossible to achieve. EPA must expeditiously apply good science in this matter in order to alleviate the public's undue concerns about the risks associated with this Facility and to prevent further significant damage to DPE's business.

Key conclusions of the 2010 IRIS Review are not based on the best available science or sound scientific practices. First, the 2010 IRIS Review rejected the findings of the strongest available epidemiological study, which concluded that there is no increased risk of cancer in workers exposed to chloroprene (some of the study cohorts actually exhibited a *lower* risk of cancer than the control population). Rather than accepting the overall study conclusions, the 2010 IRIS Review relied on select statistically non-significant comparisons of cancer incidence rates among subgroups of the larger epidemiology study to bolster its classification of chloroprene as "likely to be carcinogenic to humans." Second, the 2010 IRIS Review is flawed because it relied on laboratory animal studies, and then used the results for the most sensitive laboratory animal – female mice – as the basis for a series of overly conservative calculations to develop the human inhalation unit risk (IUR). Contrary to sound scientific practice, the 2010 IRIS Review ignored the known differences between humans and a select strain of female laboratory mice, and relied on results in those female mice to estimate an IUR for humans. Third, the 2010 IRIS Review gives chloroprene, which EPA designates only as a "likely" and not a "known" human carcinogen, the fifth highest IUR estimate of any similar chemical, including known human carcinogens, in the IRIS database. DuPont, the former Facility owner, provided similar information and analysis to EPA in comments on the draft IRIS Review, which comments were rejected in 2010. DPE's Request for Correction and the Ramboll Environ report provide new information and weight-of-evidence review not available in 2010.

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LaPlace, LA 70068

After EPA published the 2010 IRIS Review, the National Academies of Sciences' National Research Council (NRC) recommended major reforms in the IRIS process. Congress has repeatedly instructed EPA to implement the NRC's recommendations, and EPA has advised Congress that it is doing so. The 2010 IRIS Review is plagued with flaws similar to those that gave rise to these reform initiatives, and it is extremely important that the 2010 IRIS Review now be corrected in light of its scientific and procedural deficiencies.

These issues are more fully explained in DPE's Request for Correction and in the supporting toxicological and epidemiological expert review prepared by prominent scientists with the consulting firm of Ramboll Environ: Drs. Kenneth Mundt, Robinan Gentry, and Sonja Sax. Their report is entitled *Basis for Requesting Correction of the U.S. EPA Toxicological Review of Chloroprene*, dated June 2017 ("the Ramboll Environ Report," and attached hereto). The Ramboll Environ Report identifies multiple substantive errors in the 2010 IRIS Review and demonstrates that if chloroprene is to be treated as a possible human carcinogen, the 2010 IRIS Review establishes an IUR that is 156 times too high.

By way of background, DPE acquired the Neoprene Facility from DuPont on November 1, 2015. Neoprene is a synthetic rubber utilized in a wide variety of applications, including laptop sleeves, orthopedic braces, electrical insulation, and automotive fan belts. DPE is the only manufacturer of Neoprene in the United States. The Facility is a commercial mainstay of LaPlace, Louisiana. With an annual payroll of $33 million, DPE directly employs 200-250 people in manufacturing jobs and regularly employs between 125 and 150 contractors. DPE also has created 16 new corporate jobs. Additionally, DPE is investing and upgrading the Facility, including taking new measures to reduce its environmental footprint and improve its productivity and competitiveness.

The base feedstock for Neoprene is chloroprene. The Facility's air permits authorize it to emit chloroprene, and the Facility operates in compliance with those permit limits. However, shortly after DPE's acquisition of the Facility, on December 17, 2015, EPA publicly released its 2011 National Air Toxics Assessment (NATA), which identified the Facility as creating the greatest offsite risk of cancer of any manufacturing facility in the United States. The NATA findings concerning the Facility are based on the scientifically unwarranted and outdated 2010 IRIS Review and the emission profile of the Facility.

Following the public release of the NATA, EPA and the Louisiana Department of Environmental Quality (LDEQ) pressed DPE to reduce emissions to achieve an extraordinarily miniscule ambient air target concentration of 0.2 $\mu g/m^3$ for chloroprene on an annual average basis (which is intended to reflect a 100 in 1,000,000 rate of potential excess cancers in a population exposed to such concentrations continuously for 70 years). The 0.2 $\mu g/m^3$ target is based on a risk assessment that applied the erroneous and scientifically unsubstantiated IUR from the 2010 IRIS Review, and the target reflects more than a four thousand-fold reduction in the applicable Louisiana 8-hour ambient standard for chloroprene. Ramboll Environ's expert scientific opinion is that the appropriate risk-based ambient target should be 156 times larger or 31.2 $\mu g/m^3$. There is no agency rule or even proposed rule requiring the attainment of the 0.2 $\mu g/m^3$ target, yet EPA has advised DPE, LDEQ, and the public that 0.2 $\mu g/m^3$ is the appropriate target.

As a result of the flawed science embodied in the 2010 IRIS Review, and as a result of the NATA findings and the Facility's emission profile, DPE has suffered extraordinary hardship in a number of ways.

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LaPlace, LA 70068

First, despite DPE's concerns about the science behind the 2010 IRIS Review, DPE is currently spending more than $18 million on new pollution controls. On January 6, 2017, DPE entered into an Administrative Order on Consent with LDEQ to reduce chloroprene emissions by approximately 85% below the level of the Facility's 2014 emissions. DPE estimates that the capital cost of these emission reduction devices is approximately $18 million, and the devices will cost hundreds of thousands of dollars per year to operate. Even though DPE is installing the most advanced air pollution controls available, it will still not be able to meet the stringent 0.2 $\mu g/m^3$ target.

Second, because the 2010 IRIS Review is flawed, EPA's very public announcements arising out of that Review and the NATA have created unnecessary public alarm. For example, after issuing the NATA, EPA created a public webpage specifically addressing DPE's chloroprene emissions.[1] Moreover, environmental activists and plaintiffs' lawyers have had numerous meetings in the community about DPE, all based on the faulty assumption that 0.2 $\mu g/m^3$ is the "safe" level for chloroprene. Further, a local citizen's group has formed and has been handing out misleading flyers and protesting near DPE's Facility. The erroneous IUR in the 2010 IRIS Review and the resulting NATA findings have caused DPE enormous reputational damage.

Third, as a result of the NATA findings, EPA Region 6 asked the National Environmental Investigations Center (NEIC) to investigate the regulatory compliance status of the Facility. NEIC sent a team of inspectors to the Facility from June 6-10, 2016, approximately seven months after DPE's acquisition. To be clear, DPE fully respects the important function of the EPA in enforcing environmental requirements. It is simply a fact, however, that as a result of the erroneous IUR and the NATA findings, EPA has initiated an enforcement proceeding against DPE and has devoted an extraordinary amount of resources from the Department of Justice, EPA headquarters, EPA Region 6, and NEIC to developing and pursuing the issues in the NEIC report.

Finally, since acquiring the Facility in November of 2015, DPE's relatively small management team has been buffeted by continuous environmental regulatory demands resulting from the erroneous IUR and the NATA findings. In addition to Facility operation, DPE staff has been in non-stop meetings and negotiations with EPA and LDEQ. DPE's legal and consulting expenses have been enormous, in the millions of dollars. Underlying all of these expenses and burdens on DPE is the erroneous IUR in the 2010 IRIS Review, as applied in the NATA risk assessment.

DPE needs EPA's assistance in the expeditious application of good science to this matter. In meetings with EPA in 2016 concerning the need to correct the 2010 IRIS Review, EPA officials advised DPE that EPA's "queue is full". DPE respectfully requests that EPA review the science underlying the 2010 IRIS Review, withdraw the erroneous IUR, and develop a more accurate toxicological review of chloroprene. We are confident that the Ramboll Environ Report will lead you to these conclusions. Without

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1 *See* https://www.epa.gov/la/laplace-louisiana-background-information.

Denka Performance Elastomer LLC
560 Highway 44
LaPlace, LA 70068

this relief, it is uncertain whether DPE will be able to reduce emissions sufficiently to satisfy agency demands, or even continue operation.

Sincerely,

Koki Tabuchi
President and Chief Executive Officer
Denka Performance Elastomer LLC

Exhibit 4

Doris Grego

From: Kelly Petersen <Kelly.Petersen@LA.GOV>
Sent: Thursday, June 25, 2015 10:08 AM
To: GREGO, DORIS B
Subject: FW: priority facility emissions question

Doris,

EPA has asked that we verify the 2011 emissions below. They have indicated that the reported value is significantly higher than the TRI values reported. Also, in the 2011 NEI v2, this facility has the highest chloroprene and the facility total is higher by the 2nd highest facility by 2 orders of magnitude.

If you could check on this and get back with me, I would appreciate it.

Thanks,
Kelly Petersen
Air Permits Division
Louisiana Department of Environmental Quality
Phone: (225) 219-3397 Fax: (225) 325-8141 kelly.petersen@la.gov

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From: Strum, Madeleine [mailto:Strum.Madeleine@epa.gov]
Sent: Wednesday, June 24, 2015 2:47 PM
To: Kelly Petersen
Cc: Palma, Ted
Subject: priority facility emissions question

Kelly

Can you verify the emissions of chloroprene from the below facility?

Facility ID	FIPS	Tribal Code	Parameter	Pollutant	Risk Value (cancer risk reported in a million)	Facility Emissions (tpy)	Facility Name
8026611	22095		Cancer risk	Chloroprene	1816.044	130.0775	E I DuPont de Nemours & Co - Pontchartrain Site

Thanks

Madeleine Strum
U.S. Environmental Protection Agency
Office of Air Quality Planning and Standards/Air Quality Assessment Division/EIAG
919 541 2383 (voice)
919 541 0684 (fax

Exhibit 5

JOHN BEL EDWARDS
GOVERNOR

CHUCK CARR BROWN, PH.D.
SECRETARY

State of Louisiana

DEPARTMENT OF ENVIRONMENTAL QUALITY
OFFICE OF THE SECRETARY

May 27, 2016

CERTIFIED MAIL 7002 2030 0002 8909 4273
RETURN RECEIPT REQUESTED

Mr. Patrick A. Walsh, CIH
Safety, Health, and Environmental Manager
Denka Performance Elastomer LLC
560 Highway 44
LaPlace, LA 70068

RE: Denka Performance Elastomer LLC (DPE)-Pontchartrain Site; Laplace, St. John the Baptist Parish; Agency Interest No.: 199310; Air Quality Modeling Protocol and Fenceline Monitoring Proposal for Chloroprene emissions

Dear Mr. Walsh:

As you are aware, in December 2015, the Environmental Protection Agency (EPA) released the 2010 Integrated Risk Information System (IRIS) data and/or report for several pollutants, including but not limited to, Chloroprene. According to this data/report, the annual average standard for Chloroprene has been established at 0.2 µg /m^3 . Whereas, the Ambient Air Standard contained in LAC 33:III.5112-Table 51.2 for Chloroprene, a toxic air pollutant (TAP), is 857 µg/m3 (an 8-hour Average).

As a result of the December 2015 publication and to assist the Louisiana Department of Environmental Quality (the Department) in further processing of your Title V minor modification permit application submitted on December 8, 2015, the Department requested an Air Quality Modeling Protocol and Fenceline Monitoring Proposal for Chloroprene emissions from DPE for its Pontchartrain Site for review and approval. The Department has reviewed the Air Quality Modeling Protocol and Fenceline Monitoring Proposal for Chloroprene emissions which were received by the Department on or about April 13, 2016 and May 6, 2016, respectively.

The review of the Air Quality Modeling Protocol revealed that 857 µg/m3 (an 8-hour Average) will be the comparison standard for the Chloroprene emissions instead of 0.2 µg /m3 (Annual Average). As such, the Department is unable to approve this Air Quality Modeling Protocol. A revised Air Quality Modeling Protocol following EPA modeling guidelines, specifically AERMOD Dispersion Model (Version 15181), which proposes to utilize and/or
compare the Chloroprene emissions to the current updated annual standard of 0.2 µg /m3 should be prepared and submitted to the Department for review and/or approval.

The following observations were noted during the review of the Fenceline Monitoring Proposal:

- Sample Locations – the proposed locations are approved by the Department. However, the Department is requiring two (2) additional sample locations be established. One (1) location shall be located northeast of the Pontchartrain Site and the other location shall be located south of the Pontchartrain Site.

- Analytical Methodology - with an exception to the Method Detection Limit (MDL), as noted below, the analytical methodology is acceptable to the Department.

- A laboratory Method Detection Limit (MDL), of at least 0.04 µg/m3 (0.01 ppbv), isn't being proposed. This MDL is achievable by commercial laboratories and is deemed necessary for the monitoring activities to be deemed successful. Performing a study to determine if the MDL can be detected isn't warranted and therefore, is not approved by the Department.

- Sampling Frequency and Duration – the 24-hour sample type is hereby approved by the Department. However, the frequency of twice per month for 6 months is denied. The sample collection frequency shall be once every six (6) days for a minimum of six (6) months to address and or account for variations in pollutant concentration(s). However, a sample frequency of once every three (3) days is preferable.

- The Protocol does not propose to measure and/or document the following information and/or operating conditions at the facility and/or at certain relevant emission points, which are also essential to demonstrate successfulness of the monitoring activities:

    - Meteorological conditions including hourly averages of wind speed, wind direction, ambient temperature, relative humidity, and barometric pressure.

    - Production rate (per hour) of chloroprene and neoprene at the time of monitoring and the following information, as referenced in permit 2249-V8:
        - VOC emissions (both chloroprene and toluene) calculated on the day of monitoring as per Specific Requirement (SR) 147.
        - Chloroprene emissions calculated on the day of monitoring as per SR 176 and operating rate of CD refining column of EQT 0139 or EQT 0140.
        - All the parameters monitored as per SR 182 at the 1700-2 Strippers Condenser Vent (RLP 0014).
        - Temperature of the Condenser Brine Outlet as per SR 192.
        - Percent Reduction as per SR 193.
        - Compliance status of SR 196.

    - From the Halogen Acid Furnace if it is operating as per permit 206-V3:
        - Combustion chamber temperature
        - Waste flow rate
        - Dynamic scrubber differential pressure
        - Dynamic scrubber pH

Within two (2) weeks of receipt of this letter, please submit a revised Air Quality Modeling Protocol and Fenceline Monitoring Proposal which addresses and incorporates the aforementioned requirements.

If you have questions or need additional information regarding the revised Air Quality Modeling Protocol, please contact Mr. Donald Trahan at (225) 219-3408 or by e-mail at Donald.Trahan@la.gov. Questions or requests regarding the revised Fenceline Monitoring Proposal should be directed to Mr. Bob Bailey at (225) 219-3991 or via e-mail at Bob.Bailey@la.gov.

Sincerely,

Chuck Carr Brown, Ph.D.
Secretary
Louisiana Department of Environmental Quality

CCB/CJC/cjc

cc: (Via electronic mail)

Jorge Lavastida, Plant Manager, DPE
Wren Stenger, Director; Mulitmedia Division (EPA Region 6)
John Blevins, Director; Compliance Assurance & Enforcement Division (EPA Region 6)
Lourdes Iturralde, Assistant Secretary, Office of Environmental Compliance (LDEQ)
Elliott Vega, Assistant Secretary, Office of Environmental Services (LDEQ)
Herman Robinson, Esq., Office of the Secretary
Robert E. Holden, Esq., Liskow & Lewis
Donald Trahan, Environmental Division Administrator (LDEQ)
Celena J. Cage, Environmental Division Administrator (LDEQ)

Exhibit 6

RAMBOLL ENVIRON

ENVIRONMENT & HEALTH

John Vandenberg, PhD
Director of Research at NCEA
109 T.W. Alexander Drive
Research Triangle Park, NC 27709

Sent via e-mail

RE: FOLLOW-UP TO THE MEETING AT RTP

Dear Dr. Vandenberg,

August 23, 2016

Ramboll Environ
28 Amity Street
Suite 2A
Amherst, MA 01002
USA

T +1 413 8354350
www.ramboll-environ.com

Thank you for setting up and orchestrating the "listening session" on Tuesday August 9th, 2016 at your offices. Dr. Gentry and I appreciate the opportunity to present the findings from our independent review of chloroprene's potential carcinogenicity, based on all available data and state-of-the-art methods for critically reviewing and synthesizing epidemiology, toxicology and mechanistic studies, and for integrating evidence across these lines of inquiry.

As discussed after our presentation of the science, we acknowledge and appreciate your explanation of the IRIS Program's resource constraints, the complex procedures in place for selecting substances for IRIS review or re-review, as well as what you described as the "full docket" of current and future IRIS reviews. Based on this feedback, we understand that the IRIS Program will not at this time undertake a new review of chloroprene – or consider any revisions to the risk numbers – primarily due to resource constraints.

This, as you can understand, leaves our client, Denka Performance Elastomer, LLC (DPE), in a very difficult position, and unjustifiably so from a scientific standpoint. During our meeting, we outlined important new information demonstrating that an IRIS chloroprene IUR derived today would be vastly different and more compatible with other IURs for other chemicals. As we demonstrated during our meeting, properly employing validated PBPK models leads to an IUR for chloroprene that is more than 100-fold lower than the 2010 IRIS value. In fact, the 2010 IRIS Review of Chloroprene astutely acknowledged this very flaw: "Ideally, a PBPK model for the internal dose(s) of the reactive metabolite(s) would decrease some of the quantitative uncertainty in interspecies extrapolation; however, current PBPK models are inadequate for this purpose" (US EPA, 2010, Section 3) [1]. The information and methods required for chloroprene now have been peer-reviewed, published, and validated, with similar models and methods applied by EPA in comparable risk evaluations (such as vinyl chloride).

[1] US EPA 2010. Toxicological Review of Chloroprene. In support of Summary Information on the Integrated Risk Information System. Washington, DC: U.S. Environmental Protection Agency.

RAMBOLL ENVIRON

We also noted what we consider a misinterpretation of the body of epidemiological evidence, largely due to discounting the negative results published from the 2007 Marsh et al. study, which is also the strongest epidemiological study, in favor of results from much weaker studies. The integration of the entirety of epidemiological evidence supports the updated toxicology and mechanistic evidence indicating important and substantial differences between humans and mice, specifically in terms of metabolism, which are directly related to estimating the potential cancer risks for chloroprene. This no longer can be ignored. Taking the most up-to-date information into consideration in the context of using science to inform EPA policy and regulation is entirely consistent with the Agency's very public "mission statement" to ensure that "national efforts to reduce environmental risk are based on the best available scientific information." [2]

Without a commitment on the Agency's part to reexamine the 2010 IRIS assessment's IUR derivation in light of the new information, EPA and the Louisiana Department of Environmental Quality have advised DPE that it will be required to meet extremely stringent emissions limits, which may not be attainable, and that are not based on the best available science. We also have seen that the IUR is being used to inform important regulatory and other federal and state government actions, as well as public statements with respect to the possible cancer risks to people who live and work in the community in which our client's facility is located.

Notwithstanding the IRIS Program's resource constraints, we genuinely look forward to any thoughts or ideas you or Dr. Cogliano might have with respect to how we might work collaboratively with you and the program office within EPA that is relying on the 2010 IRIS Assessment, to timely improve and update the IUR. The IUR for chloroprene (as well as actions that are derivative of that IUR) should be more in line with those of other substances, such as vinyl chloride, that provide stronger evidence than chloroprene of carcinogenicity in humans.

We, too, will be exploring various available avenues, and will keep you informed. One possibility would be for us to file a request for correction (RFC). Our ultimate goal, as I initially mentioned to Dr. Cogliano when I first approached him, is to improve the risk calculation based on currently available science and evidence-based processes, which have evolved since the completion of the 2010 Chloroprene Toxicological Review, and to do so in a way that creates the lowest demands on already limited resources. Thank you again, and I look forward to continuing our discussion.

Yours sincerely

Kenneth A. Mundt, PhD, FACE
Health Sciences Practice Network Leader
D +1 413 835 4360
M +1 413 885 1345
kmundt@ramboll.com

cc: Dr. Vincent Cogliano

[2] https://www.epa.gov/aboutepa/our-mission-and-what-we-do

Exhibit D

Request for Reconsideration
Denka Performance Elastomer LLC

OMB Staff Working Comments on EPA's Toxicological Review of Chloroprene and draft IRIS Summary (dated July 2010)

August 30, 2010

General Science Comments:

- OMB staff focused this review on EPA's response to the external peer review. Where EPA agrees with the comments, we suggest that appropriate conforming changes be made in the main text of the toxicological review and the IRIS summary.

- While we note that the peer review report is already final, it would be helpful if the peer review report provided short summaries of the background of the expert reviewers. It may also be helpful if the peer review reports were to include information discussing any monetary funding (perhaps through a grant, cooperative agreement, sole-source agreement, or competitive contract) that the expert reviewer may have received from EPA's ORD. This would be consistent with generally-accepted disclosure practices for peer reviewers, particularly for reviews with significant public policy implications.

- In general, we find that Appendix A seems to lump together, in paragraph style, all the comments responding to a particular question and then lumps together the response. Clarity would be much improved, and it would be easier to follow EPA's responses, if a response was provided after each specific comment relating to the particular question.

- Page A4, we note that although suggested for inclusion by expert reviewers, EPA has not incorporated results from other epidemiology reviews. While we agree EPA should be providing an independent review, it is not clear to us why EPA is declining to present the findings of other independent reviews.

- Because EPA has been responsive to peer review comments regarding changes needed to the RfC methodology, EPA is now relying on a completely new critical effect, splenic hematopoietic proliferation in female mice, for the RfC. Since the external review in January, has EPA had this new choice of endpoint peer reviewed for its appropriateness? In reading the peer review report, it does not appear that this endpoint was mentioned, discussed or considered as a point of departure. As this is a large scientific change, EPA may want to consider a quick external review of this new choice. (We note that the previous IRIS process included a step where EPA went back to the external reviewers using a quick letter review approach to ensure that the expert reviewers were comfortable with the way their comments were addressed. Such an approach may be appropriate here). EPA could also take comment on its decision to use a 5% BMR for this endpoint, as the rationale for this choice is unclear in the toxicological review. Perhaps expert reviewers can help inform what BMR response levels would represent a biologically significant change before EPA finalizes the assessment based upon this endpoint.

- Throughout the peer review report, Dr. Hattis makes comments relating to the partial saturation of metabolic activation of chloroprene. It is not clear where in Appendix A EPA has addressed these re-occurring concerns.

- In response to an expert reviewer who questions the appropriateness of stating that choloroprene is likely to be carcinogenic by all routes of exposure (in particular through dermal exposures), it is not clear why EPA states that convincing toxicokinetic data is needed. Couldn't EPA also take an alternate science based approach, as suggested by the expert reviewer, which would consider the fact that chloroprene is non-reactive and relatively insoluble in water? It would be helpful if EPA provided a science based response to this expert commenter. We note that EPA cites the NLM hazardous substance database, but when we look closely, there is only one statement about dermal absorption and it is a study from 1968. We suggest EPA review this study to ensure its robustness and cite it directly and provide some details if it indeed provides scientific support for dermal absorption.

- Page A-23, it is unclear why conducting a meta-analysis would be beyond the scope of the choloroprene tox review. Wouldn't this help to inform cancer effects and aren't meta-analyses conducted for other IRIS chemicals?

- In section 4.7.1.1.1, shouldn't this include a discussion of specificity? It is unclear why this has been deleted. Isn't specificity still part of the Hill Criteria for causality?

- Page A-41, it appears as if EPA is adopting the Dourson 1992 recommendation. It would be helpful if EPA clarified all the criteria that are evaluated to determine when a partial or full database uncertainty factor is warranted and when it is not.

- Dr. Ruder commented that the statements of conclusions in Section 6 are less clear than those presented elsewhere. As we also found Section 6 to be not as transparent in presentation as previous IRIS assessments, it is unclear why EPA chose not to address the external reviewers comment. A clearer separation of the non-cancer and cancer discussions would be helpful.

1) - Page 2-1: The first sentence is very hard to read, for example it starts with "Beta-chloroprene monomer" and the relationship to neoprene is very confusing. We suggest this be revised to reflect the IUPAC name. We also suggest to begin the sentence with "The monomer…" and to remove the reference to neoprene as it is mentioned later in the paragraph.
2) - Page 2-1: There is much discussion on chloroprene in the environment yet there is no mention of exposure pathways. Exposure pathways should be discussed as well. Moreover, a statement should be added here, and more importantly on Page 4-1, that human exposure to chloroprene is primarily occupational.
3) - There is no mention in the document that the International Agency for Research on Cancer has classified chloroprene as a Group 2B, possibly carcinogenic to humans. There are a number of places where this should be mentioned, i.e., page 6-2 where assessments of the carcinogenic potential of chloroprene in humans are discussed.
4) - Page A1: Response to Charge Question 1: There is no mention of the comment from Melnick regarding his question as to why consideration was not given to the conclusion that chloroprene is "carcinogenic to humans" based on the animal data, mechanistic findings, and "the reasonably consistent" evidence of increased risk of liver cancer mortality "among workers exposed to chloroprene in different cohorts in different continents." Please explain.
5) - Response to charge question B2 -Five of the reviewers supported the selection of a portal of entry effect (nasal lesions) as the critical effect for this chemical. However, several of these reviewers questioned combining the lesions (atrophy and necrosis). It is unclear from this response to this question, that EPA performed modeling of additional endpoints and selected splenic hematopoietic proliferation as the "new" critical effect. CEQ suggests further explanation and justification for this change (i.e., due to changes in the BMR and application of the DAF, increased incidence of splenic hematopoietic proliferation in female mice was chosen as the critical effect based on the observation that this endpoint had the lowest POD) in the response to this charge question for completeness.
6) - A BMR of 5% was used in the modeling of splenic hematopoietic proliferation, the selected critical effect for the derivation of the RfC in this draft. However, for increased splenic hematopoietic proliferation there are no severity data presented and the footnote in Table 4-26 and 5-1 indicate that average severity and statistical significance was not reported by NTP. Section 5.3 indicates that "for increased incidence of splenic hematopoietic cell proliferation in female mice, definitive data do not exist to further inform the selection of what the appropriate BMR should be. However, the observation was made that the incidence and severity of this lesion increases in low dose animals compared to control animals; therefore a BMR of 5% extra risk was chosen based on the assumption that a 5% increase in incidence of this effect is minimally biologically significant." Was severity of splenic hematopoietic proliferation reported by NTP or did NTP state that the severity of this lesion increased in the low dose animals compared to controls? If there an additional biological basis for selecting the BMR of 5% for this endpoint in particular? The rationale for

selection of a BMR of 5% for splenic hematopoietic proliferation could be clarified and made consistent in Sections 5.2.2 and 5.3 (also in Appendix A).

7) - Page A-7, line 9-10 states that Figure 5-1 has been removed from the document. This figure still appears in Section 5.2.6.
8) - Page A-17, lines 27-31 and page A-32 lines 29-31- One reviewer suggested consideration of an alternative model incorporating the assumption of saturating metabolism in the model structure and provided an extensive example using the mouse data. It is not clear what is meant by the statement "The suggested alternative modeling approach incorporating saturating metabolism was a constructive approach that EPA will consider with regards to future methods developed for human health risk assessment." Is there a scientific basis to not pursue this model (i.e., lack of data to support these assumptions)?
9) - Page A-28, lines 32-33-The following statement is made regarding possible confounding of alcohol co-exposure: "Alcohol cannot be a confounder if it is not both related to the exposure of interest (chloroprene) and the outcome of interest (liver cancer)." It is unclear why even though alcohol may not be related to the exposure of interest, it could not have been a significant confounder (given its relationship to liver effects and cancer). Please clarify.
10) A-29, lines 1-11-This text was removed from Section 4.7.1.1.1, CEQ suggests that the response should reflect the fact that this text was removed.
11) A-15, lines 31-34 and other places in Appendix A- The following statement is made regarding toxicokinetics: "A more complete and detailed discussion of metabolism and toxicokinetic differences between species was added to Section 3.3, to indicate that differences in epoxide production in the lungs of mice and humans are not 50-fold, but may be as little as 2- to 10-fold." Please consider addition of references supporting these statements to these responses in the Appendix.
12) Did EPA consider that the lack of a reproductive toxicity study that extends beyond two generations and the absence of a developmental toxicity study are of particular concern due to the genotoxicity of chloroprene, i.e., the possibility that resulting genetic damage to the germ cells of the F1 generation may not be detected until the F2 generation? (See response to comments on the database uncertainty factor)

NIEHS/NTP Comments on Toxicological Review of Chloroprene

We commend authors of the document for preparing an excellent review of the toxicology information available on chloroprene in the literature. This is one of the best EPA documents we have reviewed recently.

The only comment we have is on the selection of endpoint used in derivation of RfC. The draft sent to the external reviewers had nasal degenerative effects as the endpoint for derivation of RfC and none of the reviewers objected to the selection of this endpoint in their response to the charge questions. The toxicology data supports the use of this endpoint based on the fact that major target of chloroprene toxicity/carcinogenicity is respiratory system in female mice. However, the current draft used increased incidences of splenic hematopoietic cell proliferation in female B6C3F1 mice as POD for derivation of RfC. No explanation is given for this change and we are wondering whether the external group would support this change. Looking at the figure 5.1, the most appropriate endpoint should be from one of the adverse effects seen in the female mouse lungs.

Submitted by:

Rajendra S. Chhabra, PhD., DABT

Exhibit E

Request for Reconsideration
Denka Performance Elastomer LLC

Prepared for
Denka Performance Elastomer LLC

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RESPONSE TO EPA DENIAL OF CHLOROPRENE RFC #17002

RAMBOLL

CONTENTS

1 INTRODUCTION

On January 25, 2018, the U.S. Environmental Protection Agency (EPA) denied the Request for Correction (RFC, US EPA 2018 a,b) of the 2010 Toxicological Review of Chloroprene (US EPA 2010a), hereafter the 2010 Review, submitted by Denka Performance Elastomer LLC (DPE) on June 26th, 2017 (DPE 2017). DPE asked Ramboll[1] to provide comments on EPA's denial, which contained two attachments: Attachment 1 was a response to the RFC (US EPA 2018a), and Attachment 2 was a "Systematic Review" of the literature published since the 2010 IRIS Toxicological Review of Chloroprene (US EPA 2018b). The science and methods at issue and that motivated the RFC are detailed in the Ramboll Technical Report (DPE 2017, Exhibit 1), hereafter the Ramboll Report.

Two general criticisms of the EPA denial are 1) it mostly failed to address the compelling scientific points raised in the RFC showing that the 2010 Review was flawed; and 2) it relied heavily on the inaccurate assumption that the review process that the 2010 Review had undergone, which included external peer review, was properly executed. This response highlights key scientific data, which EPA either ignored or misinterpreted in its denial, and which calls into question the EPA's findings in the 2010 Report. It will also point to significant deficiencies in the EPA's review process that led to the flawed 2010 Review, and will highlight key peer reviewer comments that were critical of the EPA's epidemiological and toxicological findings on chloroprene, but which EPA either ignored or inadequately addressed in both the 2010 Review and the denial.

In Section 2, we outline several limitations in the EPA peer review process. Specifically, EPA 1) either ignored or inadequately addressed critical peer-review comments; and 2) EPA made significant modifications to the 2010 Review that were not subject to peer review. As a result, we conclude that EPA's denial of the RFC on the basis that the 2010 Review was peer reviewed in its entirety is erroneous.

In Section 3, we comment on Attachment 1 of EPA's response to the RFC, which presents EPA's rationale for the denial. In this section, we reiterate the key scientific issues that were discussed in full in the Ramboll Report including the critical importance of using a physiologically-based pharmacokinetic (PBPK) model to calculate a human inhalation unit risk (IUR) that accounts for the clear and critical differences in metabolism between mice and humans. In doing so, the corrected IUR is consistent with all lines of evidence, and more in-line with IURs for substances classified as likely or known carcinogens.

In Section 4, we comment on Attachment 2 of the EPA's response to the RFC, which purports to present a "systematic review" of the literature on chloroprene published since the 2010 Review. Although the EPA concluded that key studies published since the 2010 Review have no bearing on the 2010 Review, Ramboll disagrees, as several key publications confirm the scientific weight of the evidence that unequivocally indicates that adjustments to the mice data are needed to obtain an IUR that is relevant to a human response to chloroprene exposure, and that is orders of magnitude lower than IUR published in the 2010 Review. We do agree that the one epidemiological study identified and reviewed by EPA is irrelevant to the RFC and EPA's denial.

[1] As of January 1, 2018 Ramboll Environ changed its name to Ramboll US Corporation ("Ramboll")

2 LIMITATIONS IN THE EPA PEER REVIEW PROCESS

The EPA IRIS peer review process applicable at the time of the development of the 2010 Review included a number of internal and external peer reviews. As outlined in a 2009 Guidance document (NCEA 2009), the IRIS development process included the following steps:

Step 1 - Document development;
Step 2 - Internal EPA review;
Step 3 - Interagency science consultation;
Step 4 - External peer review and public comment;
Step 5 - Document revision;
Step 6A - Final internal EPA review;
Step 6B - Interagency science discussion; and
Step 7 - Posting the final assessment on the IRIS database.

As part of the internal and interagency review, EPA may seek input on the draft document from (1) selected EPA scientists with expertise in the scientific issues raised in the draft assessment, (2) a standing group of senior health scientists representing EPA's Offices and Regions, (3) scientists in other Federal agencies and White House offices, (4) any interested members of the public, and (5) a group of external scientific experts known as the independent external peer review panel.

As noted in the guidance document (NCEA 2009), in addition to internal EPA review and interagency science consultation "EPA obtains independent input from experts in scientific disciplines germane to the science and risk issues discussed in each respective draft human health assessment, and that is independent external peer review." Although information regarding the internal and interagency science consultation on draft versions of the 2010 Review is not publicly available, the peer review panel of scientific experts, which is convened by a service provider by contractual agreement with EPA, is identified in EPA documents posted online[2].

The external peer review panel for the 2010 Review included the following six peer reviewers:

Herman J. Gibb, Ph.D., M.P.H.
Dale Hattis, Ph.D.
Ronald L. Melnick, Ph.D.
John B. Morris, Ph.D.
Avima M. Ruder, Ph.D.
Richard B. Schlesinger, Ph.D.

Of these, two are epidemiologists, Dr. Gibb and Dr. Ruder (deceased). Dr. Hattis is a statistician and modeler, with expertise in PBPK models. Drs. Melnick, Morris and Schlesinger have expertise in toxicology.

The specific comments that these external peer reviewers provided to EPA in a meeting on a draft version of 2010 Review, hereafter the Draft Review (US EPA 2010b[3]) are documented in a peer review report (Versar 2010) and summarized in the 2010 Review, which is the subject of the RFC, together with the EPA's response to the comments (US EPA 2010a, Appendix A). To our knowledge there is no publicly available information regarding any consultations with the external peer reviewers on the revised 2010 Review (US EPA 2010a). There is no information, therefore, as to whether the experts who provided the initial peer-review were able to verify that their comments were adequately

[2] https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=56468
[3] https://cfpub.epa.gov/si/si_public_record_report.cfm?dirEntryId=56468

addressed, if addressed at all. This observation in no way challenges the expertise of the peer reviewers or the quality of their reviews, but calls into question the EPA's peer-review process and the resulting thoroughness of the peer-review. However, because the EPA's rationale for denial rests so firmly on their assertion of a quality and thorough peer-review process, that assertion must be carefully examined.

Following the external peer review by the panel identified above, a revised Draft Review (dated July 2010) was reviewed by staff within EPA and other agencies, including the Office of Management and Budget (OMB), Council on Environmental Quality (CEQ), and National Institute of Environmental Health Sciences/National Toxicology Program (NIEHS/NTP)[4].

Our review of the Draft Review (US EPA 2010b) and peer reviewer comments identified several gaps or deficiencies in the peer review process that challenge EPA's assertion that EPA's key findings in the 2010 Review (US EPA 2010a) are correct simply because they survived multiple reviews and peer review by an external expert panel. Central to the RFC is the fact that critical peer review comments, especially with respect to the epidemiologic data and the derivation of the IUR for chloroprene based on the mice data, were not fully or properly addressed by EPA (as discussed in the following section).

In fact, inter-agency reviewers (*e.g.*, OMB staff) highlighted that significant scientific changes were made to the Draft Review (US EPA 2010b) following the external peer review that were not put before the external peer review panel. In other words, there are substantial sections of the 2010 Review that include important EPA discussions and findings that, it appears, were never seen by the external peer review panel. We therefore challenge the notion that the peer review process was complete or reliable. EPA cannot validly rely on the incomplete peer-review process to support many of the scientific conclusions in the 2010 Review. This includes the final derivation of the IUR for chloroprene.

If EPA upholds its denial and refuses to correct the grossly inaccurate and misleading IUR for chloroprene, we recommend that the 2010 Review be withdrawn for failing to meet current scientific standards and be re-evaluated because (a) as outlined by NRC (2011, 2014) and in light of the deficiencies in the peer review process, EPA should improve the scientific rigor of the 2010 Review, and (b) there are clear errors in EPA's interpretation and integration of the epidemiological and toxicological data as well as with the approach and specific methods used to calculate an implausible IUR for chloroprene.

3 COMMENTS ON EPA RESPONSE: ATTACHMENT 1

In the EPA (2018a) denial, EPA commented on the following topics raised in the DPE (2017) RFC:

A. Epidemiological Evidence Shows No Increase in Cancers Among Workers Highly Exposed to Chloroprene

B. The IUR Does Not Reflect the Best Available Science or Sound and Objective Scientific Practices

1. The IUR is Primarily Based on Data from the Female Mouse, which is Uniquely Sensitive to Chloroprene Exposure

2. The IUR Rests on the Unwarranted Assumption that Different Tumor Types are Statistically Independent

[4] https://cfpub.epa.gov/si/si_public_record_report.cfm?dirEntryId=213750

3. The IUR Rests on the Assumption that Chloroprene Has a Mutagenic Mode of Action, but the Available Evidence Does Not Support that Assumption

4. The IUR Must Be Corrected by Employing the PBPK Model to Sufficiently Account for Differences in Mice and Humans

5. The Correct Chloroprene IUR is 156 Times Lower than the Chloroprene IUR Derived by EPA

C. EPA's IUR for Chloroprene is Drastically Higher Than IURs for Similar Chemicals

D. EPA's Classification of Chloroprene as "Likely to be Carcinogenic to Humans" Should Be Reviewed

E. EPA's Reference Concentration (RfC) for Chronic Inhalation Exposure Should Be Reviewed

In the following sections, we restate the arguments raised in the DPE (2017) RFC for each of these topic areas, summarize EPA's response(s), and present Ramboll's evaluation of EPA's responses, highlighting where those responses were incorrect or incomplete.

3.1 Topic A: Epidemiological Evidence Shows No Increase in Cancers Among Workers Highly Exposed to Chloroprene

3.1.1 RFC arguments

As noted in the RFC, EPA (2010a) based its criteria of "likely to be a human carcinogen" in part on misinterpretation of the epidemiological data. That is, EPA concluded that there was "an association between liver cancer risk and occupational exposure to chloroprene" and "suggestive evidence of an association between lung cancer risk and occupational exposure." The EPA (2010a) evaluation of the epidemiological evidence was flawed because it did not properly weigh the evidence with regards to study quality, therefore relying on evidence from poorly conducted studies in Armenia, Russia and China to support its conclusions. In contrast, the largest and most rigorous study that should have been given the most weight in the evaluation of the epidemiological data, *i.e*. the Marsh *et al.* studies (2007 a,b), were only discussed as part of the evidence. In addition, findings from the Marsh studies were misinterpreted.

3.1.2 EPA response

EPA (2018a) notes in its response that this topic is related to topic "D" – EPA's classification of Chloroprene as "Likely to be Carcinogenic to Humans." As with other topics, EPA (2018a) stresses the peer review process as support for the scientific findings outlined in the 2010 Review.

3.1.3 Ramboll response

In its denial, EPA relies on its assertion that the peer-review process was adequate and therefore the classification of chloroprene is correct. EPA does not address the issue of its misinterpretation of the epidemiological evidence, which has considerable bearing on the classification. As discussed in detail in the Ramboll Report, EPA's evaluation of the epidemiological evidence as supportive of a causal relationship lacked transparency in whether and how it assessed study quality and weighed the evidence. Specifically, EPA (2010a) equally weighed the strongest and most robust Marsh *et al.* (2007 a,b) studies with poorer quality Russian, Armenian, and Chinese studies, contrary to standard methods for quality-based evaluations. Although study quality evaluations and methods for weighing the epidemiological literature are included in the 2005 Guidelines for Risk Assessment (US EPA 2005),

a more extensive and proscriptive set of recommendations have been set forth by the National Research Council (NRC 2011, 2014), and these should be implemented in the evaluation of the chloroprene epidemiological literature.

Dr. Gibb, one of the two epidemiology experts on the peer review panel, also raised this point, providing extensive commentary challenging reliance on the findings by Li *et al*. (1989) because China has the highest liver cancer rates in the world, likely resulting from risk factors such as Hepatitis B and aflatoxin exposure. He noted that the role of these important confounding factors was not addressed by EPA, and he discounted the EPA claims that the healthy worker effect could have played some role in the evaluation of liver cancer mortality risks. He also noted that it was inappropriate to evaluate separately studies by Leet and Selevan (1982) and Colonna and Leydavant (2011) as these cohorts were included in the Marsh *et al*. (2007 a,b) analyses (Versar 2010). All of these comments were also provided during the public comment period by DuPont, and reiterated in the Ramboll Report, but were ignored by EPA and continue to be ignored by EPA.

Dr. Gibb also noted that "The other study in Table 4-11 that suggests a dose-response is Bulbulyan (1999), but the relative risks in the high and low dose are not statistically different. The statement at the bottom of page 4-18 that there is evidence of a dose-response relationship in different cohorts in different continents (U.S., China, Russia, and Armenia) grossly misrepresents the evidence." (Versar 2010, pg. 25) In addressing the classification of chloroprene as a "likely human carcinogen," Dr. Gibb also noted that the epidemiological evidence was overstated (Versar 2010, pg. 7). Yet, in the 2010 Review, EPA notes "The relative risk of liver cancer mortality also increased with increasing cumulative exposures indicating a potential dose-response trend" (US EPA, 2010a). This shows that EPA ignored the peer reviewer comments and continued to assert that an association between chloroprene exposure and liver cancer was observed in these studies.

Although EPA asserted that discussion of the epidemiological studies was added to address these comments, there remained a lack of transparency in how EPA evaluated the epidemiological evidence with respect to study quality (US EPA 2010a, pgs. A1-A4). Furthermore, the gross discrepancy between EPA's conclusions and peer-reviewer's comments, as well as the conclusions by Marsh *et al.* (2007 a,b) further indicates that EPA was unresponsive to the peer reviewer comments and may not have had the epidemiological expertise required to resolve these issues.

Furthermore, EPA did not describe the process it used (if any) to critically evaluate and weigh the individual studies, which is a key part of the evaluation of evidence as has been stressed by the NRC (2011, 2014). Such a study evaluation was conducted by Bukowski (2009), who clearly demonstrates that the cited chloroprene studies are not of equal quality. Most importantly, the Bukowski (2009) critical review shows that several studies that EPA relied upon were seriously flawed and/or weak relative to the Marsh *et al.* (2007a, b) studies. As EPA today strives to develop methods and establish leadership in the systematic review process, it is incongruous for EPA to assert that its evaluation of the epidemiological literature in the 2010 Review somehow meets or even approaches scientific standards for good epidemiology practices.

EPA (2010a) does not even mention the Bukowski (2009) study in the 2010 Review, despite the comment by Dr. Gibb (from the external peer review panel) recommending the inclusion or consideration of the Bukowski (2009) and Acquavella and Leonard (2001) reviews (Versar 2010). If nothing else, Bukowski (2009) might have informed EPA on how consideration of study quality is critical to the valid interpretation of the evidence (a perspective IRIS today champions). EPA responded that "the two additional reviews of the primary epidemiology literature (Acquavella and Leonard, 2001; Bukowski, 2009) were reviews of primary literature already included in the assessment. Therefore, these reviews were not added to the document as the purpose of the 2010

Review is to provide information on the EPA's independent review of the epidemiology database." (US EPA 2010a) During the interagency review, OMB also questioned why EPA did not include discussion of the reviews noting that "although suggested for inclusion by expert reviewers, EPA has not incorporated results from other epidemiology reviews. While we agree EPA should be providing an independent review, it is not clear to us why EPA is declining to present the findings of other independent reviews (OMB 2010)." EPA (2010a) did, however, include a discussion of the Rice and Boffetta (2001) review in the 2010 Review, therefore allowing for inclusion of some reviews and not others, which indicates further inconsistencies in its approach and methods.

As summarized in the Ramboll Report, Marsh *et al.* (2007a, b) reported no excess occurrence of lung or liver cancers among chloroprene exposed workers. In fact, overall and for all sub-cohorts defined by specific plant(s), standardized morality ratios (SMRs) based on methodologically preferred local reference rates were all below 1.0, providing no indication of any excess of these cancers among chloroprene exposed workers. In contrast, EPA (2010a) disregarded this evaluation, and instead focused on a statistical correlation between exposure level and risk relative to a comparison subgroup where the comparison group exhibited anomalously fewer cancers than expected (based on only two observed liver cancer deaths). This ultimately created the appearance of an increased risk in the higher exposure groups where none existed – an anomaly clearly noted by Marsh *et al*. (2007b) and reiterated in public comments provided by Dr. Marsh. The EPA (2010a) summary of the Marsh *et al*. study indicates incomplete evaluation and misinterpretation of the published results. Properly interpreted, the evidence does not demonstrate an association between occupational chloroprene exposure and human cancer incidence.

The Marsh *et al*. (2007 a,b) findings challenge the use of epidemiological findings to support a classification of chloroprene as a "likely human carcinogen," as no increased risk was demonstrated, even among highly exposed workers. This also directly calls into question the highly elevated IUR, which is orders of magnitude higher than IURs for known carcinogens, and challenges its relevance for estimating risks among those non-occupationally exposed to much lower concentrations.

In addition to the peer reviewer comments, public comments included an extensive critique of EPA's interpretation and weighing of the epidemiological evidence.[1] These comments were clearly and broadly disregarded by EPA in the 2010 Review (US EPA 2010a). For example, the public comments provided in the docket included the following comment:

> US EPA interpretation of the potential for lung and liver cancer risks of chloroprene based on the Marsh *et al*. (2007, a,b) study did not fully consider the impact of inordinately low death rates for lung and liver cancer among workers in the baseline categories.

To which EPA (2010a, p. A-34) responded:

> Although the authors highlight some "exceedingly" low mortality figures in the "baseline" exposure levels (i.e., lowest exposure category), comparable numbers of deaths are found in low-, intermediate-, and some high-exposure groups across different outcomes (those RRs ≤ 1.00 for all cancers, respiratory and liver cancer mortality). It is unclear why the authors consider any RRs in excess of 1.00 to be due to an "exceedingly" low baseline mortality rate. There is little evidence to suggest that this is not a valid population in which to base comparisons on, and the results of the internal analyses are preferred given the strong evidence of the healthy worker effect in the SMR analyses. In addition, given the fact that such strong RRs were detected in healthy workers, one would be more concerned about potential risk among less healthy populations under similar circumstances.

Dr. Gary Marsh provided detailed comments regarding the interpretation of the epidemiological evidence during the public comment period as part of DuPont's submitted comments to the docket (Dupont 2009, Attachment A), further emphasizing the need to consider the weight-of-the-evidence of the epidemiological studies and properly weight the evidence based on study quality. The DuPont comments included additional analyses conducted by Dr. Marsh showing a lack of dose-response for liver cancer with increased chloroprene exposures. Dr. Marsh specifically concluded that "the available data for liver cancer in relation to chloroprene exposure from the Marsh *et al*. (2007a, b) study Louisville cohort provide no evidence of an exposure-response for chloroprene and liver cancer." (DuPont 2009, pg. 26).

In addition, as discussed by Marsh *et al.* (2007b):

> When we used external comparisons of the surrounding county populations of each study plant, we observed many deficits in death from all cancers combined, [respiratory system cancers] RSC and liver cancer that were often largest among the unexposed workers, but still present among workers in the non-baseline exposure categories. This pattern of findings by exposure category in the external population based SMRs led to elevated relative rates (RRs) of disease when rates for non-baseline categories were compared to the baseline (unexposed) rates… Although RRs for the cancer sites and exposure measures considered were elevated in many non-baseline categories due to the low baseline rates, we observed no consistent evidence that RRs were positively associated with increasing exposure in any of the study plants.

EPA's responses in the 2010 Review as well as in the denial of the RFC clearly indicate a poor understanding of the underlying evidence and the criticisms raised by the study authors, peer reviewers and in the public comments. EPA's reiteration of these misconceptions in the denial and refusal to accept that the epidemiological evidence does not support the carcinogenicity of chloroprene in humans cannot go scientifically unchallenged.

3.2 Topic B: The IUR Does Not Reflect the Best Available Science or Sound and Objective Scientific Practices

EPA (2018a) asserts that it received and addressed extensive peer review and comments related to this question from DuPont and others. Despite this assertion, it appears that EPA failed to address the questions and comments raised by DuPont and others, which are reiterated and expanded upon in Ramboll's Report (DPE 2017, Exhibit 1). Importantly, new guidelines set forth by the National Research Council (NRC 2011, 2014) should be implemented in a full review of the toxicological literature. As extensively discussed in the Ramboll Report, EPA (2010a) did not appropriately weigh the toxicological evidence, concluding that chloroprene was mutagenic and as carcinogenic to humans as experimental animals, specifically the female mouse. Furthermore, by using default methodology to calculate an IUR, EPA (2010a) neglected to consider all the evidence that provides scientific support that the mouse is significantly different from the human, both in pharmacokinetics and tumor development, calling into question its relevance as an animal model. As a result, EPA (2010a) calculated a highly inflated IUR that is inconsistent with a full integration of the evidence. We provide details on each of these arguments in the following sections.

3.2.1 Topic B1: The IUR is Primarily Based on Data from the Female Mouse, which is Uniquely Sensitive to Chloroprene Exposure

3.2.1.1 RFC arguments

In the RFC, DPE asserts that EPA's (2010a) reliance on the female mouse for the calculation of the chloroprene IUR without adjustment based on PBPK modeling resulted in an overly conservative IUR because of demonstrated pharmacokinetic differences between mice and humans. Furthermore, DPE notes that there was little consistency in the relative number of tumors and tumor sites across species. In fact, even though tumors were significantly elevated with chloroprene exposure in female and male mice, no other species tested had significant increased incidences of lung tumors following chloroprene inhalation exposure. In addition, incidences of liver tumors were only significantly increased in female mice at the highest exposure level (80 ppm), with no observed increase in liver tumors in rats or hamsters following chloroprene exposure. The RFC also noted that "in the study by Trochimowicz *et al.* (1998), there were few statistically significant increases in tumor incidence, no statistically significant trends observed with increasing concentration, and, in hamsters, only a small proportion of animals (20% or less) had any observed tumors." The NTP (1998) and Trochimowicz *et al.* (1998) study results indicate that there are substantial differences across species and the mouse appears to be more responsive to chloroprene exposures.

Despite the near lack of evidence of increased tumor formation associated with chloroprene exposure in any animal model except for the mouse (and greatest in the female mouse), EPA did not address these profound observed differences across species in deriving the IUR.

3.2.1.2 EPA response

EPA (2018a) notes that "In accordance with the EPA Guidelines for Carcinogen Risk Assessment (2005), in the absence of data to the contrary, EPA utilizes the most sensitive species and sex in estimating cancer risk to humans, which in the case of chloroprene, is the female mouse." (US EPA, 2018a). EPA (2018a) also takes issue with the RFC comments regarding the female mouse as being uniquely sensitive to chloroprene by pointing to results presented by Yang *et al*. (2012) in Tables 3 and 4, in which the authors reported that metabolism varies between female and male mice, with the male mouse having a much higher Vmax and corresponding internal dose. EPA (2018a) notes, however, that the tumor response is equivalent between the female and male mouse.

3.2.1.3 Ramboll response

EPA (2018a) did not address DPE's argument that the mouse response to chloroprene is significantly different from that of other laboratory animals and humans and therefore that the IUR based on mice that is unadjusted for these differences overestimates risk to humans. Instead, EPA (2018a) focused on contesting the results from Yang *et al.* (2012), a peer reviewed publication, with respect to small differences in metabolism estimates between female vs. male mice. The key issue that the EPA (2018a) did not address is that the available scientific evidence supports much larger and more significant differences in metabolism of chloroprene ***across*** species, leading to clear differences in response in different animals and in humans. This is the issue that needs to be addressed using the PBPK model to arrive at a risk estimate that is relevant to humans.

EPA (2018a) refers to 2005 cancer risk assessment guidance (US EPA 2005) as support for the selection of the female mouse as the most sensitive species. However, the 2005 guidance does not contain any language related to the selection of the most sensitive species. Earlier EPA documents do provide this type of guidance. For example, EPA, (1992)[5] states that the choice of the most appropriate data set should consider (emphasis added):

[5] https://www.epa.gov/iris/epas-approach-assessing-risks-associated-chronic-exposure-carcinogens

1. Human data are preferable to animal data;
2. In the absence of appropriate human data, ***information from an animal species whose biological responses are most like those of humans (e.g., similar metabolism) is preferable***;
3. ***In the absence of the ability to identify such a species*** or to select such data, data from ***the most sensitive animal species/strain/sex combination are given the greatest emphasis***;
4. The route of administration which most resembles the route of human exposure is used. Where this is not possible, the differences in route are noted as a source of uncertainty;
5. When the incidence of tumors is significantly elevated at more than one anatomical site by the agent, estimates of overall risk are made by determining the number of animals with tumors at one or more of these sites;
6. Benign tumors are generally combined with malignant tumors, unless the benign tumors are not considered to have potential to progress to the associated malignancies of the same historgenic origin [see McConnell et al. (1986) for guidance].

The 2005 cancer guidelines (US EPA 2005) also cite the 1994 EPA guidelines for the derivation of the inhalation reference dose (RfC), which is consistent with EPA (1992). These guidelines (US EPA 1994) note the following:

> Although it is preferable to use human studies as the basis for the dose-response derivation, adequate human data are not always available, often forcing reliance on laboratory animal data. Presented with data from several animal studies, the risk assessor first seeks to identify the animal model that is most relevant to humans, based on comparability of biological effects using the most defensible biological rationale; for instance, by using comparative metabolic, pharmacokinetic, and pharmacodynamic data. In the absence of a clearly most relevant species, however, the most sensitive species is used as a matter of science policy at the EPA.

Both of the above EPA sources stress that the risk assessor should first determine which species is most similar to humans (*e.g.*, based on pharmacokinetics) before defaulting to the most sensitive species. Point #2 in EPA (1992) above is particularly important to consider because, contrary to EPA's finding of "no evidence to the contrary," there are significant data summarized in Section 3.3 of the 2010 Review (US EPA, 2010a) and briefly below, which indicate that the oxidation metabolism of chloroprene to a reactive intermediate is faster in the mouse than other species (including humans); however, hydrolysis (the detoxification of the chloroprene metabolite) is much slower in the mouse compared to other species. Specifically, EPA (2010a) notes "Chloroprene oxidation in lung microsomes was much greater (approximately 50-fold) for mice compared with the other species." In addition, EPA (2010a) further notes that "mice generally metabolized chloroprene into its epoxide metabolite at equal or faster rates than other species and hydrolyzed the epoxide more slowly may" (US EPA, 2010a). This conclusion demonstrates a scientific understanding that the mouse is different from other species, including humans, and calls for a pharmacokinetic (or other appropriate) correction. Importantly, in the absence of such a correction, and following EPA guidelines for selection of an appropriate species, the mouse would be an inappropriate choice for deriving an IUR for chloroprene due to the recognized pharmacokinetic differences between mice and the humans.

Evidence supporting DPE's position that the mouse-derived IUR overestimates human response to chloroprene is provided by Himmelstein *et al*. (2004b), who demonstrated that there was no dose-response relationship when air concentrations from animal chambers (the administered dose) were used, whereas when the internal dose (total metabolism of chloroprene in the lung to a reactive

intermediate) was used (obtained from the PBPK model) that adjusts for differences in pharmacokinetics between species, Himmelstein et al. (2004b) reported a dose-response was observed with relation to the observed incidence of lung tumors. The results are summarized Table 1. This table shows results that demonstrate that the differences in pharmacokinetics can clearly explain the differences in response in the mouse.

Table 1. Exposure-Dose-Response for Rodent Lung Tumors

	Exposure concentration (ppm)	PBPK internal dose [a]	Lung tumor incidence	Number of animals	Extra risk (%)[b]
Hamster	0	0	0	100	0
	10	0.18	0	97	0
	50	0.88	0	97	0
Wistar rat	0	0	0	97	0
	10	0.18	0	13	0
	50	0.89	0	100	0
Fischer rat	0	0	3	50	0
	12.8	0.22	3	50	0.3
	32	0.55	6	49	7.7
	80	1.37	9	50	14.0
B6C3F1 mouse[d]	0	0	15	50	0
	12.8	3.46	32	50	48.3
	32	5.30	40	50	70.4
	80	7.18	46	50	89.9

(a) Internal dose - average daily mg Chloroprene metabolized/g lung tissue (AMPLU).
(b) The incidence data were corrected for extra risk equal to (Pi – Po)/(1 –Po), where P is the probability of tumor incidence in "i" exposed and "o" control animals (Himmelstein *et al*. 2004b).
(c) Male Syrian hamster and Wistar rat data from Trochimowicz *et al.* (1998).
(d) Male Fischer rat and B6C3F1 mouse data from Melnick *et al*. (1996).

EPA's (2010a) selection of the female mouse was questioned by some expert external peer reviewers with regard to the relevance to humans, given the substantial evidence that mice metabolize chloroprene very differently than other species, including human (US EPA, 2010a pg. A-14, Versar 2010). For example, Dr. Morris, an expert in inhalation toxicology, noted:

> If tumors are to be combined, then the human relevance of each tumor type must be considered. As noted above, in my view, some skepticism is appropriate relative to the quantitative importance of mouse bronchiolar tumors. The mode of action includes metabolic activation as the first step. The metabolic activation rates in the mouse exceed those in other species by 50-fold (Table 3-4). Clearly this is a critical observation relative to quantitative risk extrapolation. This pattern of mouse vs. human bronchiolar metabolism is certainly not unique to chloroprene. The large differences in mouse vs. human relative to pulmonary activation raise questions as to the relevance of the mouse lesions. (Versar 2010)

Similarly, Dr. Schlesinger commented that EPA "may want to consider the fact that metabolic activation rate in the rat is closer to that occurring in humans than is the situation in mice." (Versar 2010)

EPA responded that "Additional mouse and human metabolic and toxicokinetic data (Himmelstein et al., 2004a; Himmelstein et al., 2004b) added to the document indicated that the metabolic differences between humans and mice are not as great as previously represented in the document." (US EPA, 2010a) as support for using the mouse model. However, this contradicts direct quotes from the 2010 Review as noted above, and misrepresents the data as shown in Table 1. Further, EPA provides little explanation for this new finding, which was not subjected to peer review.

EPA (2018a), which relies on the peer-review process to support its 2010 IUR value, does not acknowledge the fact that the peer reviewers repeatedly questioned EPA's selection of the mouse for the derivation of the IUR anywhere in its denial.

Additionally, Dr. Morris (Versar 2010) noted the following:

> I don't know if it is possible, but some comparison of the unit risk versus the observed tumor risks in the worker populations would seem warranted. Is it possible to estimate an upper bound risk from the human data? Alternatively, is it possible to project human occupational risks from the unit risk factor to determine if the unit risk factors are consistent with epidemiologic observations? I recognize that only crude comparisons could be made, but a large discordance would be a cause of concern.

In response to Dr. Morris' comment, EPA (2010a) presented a calculation of the estimated number of cancers that would be expected in the occupational cohort based on exposure estimates from Marsh *et al.* (2007 a,b) studies, using the Louisville plant as an example. In its calculation, however, EPA incorrectly used a composite IUR for male mice (1.4×10^{-4} per $\mu g/m^3$), which is 3.5 times lower than the final recommended and upwardly adjusted IUR that EPA developed for chloroprene based on female mice (5×10^{-4} per $\mu g/m^3$). In addition, EPA estimated the total number of expected cancer cases by the number of workers with a known cause of death (2,282 workers) rather than the total number of *exposed* workers in the plant (5,468 workers), which is the number of workers that would be at risk for developing cancer from chloroprene exposure. As a result, EPA's calculation underestimated the upper bound of cancer cases at approximately 300, which EPA (2010a) claimed was consistent with the observed number of cancer mortality cases reported in the Marsh *et al.* (2007 a,b) Louisville cohort (*i.e.*, 283 deaths due to either respiratory or liver cancer).

In contrast, by using the appropriate numbers in the risk calculation, you get a considerably higher upper-bound cancer risk estimate. That is, if the final EPA (2010a) recommended IUR (5×10^{-4} per $\mu g/m^3$) is used and the lifetime exposures are adjusted by 70, the expected cancer cases for the Louisville worker population (using the total number of at risk workers) would be 2,594 cancer cases (approximately 9 times more than the 300 cases EPA incorrectly calculated). Clearly, the IUR predicts a much higher occupational cancer risk than the 298 combined number of lung and liver cancer deaths reported in the Marsh *et al*. (2007a,b) studies, and is even much higher the total number of all cancer mortality cases observed in the full cohort (652 cases). This demonstrates that the 2010 EPA IUR is a highly inflated value because is greatly overestimates cancer risk when applied to estimates of occupational exposures to chloroprene and compared to actual observed cancers in the occupational cohort in the highest quality epidemiological study. The results from a similar analysis included in the Ramboll Report in which the recommended IUR was applied, also demonstrated that the IUR is greatly inflated and predicts a much higher risk of cancer mortality based on estimated occupational exposures from the Marsh *et al.* (2007b) study than those actually observed in the exposed worker population.

Importantly, although there may be differences in sensitivity to chloroprene across gender within a species, there are clearly much larger differences in response across species, and this is the key factor that needs to be addressed in the development of a chloroprene IUR. The large differences are not only in the relative number of tumors observed in mice, rats and hamsters, but there are also differences related to the tumor site. The clear evidence of pharmacokinetic differences related to the metabolism of chloroprene and detoxification of the chloroprene metabolite help explain the tumor data.

3.2.2 Topic B2: The IUR Rests on the Unwarranted Assumption that Different Tumor Types are Statistically Independent

3.2.2.1 RFC arguments

EPA (2010a) recommended a composite IUR that was based on multiple tumor types, rather than selecting the most sensitive species, gender, and target site (*i.e.,* the female mouse lung). This approach is based on the assumption that different tumor types are statistically independent. The underlying data do not demonstrate mechanistic or biological independence. That is, the mechanism of action in multiple tissues could be due to dependent events; for example, a liver tumor could be dependent on the generation of the same metabolite that leads to the development of a lung tumor.

Furthermore, EPA's assumption of tumor types as independent tumors led EPA to consider individual animals multiple times if they had multiple types of tumors and this approach significantly contributes to the overstatement of carcinogenic risks of chloroprene.

3.2.2.2 EPA response

EPA (2018a) cites the NRC (1994) report Science and Judgment in Risk Assessment as providing results supporting this multi-tumor approach from a study that was conducted to assess the degree of statistically significant correlations between tumors in standard National Toxicology Program (NTP) chronic bioassays. In conducting an evaluation of the available data from NTP bioassays, the NRC (1994) concluded that there was little evidence of tumor-type correlations for most tumor-type pairs. EPA (2018a) uses the results from this evaluation as justification for the development of a composite IUR based on the incidence of multiple tumor types observed in the female mouse.

3.2.2.3 Ramboll response

As noted by EPA (2018a), an analysis of statistical independence was not conducted with the chloroprene-specific data to support the use of a multi-tumor approach. This approach only adds to the already overly conservative chloroprene IUR. This method also deviates from the standard methodology that EPA has employed for many other chemicals in IRIS assessments, and is inconsistent with their own cancer risk assessment guidance (as it cited) in which the default approach is to use the most sensitive species and site, absence any relevant data to suggest differences between the animal model and humans.

However, we have shown above that there is substantial evidence that the mouse is unique with regards to its response to chloroprene exposure compared to other species based on NTP tumor findings, as well as findings of significant pharmacokinetic differences. Yet EPA not only selected the mouse as the most sensitive species as the basis of the IUR, without adjustment for key pharmacokinetic differences, but added the multi-tumor analysis, inflating the IUR further, without

evidence to support this assessment. As discussed in the Ramboll Report, this approach not only inflates the IUR further, but adds a large amount of uncertainty, particularly considering the species differences.

Importantly, EPA (2010a), without considering other possibilities, assumes that chloroprene has a single mutagenic mode of action (MOA), which suggests a lack of independence across tumors. In fact, this multi-tumor approach results in counting the incidence of multiple tumors in the same animal as if each were an additional animal contributing to the estimate of risk, inflating the cancer risk estimate. In the case of tumors of the lung, this would suggest that chloroprene is delivered systemically and then travels to the lung for metabolism or is systemically delivered, metabolized in one organ, such as the liver, and the toxic moiety (*i.e.,* the reactive intermediate metabolite) travels back to the lung where it causes tumor growth. This argument is inconsistent with the understanding of the pharmacokinetics of chloroprene and with an independent effect.

Given the lack of evidence of cancer in humans, lack of concordance with respect to overall tumor response and tumor site concordance among different animal species and between animals and humans, this added level of conservativism is not scientifically supported.

3.2.3 Topic B3: The IUR Rests on the Assumption that Chloroprene has a Mutagenic Mode of Action, But the Available Evidence Does Not Support that Assumption

3.2.3.1 RFC argument

EPA (2010a) applied an age-dependent upward adjustment factor based on the hypothesis that chloroprene has a mutagenic MOA. The available evidence, however, does not support a mutagenic MOA for chloroprene. An evaluation consistent with the NRC (2011, 2014) recommendations indicates that chloroprene's genotoxicity profile lacks several attributes necessary to conclude that it operates via a mutagenic MOA, including negative findings from an *in vivo* test of genotoxicity and lack of consistent findings of point mutation induction in *in vitro* and *in vivo* studies.

3.2.3.2 EPA response

EPA's response notes that the external peer reviewer panel unanimously agreed with the proposed MOA. EPA (2018a) also notes that the studies that Ramboll cites support a mutagenic MOA (e.g., Himmelstein et al., Yang et al., Allen et al.).

3.2.3.3 Ramboll response

EPA (2018a) did not address any of the RFC's substantive points regarding the mutagenicity of chloroprene.

As discussed in detail in the Ramboll Report, the evidence for a mutagenic MOA is equivocal at best. Importantly, the NTP (1998) study that EPA (2010a) relies on for deriving the IUR, and one that is considered the gold standard, reported that chloroprene was not mutagenic in any of the tests that were performed. As noted by NTP (1998):

> Chloroprene was not mutagenic in any of the tests performed by the NTP. No induction of mutations was noted in any of four strains of *S. typhimurium* in the presence or the absence of S9 metabolic activation enzymes, and no induction of sex-linked recessive lethal mutations was observed in germ cells of male *melanogaster* treated with chloroprene via feeding or injection. In male mice exposed to chloroprene by inhalation for 12 days over a 16-day period, no induction of chromosomal aberrations, sister chromatid exchanges, or micronucleated erythrocytes in bone marrow or peripheral blood occurred. Results of a second micronucleus assay in male and female mice after 13 weeks of exposure to chloroprene via inhalation were also negative.

As stated by EPA (2018a), the external peer reviewer panel agreed with the proposed MOA. However, as noted above, several commented on the need to conduct a risk assessment to compare the IUR to results from epidemiological studies to justify such an elevated IUR. Specifically, Dr. Morris commented that "If, however, it is concluded that a metabolite represents the ultimate toxic species, then the quantitative risk assessment should be discussed/validated in light of the large species differences in metabolism rate." (Versar 2010).

In addition, as discussed in detail in the Ramboll Report, there are clear differences in mutagenicity of 1,3-butadiene and chloroprene, despite EPA's assertion of a similar MOA based on chemical similarities. In addition, mutagenicity is not confirmed *in vivo* for chloroprene, and several of the positive findings *in vitro* are likely due to aged chloroprene.

With respect to EPA's (2018a) assertion that the studies that Ramboll cites support a mutagenic MOA (Himmelstein *et al.,* Yang *et al.,* Allen *et al*.), all of these studies were conducted under the assumption of the proposed MOA, but all use the appropriate extrapolation methods (*i.e*., PBPK model) to account for clear differences in the metabolism of animals *vs*. humans. In addition, although mutagenicity may be one plausible MOA, other MOAs may be as likely (*e.g.,* cytotoxicity) and could be relevant at different exposure concentrations.

3.2.4 Topic B4: The IUR Must Be Corrected by Employing the PBPK Model to Sufficiently Account for Differences in Mice and Humans

3.2.4.1 RFC argument

Because of the differences in tumor incidence between the female mouse and other species, as well as the lack of evidence for a mutagenic MOA, it is important to evaluate the pharmacokinetics to understand if differences across species may explain the differences in response. Himmelstein *et al*. (2004 a, b) developed a chloroprene PBPK model to explain the divergent results observed across species. The model integrated the available quantitative data regarding the metabolism of chloroprene in mice, rats, and hamsters following inhalation exposure.

In comparing external concentrations and internal dose metrics, Himmelstein *et al.* (2004 a, b) demonstrated a greater correspondence between the amount of metabolized chloroprene in lung tissue (internal dose) and the tumor incidence results observed across species than results based on inhaled concentrations (external concentrations). This finding supports a MOA for chloroprene that involves the generation and detoxification of metabolites responsible for incidence of tumors in animals, and because different animals metabolize and detoxify chloroprene at different rates, toxicity across species differs. Himmelstein *et al.*'s (2004 a, b) results demonstrate that the differences in

metabolism of chloroprene in the mouse compared to humans may explain the differences in response across species.

EPA (2010a) explained that it did not use the PBPK model developed by Himmelstein *et al.* (2004 a, b) because the data required to validate the model had not been published among other reasons. However, all of the quantitative data necessary to refine and verify the critical parameters for the existing peer-reviewed PBPK model for chloroprene (Himmelstein *et al.* 2004b) were available at that time and could have been applied to adjust the cancer unit risk to account for species-specific target-tissue dosimetry.

3.2.4.2 EPA response

EPA raises concerns about the Himmelstein *et al*. (2001 a,b; 2004 a,b) model, and the application of this modified model in Yang *et al*. (2012) and Allen *et al.* (2014) studies.

3.2.4.3 Ramboll response

Two expert external peer reviewers, with knowledge on the topic, commented on the usefulness of a PBPK model with respect to human risk projection. Specifically, Dr. Morris noted that "PBPK modeling would be a highly appropriate way to incorporate kinetic data into the risk assessment." (Versar 2010) Similarly, Dr. Hattis noted that "The PBPK model may well be considered not sufficiently tested against human data for un-caveated application to human risk projection, but I think its implications should at least be explored for sensitivity analyses." (Versar 2010) Indeed, a sensitivity analysis that employed the PBPK estimates would have shown a very large difference in the estimated IUR based on the appropriate correction of the mouse data. While the remaining external peer reviewers did not explicitly comment on this issue, PBPK modeling is likely outside their area of expertise.

Even though PBPK modeling and toxicokinetic analysis are integral to the risk assessment process, EPA did not specifically address either the PBPK model issue or the general issue of differences in metabolism of chloroprene across species in the peer review charge questions. Indeed, Dr. Morris commented that "It is interesting that there are no charge questions relating to the toxicokinetics of chloroprene." (Versar 2010).

Ramboll is currently working to provide EPA with a working PBPK model in the R platform, which will serve to verify the PBPK results from Yang *et al.* (2012) and Allen *et al*. (2014) and address the concerns that EPA has raised in the response to the RFC related to the application of the published PBPK model in the estimation of an IUR for chloroprene. The details of the PBPK model development are attached to this RFR.

As discussed in detail in the Ramboll Report, as well as in comments submitted by Dupont, there is substantial support for use of a PBPK model, including:

- Significant and documented species differences in metabolism
    - The peer-reviewed literature (Munter *et al*. 2007a, b; Himmelstein *et al*. 2004 a,b; Cottrell *et al*. 2001) show that there are significant differences in metabolism of chloroprene across species that impact target tissue dose.
    - Based on the proposed MOA for chloroprene, which is dependent on the generation of a metabolite, the Human Equivalent Concentrations (HECs) should incorporate species differences in metabolism.

- Analyses support the use of the physiologically based pharmacokinetic (PBPK) model
    - Based on the peer-reviewed PBPK model (Himmelstein *et al*. 2004b), internal dose for the lung was calculated and applied in a dose-response analysis of lung tumors, and this showed a better correlation between the incidence of lung tumors and internal dose, compared to external exposure concentrations. This supports an association between the target tissue dose estimated by the model and the observation of lung tumors in mice and rats.
- New Data presented at the time of the Draft Review further provided support the use of the PBPK model including:
    - Time-course data for chloroprene in blood
    - New probabilistic analysis using PBPK model results (*in vitro* chloroprene metabolism in liver and lung microsomes of female mice and rats, in kidney microsomes of male and female mice and rats, and mixed-gender pooled kidney microsomes from humans) and epidemiological data (published by Allen et al. 2014)
    - New genomics information provides evidence of differences in response across species (mice and rats) that reflects more than just kinetic differences in the production and retention of reactive metabolites (published in Thomas et al. 2012).

3.2.5 Topic B5: The Correct Chloroprene IUR is 156 Times Lower than the Chloroprene IUR Derived by EPA

3.2.5.1 RFC argument

Ramboll recalculated the IUR to correct the scientific deficiencies identified in the RFC. Specifically, Ramboll used PBPK model results to account for species-specific pharmacokinetic differences. Based on this approach, Ramboll calculated an IUR of 3.2 x 10-6 per µg/m^3 (which is of the same order of magnitude as the IUR derived by Allen *et al.* (2014), and 156 times lower than EPA's IUR. This IUR yields an ambient target concentration of 31.2 µg/m^3, 156 times higher than EPA's proffered value.

3.2.5.2 EPA response

EPA's (2018a) response was that it "concluded that the PBPK model available at the time of the assessment was inadequate for calculation of internal dose metrics or interspecies dosimetry extrapolations for a number of reasons, including the lack of sensitivity analyses to indicate whether chamber loss of chloroprene was sensitive to metabolism, the fact that chamber data were fit by varying alveolar ventilation and cardiac output, and the lack of blood or tissue time-course concentration data."

3.2.5.3 Ramboll response

Ramboll recalculated the IUR using standard EPA methodologies and the results from the peer-reviewed publication by Yang *et al*. (2012) to calculate an IUR that properly accounts for clear differences in pharmacokinetics between the female mouse and humans. The corrected IUR is consistent with epidemiological and toxicological findings that clearly show there are important differences between animals and humans that need to be accounted for in the derivation of an IUR. Based on recent publications such as Allen *et al*. (2014), as well as all of the supporting evidence that

was highlighted in the Ramboll Report and briefly summarized here, it is clear that if EPA is to use animal data, particularly the mice data, a dose adjustment based on a PBPK model is needed. Without this adjustment the cancer risk from chloroprene exposures in humans is grossly overstated.

Ramboll will address EPA's concerns regarding the PBPK model as outlined in a workplan provided to the EPA.

3.3 Topic C: EPA's IUR for Chloroprene is Drastically Higher Than IURs for Similar Chemicals

3.3.1 RFC argument

EPA's (2010a) IUR for chloroprene is significantly higher than IURs for similar chemicals. Although the differences do not directly demonstrate that the 2010 chloroprene IUR is incorrect, it provides a "reality check" and a basis for additional scrutiny. The difference in the 2010 chloroprene IUR and those of similar chemicals translates into differences between technologically feasible and infeasible emission control technologies.

The IURs for several known carcinogenic compounds are 1 to 2 orders of magnitude lower than the chloroprene IUR, and are supported by stronger human epidemiological evidence (1,3-butadiene and benzene) or reflect the application of PBPK modeling to extrapolate results from animals to humans (vinyl chloride). In addition one of EPA's stated reasons for characterizing chloroprene as a "likely" human carcinogen is the structural similarity between chloroprene and "known" carcinogens, like vinyl chloride and 1,3-butadiene.

3.3.2 EPA response

EPA (2018a) notes that the IUR differs among chemicals because of the mechanisms underlying potency of chemicals to produce cancer is known to vary depending on factors such as chemical structure, bioavailability, and metabolic profiles and capacities of tissue types and species.

Also, EPA (2018a) notes that the IURs for other chemicals identified in the RFC, i.e., 1,3-butadiene, benzene and vinyl chloride, are different from that derived for chloroprene because of differences in the nature and extent of epidemiological and toxicological available for each chemical. These chemicals have structural similarities that support the EPA conclusion that chloroprene is likely to be a carcinogen in humans.

3.3.3 Ramboll response

Despite documented differences in mutagenicity, EPA (2010a, 2018a) draws similarities between chloroprene and 1,3-butadiene as support for the carcinogenicity of chloroprene. While it is true that IURs will likely differ depending on the underlying mechanisms for carcinogenicity, if there are similarities in MOA between two chemicals that are structurally similar, it would be very surprising to have an order of magnitude or more difference in the IUR.

The chloroprene IUR, the carcinogenicity of which is decidedly not supported by the epidemiology evidence, is in fact much higher than the IURs of similar compounds that are associated with stronger evidence of human carcinogenicity (e.g., benzene, vinyl chloride). As Dr. Gibb pointed out in his peer-review comments, "It is interesting . . . that the inhalation unit risk estimate for chloroprene is an order of magnitude higher than the inhalation unit risk estimate for butadiene which is considered a structural analog and characterized by EPA as carcinogenic to humans." He added, "A reality check on

the unit risk for chloroprene by comparing it with an upper bound on the cancer risk in the Louisville cohort studied by Marsh et al. should be performed. The Louisville cohort has the best exposure information for this purpose. From the resulting comparison, it may be necessary to adjust the unit risk estimate." (Versar 2010) As discussed above (Section 3.2.1), such a "reality check" clearly indicates that the IUR is vastly inconsistent with the observed number of cancers in occupational studies. EPA did not address this particular comment in its response.

All the supporting evidence as presented in the Ramboll Report, as well as based on the results from Himmelstein *et al*. (2004a, b) and Allen *et al.* (2014) indicates that the IUR should be at least 100 fold lower than the current 2010 recommended IUR. A considerably lower IUR would also be more consistent with IURs for similar carcinogens, as shown in Table 2.

Table 2. Summary of Potentially Carcinogenic Compounds by IUR Listed in IRIS

Chemical Name	US EPA WOE	Year	IARC WOE	Year	IUR per µg/m3	MOA	Basis of IUR/ Endpoint	Strength of Epidemiology Evidence
Chloroprene	LH	2010	2B	1999	0.0005	M*	Mouse/ multiple	Limited
Acrylamide	LH	2010	2A	1994	0.0001	M*	Rat/ thyroid	Limited
Polychlorinated biphenyls	B2	1996	2A	2013	0.0001		Rat/liver	Very limited
1,3-Butadiene	CH	2002	1	2012	0.00003		Human/ leukemia	Strong (high exposures)
Formaldehyde	B1		1		0.000013		Human/ nasal	Moderate (high exposures)
Vinyl chloride	CH	2010 Draft	1	2012	0.0000088		Rat/liver	Moderate (high exposures)
Benzene	CH	2003	1	2012	0.0000078		Human/ leukemia	Strong (high exposures)
Trichloroethylene	CH	2011	2A	2014	0.0000041	M*	Human/ kidney	Moderate
Epichlorohydrin	B2	1988	2A	1999	0.0000012		Rat/ kidney	Very limited
Tetrachloroethene	LH	2012	2A	2014	0.00000026		Mouse/ liver	Limited for bladder/NHL/ MM

US EPA (2005): CH - carcinogenic to humans; LH - likely to be carcinogenic; US EPA (1986): A - human carcinogen; B1 - probable carcinogen, limited human evidence; B2 - probable carcinogen, sufficient evidence in animals; IARC (1 - carcinogenic; 2A - probably carcinogenic; 2B - possibly carcinogenic); M* - mutagenic; NHL- non-Hodgkin lymphoma; MM – multiple myeloma

3.4 Topic D: EPA's Classification of Chloroprene as "Likely to be Carcinogenic to Humans" Should Be Reviewed

3.4.1 RFC argument

EPA should reconsider the cancer classification for chloroprene. In the 2010 Review, EPA characterized chloroprene as "likely to be carcinogenic to humans" based on:

(1) statistically significant and dose-related information from the NTP (1998) chronic inhalation bioassay data demonstrating the early appearance of tumors, development of malignant tumors, and the occurrence of multiple tumors within and across animal species;
(2) evidence of an association between liver cancer risk and occupational exposure to chloroprene;
(3) suggestive evidence of an association between lung cancer risk and occupational exposure;
(4) a proposed mutagenic mode of action (MOA); and
(5) structural similarities between chloroprene and known human carcinogens, 1,3-butadiene and vinyl chloride.

Three of the five criteria, however, are based on EPA's misinterpretation of the underlying data. Further, the last criterion (structural similarities with known human carcinogens) is not informative because chloroprene likely has a different MOA. In sum, based on the limited evidence remaining to support the potential carcinogenicity of chloroprene. As noted in the Ramboll Report "a more appropriate classification of chloroprene is suggestive evidence of carcinogenic potential."

3.4.2 EPA response

EPA noted that it fully addressed this issue during the development of the 2010 Review, and the classification had the support of the peer reviewers. Specifically, the EPA denial (2018a) states that the external peer reviewers "unanimously concluded that EPA's characterization of chloroprene as "likely to be carcinogenic to humans" was appropriate and clearly justified based on the animal and genotoxicity data."

3.4.3 Ramboll response

Ramboll questioned the classification of "likely to be carcinogenic to humans" based on a lack of clearly supportive epidemiological evidence and a full integration of the evidence indicating differences in chloroprene metabolism , which explains the differences in response to chloroprene exposures across animal species and between animals and humans. EPA external peer-reviewers also disagreed with EPA's interpretation of the epidemiological data, as discussed in Section 3.1. Because EPA's determination that chloroprene is a "likely" human carcinogen is based in part on its misinterpretation of the epidemiologic data, EPA should withdraw and re-evaluate that determination.

3.5 Topic E: EPA's Reference Concentration (RfC) for Chronic Inhalation Exposure Should Be Reviewed

3.5.1 RFC argument

The RfC calculated by EPA and published in the 2010 Review is likely to be inaccurate for the same reasons as the IUR. That is, EPA did not use a PBPK model to adjust the RfC to account for different species' differing response to chloroprene. PBPK methods have been used to derive appropriate RfCs for other relevant chemicals, including vinyl chloride.

As discussed in the Ramboll Report, the RfC reflects the application of unwarranted conservative adjustments. For instance, EPA applied an uncertainty factor of 3 to account for database deficiencies related to the lack of a 2-generation reproductive study. This adjustment should not be applied because a 1-generation study adequately provides the evidence of any potential reproductive effects following exposure to chloroprene.

3.5.2 EPA response

EPA again notes that it fully addressed this issue during the development of the 2010 Review, which was subject to peer review. EPA points to detailed responses of the external peer review panel on issues related to the suitability of the 2-year NTP study for RfC derivation (Charge Question 4, page A-4), choice of endpoints on which to basis the derivation of the RfC (Charge Question 5, page A-5), the use of Benchmark Dose modeling for RfC derivation (Charge Question 6, page A-7), and the rationale for the selection of the uncertainty factors for the derivation of the RfC (Charge Question 7, page A-9).

3.5.3 Ramboll response

Given the differences in sensitivity to chloroprene exposures between animals and humans, it is worth revisiting the RfC to assess whether some adjustment for these differences is needed for noncancer endpoints.

As detailed below, peer reviewers voiced concerns regarding the selection of endpoint, the assumption EPA used to calculate the RfC, and the application of uncertainty values. In response, EPA made substantial revisions to the RfC calculation that, it appears, were never peer reviewed. In fact, because of the substantial changes made to the RfC calculation, OMB staff questioned why EPA did not seek approval of the final draft document from the external peer reviewers (OMB 2010).

Several reviewers questioned EPA's approach for deriving the RfC and the assumptions EPA made in deriving the RfC. For example, Dr. Hattis noted that "The saturation of metabolism to the active metabolites could be clarified with the use of the PBPK model mentioned earlier." He also "agree[d] with some of the other reviewers that the RfC should be derived using the procedures for a category 3 rather than a category 1 vapor." Similarly Dr. Melnick noted that "The characterization of chloroprene as a Category 1 gas and the application of a dosimetric adjustment factor for portal-of-entry effects have not been adequately justified." (Versar 2010)

Dr. Morris stated "I do not concur with the approach used to derive the POD-HEC. Multiple POD-HEC values were derived for differing lesions and the most sensitive was then selected. I note that the POD values (prior to DAF correction) for all the lesions are virtually identical, spanning 2.1-8.3 mg/m3 range. The only reason the POD-HEC is lower for the nasal lesions is that the DAF is so low. Thus, the selection of the nasal lesions as the most sensitive response is simply an artifact of the DAF (RGDR) calculation and not based on the primary experimental observations." He also stated "In my view, the assumption that chloroprene is a category 1 gas is also flawed (see below)." (Versar 2010)

On the selection of uncertainty factors Dr. Morris noted that "Discussion should also be included on the basis for inclusion of a database limitation uncertainty factor as a multi-generation study is available. It should be stated if this is policy-based rather than scientifically-based decision." (Versar 2010) EPA (2010a) responded that "The Appelman and Dreef van der Meulen (1979) study was an unpublished report in which F0 and F1 rats were exposed to chloroprene. However, this study did not involve the mating of the F1 generation, so developmental effects to the F2 generation could not be assessed." However, Dr. Hattis commented that "The only area of modest controversy might be the choice of a database uncertainty factor of 3. This seems adequately justified by the absence of a two-generation reproductive study, although the negative findings for teratogenesis and dominant lethal effects could have been considered an adequate substitute." (Versar 2010) Therefore, at least two expert reviewers considered EPA's addition of the database uncertainty factor of 3 was not justified.

Overall, several of the peer reviewers took issue with the EPA methodology for deriving the RfC and the assumptions EPA applied to arrive at that RfC. One reviewer advocated for the use of a PBPK model. As a result, EPA substantially changed the approach and selection of critical endpoints for use

in calculating the RfC, although EPA did not apply PBPK model results. In response to the EPA's change in the RfC methodology, OMB staff noted, "As this is a large scientific change, EPA may want to consider a quick external review of this new choice. (We note that the previous IRIS process included a step where EPA went back to the external reviewers using a quick letter review approach to ensure that the expert reviewers were comfortable with the way their comments were addressed. Such an approach may be appropriate here)." (OMB, 2010) To our knowledge no such additional external review was performed on the 2010 Review.

Overall, for the same reasons that we question the methods used to derive the IUR, the RfC requires re-evaluation by EPA. We also challenge EPA's assertion that the RfC published in the Final 2010 Review received full external peer review based on the fact that substantial changes to the assumptions that went into that calculation were made after the peer review process was complete.

4 COMMENTS ON EPA RESPONSE: ATTACHMENT 2

EPA (2018b) conducted what it calls a "systematic review" of the literature available since the publication of the 2010 Review. This review was conducted to identify relevant publications that would impact the results from the review previous literature. EPA's (2018b) review included use of the population, exposure, comparator, and outcome (PECO) framework and study quality evaluation (sensitivity and risk of bias) for individual studies. Of 182 studies identified in the literature search, 7 studies were considered for further evaluation. Of these studies, there were no animal studies, one (irrelevant) epidemiology study that included analysis of ambient hazardous air pollutant exposures and breast cancer risk (Garcia *et al.,* 2015), three studies related to PBPK and dose-response modeling (including the key Allen *et al.,* 2014 and Yang *et al*., 2012, an irrelevant study by Eckert *et al.,* 2013), and three mechanistic studies (Thomas *et al*., 2013; Guo and Xing *et al*., 2016 and Wadugu *et al.,* 2010).

In the sections below, we discuss the limitations associated with this review by EPA (Section 3.1) and address specific critiques by EPA (2018b) of the two key new studies published since the 2010 Review that support the application of a PBPK model to correct the chloroprene IUR, namely Yang *et al*. (2012) in Section 3.2 and Allen *et al*. (2014) in Section 3.3.

4.1 Limitations of EPA's Systematic Review

The systematic review conducted by EPA was inadequate for a number of reasons:

a) It limited its focus to studies published after the 2010 Review. Little new relevant research has been conducted to evaluate the health impacts, including carcinogenicity of chloroprene, since the 2010 Review. The true need as stated in the RFC was a proper systematic review of the entire body of evidence, most of which predates the 2010 Review.
b) The systematic review assumes that the prior evaluation of the epidemiological literature was done correctly, but we note many deficiencies in EPA's evaluation of the evidence in the 2010 Review (Section 3).
c) EPA did not fully consider the validity of the new research – including the analysis of Yang *et al.* 2012 and Allen *et al.* 2014, two peer-reviewed publications that substantially bolstered the importance of applying species adjustments to the chloroprene IUR.
d) EPA included studies in their review that were irrelevant, such as the epidemiological study by Garcia *et al.* (2015).

4.2 Comments regarding EPA's Critique of the Yang et al. (2012) Study

Chloroprene PBPK modeling results for mice, rats, and humans are reported in Yang *et al*. (2012). Specifically, the internal dose estimates associated with the concentrations administered to both mice and rats in the NTP (1998) study are provided, including gender-specific internal tissue doses, *i.e*., the average amount of chloroprene metabolized per day per gram of lung (AMPLU), based on the PBPK model. These internal doses represent the concentration of the proposed toxic moiety (*i.e*., the chloroprene metabolite) identified by EPA (2010a) as the key carcinogenic metabolite. The Yang *et al*. (2012) analysis showed that mice had the greatest amount of chloroprene metabolized per gram of lung, followed by rats and then humans.

EPA raised a number of issues related to the Yang *et al*. (2012) study including:

- Technical (available code): EPA noted that the model codes from the Yang *et al*. (2012) publication are not published or publicly available and are necessary for EPA to conduct quality assurance and quality control review.

Scientific (biological basis) and technical (parameters): EPA noted some discrepancies in the female and male lung metabolism and internal doses in Yang *et al.* (2012) and that there were possible errors in model optimization for kidney metabolism.

- Technical (MCMC/statistics): EPA raised concerns regarding underestimation of uncertainty and overestimation of the significance of differences in parameters between species and sexes
- Technical: model validation *vs*. *in vivo* data

Ramboll disagrees with EPA's criticism of the Yang *et al*. (2012) peer-reviewed model, especially in light of the degree to which the IUR overestimates risk based on a full integration of the evidence. In other words, even a PBPK model that is associated with some degree of uncertainty would yield an IUR that is more relevant to human exposures than using the default methodology that EPA employed.

Nevertheless, to satisfy EPA's request for the model code, Ramboll developed a workplan that includes reproducing the model code and transferring the code to the "R" platform that EPA prefers so that EPA can run and verify the model. Other biological and technical issues raised by EPA will also be addressed as part of the model testing and by conducting additional sensitivity and uncertainty analyses.

4.3 Comments regarding EPA's Critique of the Allen et al. (2014) study

As with Yang *et al.* (2012) study, EPA (2018b) raised concerns regarding the analysis conducted by Allen *et al*. (2014). Allen *et al.* (2014) combined the results from the most recent PBPK models for chloroprene (Yang *et al.* 2012) with a statistical maximum likelihood approach to test commonality of low-dose risk across species. Using this method, Allen *et al*. (2014) evaluated the difference between risk estimates obtained using external (chamber air concentrations) and internal dose (calculated with the PBPK model) metrics. The PBPK model for chloroprene incorporates data regarding species differences in metabolism of chloroprene, and allows species-specific estimation of internal exposure metrics, specifically the amount of chloroprene metabolized per gram of lung tissue. By using this model, IURs can then be compared across species based on equivalent internal exposure metrics rather than external air concentrations measured outside of the body. This is critical consideration when the toxicity of a compound is related to how the compound is metabolized in animals *vs*. humans.

Allen *et al*. (2014) found that for chloroprene, external concentration-based estimates were not appropriate for calculating and comparing cancer risks across species. As discussed in the Ramboll Report (DPE 2017, Exhibit 1), epidemiological studies related to occupational exposures to chloroprene must also be considered in evaluating the unit risk estimate. These epidemiological studies provide little or no scientific support for the hypothesis that human and animal low-dose risks were equivalent when expressed as a function of air concentrations. In contrast, by accounting for the daily amount of chloroprene that is metabolized per gram of tissue at the target site for different species, the PBPK results provided a substantially better fit of the models to the data. Importantly, the differences in internal dose across species explained the greater responses in mice (Himmelstein *et al*. 2004b), compared to the lack of evidence of carcinogenicity in humans.

As noted by EPA (2018b), the dose-response analysis by Allen *et al*. (2014) only incorporated female mouse data, because this was the most sensitive species/gender. In the Ramboll workplan we include an additional analyses of the male mouse metabolic parameters to address any EPA (2018b) concerns regarding these data.

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Exhibit F

Request for Reconsideration
Denka Performance Elastomer LLC

Critical Review of US EPA Epidemiologic Review of Chloroprene Carcinogenicity Underlying the 2010 Toxicological Review of Chloroprene and EPA's Denial of Denka Performance Elastomer LLC's Request for Correction (RFC #17002)

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Shaping the Future

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I. INTRODUCTION AND PURPOSE OF MEMO

Denka Performance Elastomer LLC (DPE) requested that Cardno ChemRisk provide a review of the epidemiological data underlying the EPA Integrated Risk Information System (IRIS) 2010 Toxicological Review of Chloroprene ("2010 Review") and the EPA January 25, 2018 denial ("the Denial") of Denka Performance Elastomer LLC's Request for Correction (# 17002). On behalf of Cardno ChemRisk, Dr. Gary Marsh and Dr. Natalie Egnot prepared this memorandum. The curriculum vitae of the authors are included as Attachments 1 and 2 to this memorandum.

Overview of Memo Contents and Conclusions

- The epidemiological literature regarding chloroprene exposure and cancer mortality reviewed by the US EPA in the 2010 Review consists of evidence from seven independent worker cohorts, four of which were included within the most comprehensive and definitive study on this topic: the 2007 University of Pittsburgh study of workers from the US, Ireland, and France who were occupationally exposed to chloroprene.

- The University of Pittsburgh study did not identify statistically significant elevations in all-cancer, lung cancer, or liver cancer deaths among workers exposed to chloroprene compared to the appropriate national or regional population rates.

- Similarly, no statistically significant evidence of a positive trend between the duration or level of chloroprene exposure and liver cancer was observed among workers in this rigorous study.

- EPA incorrectly concluded in the 2010 Review that the University of Pittsburgh study revealed evidence of a dose-response relationship between cumulative chloroprene exposure and liver cancer mortality risk. This conclusion was based on EPA's misinterpretation of certain risk values that were inflated by inordinately low liver cancer mortality rates in the baseline category used to calculate relative risks.

- EPA's assertion of a dose-response relationship for chloroprene and liver cancer starkly contrasts the University of Pittsburgh study authors' conclusion that the study provided no evidence of such an exposure-response relationship.

- Overall, the available epidemiological evidence provides no consistent or credible evidence of chloroprene carcinogenicity in humans.

II. BACKGROUND AND OVERVIEW OF MARSH ET AL. 2007 CHLOROPRENE STUDY

In the early 2000s, I, Dr. Gary Marsh, along with colleagues at the University of Pittsburgh and collaborators from the University of Illinois and University of Oklahoma, conducted the largest and most comprehensive historical cohort study of industrial workers exposed to chloroprene. The study, which specifically investigated mortality due to malignant and non-malignant causes among workers exposed to chloroprene and vinyl chloride, included 12,430 individuals employed at one of two U.S. industrial sites (Louisville, KY (n=5,507) or Pontchartrain, LA (n=1,357)) or two European sites (Maydown, North Ireland (n=4,849) or Grenoble, France (n=717)). Investigators from the University of Illinois and University of Oklahoma conducted a comprehensive retrospective exposure assessment of chloroprene, and the results of that assessment were linked to the epidemiological data from the worker cohorts in order to evaluate exposure-response relationships for lung and liver cancer. We computed standardized mortality ratios (SMRs) comparing mortality rates among the chloroprene-exposed workers to the age-sex-race-time-specific mortality rates of national and regional reference populations. We also conducted internal mortality comparisons (worker to worker comparisons) for liver and lung cancer in relation to duration and level of chloroprene exposure.

This comprehensive and definitive study (referred to as the University of Pittsburgh or UPitt) study was designed to address the major limitations of prior studies regarding the health effects of chloroprene exposure, including but not limited to small sample size, inadequate exposure assessment, and questionably appropriate reference rates of cancer mortality for the regional or national population. The results of UPitt study were reported in 2007 in a series of publications in the peer-reviewed journal, *Chemico-Biological Interactions* (Esmen et al. 2007a; Esmen et al. 2007b; Hall et al. 2007; Leonard et al. 2007; Marsh et al. 2007b, 2007a).

Ultimately, the results of the UPitt study did not identify any elevated risks of cancer, including liver and lung cancers, among the cohort of chloroprene-exposed workers. In fact, my colleagues and I identified statistically significant overall *deficits* (that is, a smaller than statistically expected number of deaths) in mortality from all-cancers among the cohorts of workers when compared to the national or corresponding regional population. Specifically, when compared to their corresponding regional populations, we consistently identified overall deficits in both liver and lung cancer mortality rates among workers in the Louisville cohort (17 deaths, SMR=0.90 95% CI=0.52-1.44, and 252 deaths, SMR=0.75 95% CI=0.66-0.85, respectively), Maydown cohort (1 death, SMR=0.24 95% CI=0.01-1.34, and 43 deaths, SMR=0.78 95% CI=0.56-1.05, respectively), and Grenoble cohort (1 death, SMR=0.56 95% CI=0.01-3.12, and 4 deaths, SMR=0.47 95% CI=0.13-1.20, respectively) (Marsh et al. 2007a). No cases of liver cancer were identified among workers in the Pontchartrain cohort; therefore, SMRs for this outcome could not be calculated for workers in this facility. However, similar to the other study sites, we observed a deficit in lung cancer mortality when comparing the Pontchartrain cohort to the regional population (10 deaths, SMR=0.55 95% CI=0.26-1.00) (Marsh et al. 2007a).

We conducted additional analyses of certain subgroups, including only those workers who had been exposed to chloroprene. Across all plants, deficits in all-cancer mortality (806 deaths, SMR=0.71 95% CI=0.66-0.76), lung cancer mortality (330 deaths, SMR=0.75 95% CI=0.67-0.84) and liver cancer mortality (17 deaths, SMR=0.71 95% CI=0.42-1.14) were observed among the exposed workers. The deficits for all-cancer and lung cancer were statistically significant. Among liver cancer cases identified within the Louisville cohort (n=17), we conducted an exposure-response analysis to evaluate possible trends in liver cancer mortality risk associated with increasing chloroprene exposure. This analysis could only be conducted within the Louisville cohort because no cases of liver cancer were identified within the entire Pontchartrain cohort, and the investigation of the Maydown and Grenoble cohorts identified only one confirmed liver cancer case at each site. The exposure-response analyses revealed no statistically significant elevations in liver cancer mortality risk among individuals at any level of chloroprene exposure, and revealed no evidence of any statistically significant trends in liver cancer mortality risk relative to three metrics of chloroprene exposure (duration of exposure, average intensity of exposure, and cumulative exposure).

III. CRITIQUE OF EPA EVALUATION AND INTERPRETATION OF STUDIES PUBLISHED PRIOR TO UPITT STUDY

In their 2010 Toxicological Review of Chloroprene, the EPA authors reviewed epidemiological studies conducted among seven worker cohorts from Armenia (Bulbulyan et al. 1999), China (Li et al. 1989), France (Colonna et al. 2001; Marsh et al. 2007b, 2007a), Ireland (Marsh et al. 2007b, 2007a), Russia (Bulbulyan et al. 1998), and the US (Marsh et al. 2007b, 2007a; Leet et al. 1982), each of which included individuals who were occupationally exposed to chloroprene. The authors of the 2010 Review made several critical errors when evaluating the studies published prior to the UPitt study. First, two of the studies considered in the 2010 Review assessed mortality among workers from the same facility that eventually constituted the Louisville cohort within the UPitt study (Leet et al. 1982; Pell 1978). The results of these studies were inappropriately considered as independent of the UPitt study within the 2010 Review even though the UPitt study included members of the prior cohorts and was specifically designed to address limitations of these studies. Second, the epidemiological studies published before the UPitt study have substantial limitations in terms of study design and analytical methods, many of which were identified in the 2010 Review's evaluation of these studies. Despite acknowledging these limitations, the authors of the 2010 Review utilized the considerably flawed epidemiological literature published prior to the UPitt study to support their conclusion that chloroprene is "*likely to be carcinogenic*" in humans (US EPA 2010b). Third, when interpreting the epidemiological evidence used to support their conclusions regarding chloroprene carcinogenicity, the authors of the 2010 Review gave many of the poorer quality studies the same weight as the more robust UPitt study.

The 2010 Review should not have treated the Leet and Selevan study as independent of the UPitt study. In 1982, Leet and Selevan reanalyzed the data collected from the DuPont Louisville facility by Pell et al. in 1978 using a modified life-table analysis, and identified a statistically significant elevation in liver/biliary cancer (4 deaths, p=0.01) among exposed workers. No statistically significant trends were identified in regard to latency or duration of chloroprene exposure. The Leet and Selevan findings were based on a crude, qualitative exposure assessment, and suffered from small sample sizes within stratified analyses. The UPitt study provided an updated and more thorough analysis of the Louisville cohort that had previously been evaluated by Leet and Selevan. The 2010 Review states that "*sufficient differences between these two studies investigating the Louisville cohort warrant independent analyses of each*" (US EPA 2010; pp.A-13). The differences in analytical approaches between these two studies do not supersede the fact that their subjects are not independent. Further, the UPitt study employed a more methodologically rigorous analytical strategy when evaluating the cohort of Louisville workers. Because these two studies included overlapping members of the same cohort and the UPitt study provided a more rigorous evaluation of these participants, it was not appropriate for the EPA to include the Leet and Selevan study in their evaluation of chloroprene carcinogenicity.

The remaining cohort studies of chloroprene and cancer mortality that the EPA considered in the 2010 Review suffer from substantial limitations such as a lack of an appropriate comparison group for effect estimate calculation, weak exposure assessment, and small sample size particularly in stratified analyses, all of which were addressed in the design of the 2007 UPitt study. For example, Li et al. published the results of a cohort mortality study of Chinese chloroprene-exposed workers in 1989 that lacked representative mortality rates to which the cohort could be compared, and conducted only a qualitative exposure assessment (Li et al. 1989). Specifically, although mortality follow-up was conducted from 1969-1983, local age- and sex-specific rates used to calculate SMRs were obtained only from 1973-1975. Similar to the Chinese study, Bulbulyan et al. utilized local liver cancer incidence and mortality rates from only two years (1992-1993) in order to calculate SMRs for liver cancer among a Russian cohort although mortality follow-up lasted from 1979-1993 (Bulbulyan et al. 1998). Internal-comparison analyses were conducted based on a qualitative assessment of chloroprene exposure, duration of high exposure, and cumulative exposure. These analyses suffered from very small sample sizes, and imprecise risk estimates. For example, the only statistically significant result among these internal comparisons was an elevated relative risk (RR) of liver cancer (RR=45) based on only one observed case of liver cancer among those with 20+ years of high chloroprene exposure resulting in a 95% confidence interval ranging from 2.2-903.

Bulbulyan et al. also conducted a mortality study among an Armenian cohort of chloroprene-exposed workers which suffered from the same limitations as the Russian study, and resulted in similarly imprecise risk estimates due to small sample size (Bulbulyan et al. 1999). More recently, Colonna and Laydevant conducted a cohort study of chloroprene exposure and cancer incidence among workers at the Isere/Grenoble facility evaluated in the UPitt study (Colonna et al. 2001). This study collected cancer incidence data from 1979-1997 and utilized cancer incidence rates from a local registry for the same time period in order to facilitate comparisons. Only one case of liver cancer was identified among the cohort and no statistically significant elevations in incidence of all-cancers, lung cancer, or liver cancer were observed within the cohort.

Ultimately, despite the substantial limitations of the studies published prior to the UPitt study, the authors of the 2010 Review gave the results of these studies equal consideration to the results of the UPitt study when forming conclusions regarding the epidemiological evidence of chloroprene carcinogenicity. The UPitt study overcame the limitations of the earlier studies by including a greater number of participants, conducting a more rigorous and comprehensive exposure assessment, and using appropriate comparison groups for the calculation of SMRs. The UPitt study included more participants than all other studies conducted on this topic combined, and included more than 350,000 person-years of follow up. Moreover, the 2007 study utilized age-sex-race-time-specific mortality rates from appropriate comparison populations (national, regional, and internal), and included detailed data on participant demographic, work history and chloroprene exposure information that was lacking in the other cohorts. Therefore, the authors of the 2010 Review should have given the conclusions of the UPitt study greater weight than the other studies published on this topic when considering the epidemiological literature. Instead, the EPA's conclusion that chloroprene is *likely carcinogenic in humans* based on the epidemiological literature is reliant on the limited and biased studies published prior to the UPitt study.

IV. EPA'S MISREPRESENTATION OF UPITT EXPOSURE-RESPONSE ANALYSIS FOR LIVER CANCER

The authors of the 2010 Review also grossly misrepresented the results of the UPitt historical cohort study in their 2010 Report. Specifically, the 2010 Review focused on a limited series of results from the UPitt study based on internal comparisons among workers at the Louisville plant, and others based on comparisons among DuPont workers nationally. Our serious concerns about how the US EPA interpreted and reported the UPitt study results are described in further detail below.

The 2010 Review suggests that the results of the UPitt study provide evidence in support of an exposure-response trend between chloroprene exposure and liver cancer. Specifically, Appendix A of the 2010 Review states, "*Although no statistically significant increase in risk of liver cancer was detected in the most recent and comprehensive cohort study involving workers at four plants (Marsh et al., 2007), the observed RR [of liver cancer] increased with increasing cumulative exposure in the plant with the highest exposure levels, indicating a dose-response trend* " (US EPA 2010b). The US EPA authors obtained these results from a limited exposure-response analysis based on a total of only 17 liver cancer deaths observed in the Louisville cohort, which was fewer liver cancer deaths than statistically expected based on regional rates. Only two liver cancer deaths were observed among the other UPitt study sites combined. The Table below shows the relevant results from the Louisville cohort in the UPitt study.

Table: Exposure-response analysis for chloroprene and liver cancer by exposure metric. Louisville plant, relative risks (RR) and standardized morality ratios (SMR). From Marsh et al. 2007b.

Metric[a]	Observed Deaths	Internal Rate Analysis			External Rate Analysis[b]	
		Non-cases[c]	RR[d] (95% CI)	p-value	Person-Years[e]	SMR (95% CI)
Duration of Exposure (years)						
<10	6	1500	1.00	Global=0.24	131,276	0.61 (0.22-1.32)
10-19	4	216	3.85 (0.76-17.09)	Trend=0.36	30,404	2.08 (0.57-5.33)
20+	7	965	1.75 (0.49-6.44)		36,239	0.99 (0.40-2.04)
Average Intensity of Exposure[f]						
<3.6216	3	714	1.00	Global=0.22	69,274	0.62 (0.13-1.80)
3.6216-8.1245	7	568	3.81 (0.77-25.76)	Trend=0.84	27,933	1.73 (0.70-3.56)
8.1246-15.99	3	388	1.84 (0.22-15.74)		28,689	0.94 (0.19-2/74)
16.0+	4	1011	1.31 (0.20-10.07)		72,023	0.59 (0.16-1.52)
Cumulative Exposure[g]						
<4.747	2	744	1.00	Global=0.17	68,918	0.43 (0.05-1.55)
4.747-55.918	3	725	1.90 (0.21-23.81)	Trend=0.09	56,737	0.59 (0.12-1.74)
55.919-164.052	7	653	5.10 (0.88-54.64)		39,840	1.62 (0.65-3.33)
164.053+	5	559	3.33 (0.48-39.26)		32,424	1.00 (0.33-2.34)

[a] Decimal places of cut points reflect precision needed for computational purposes only and not precision of exposure assessment
[b] Local county rates
[c] The number of persons in decedent's risk set used in calculation of RR
[d] Adjusted for sex
[e] Number of person-years used in calculation of SMR
[f] Ratio of cumulative exposure to duration of exposure (in ppm)
[g] Product of the number of dates in each job function and estimated average daily exposure (in ppm years)

The 2010 Review inappropriately and inaccurately suggests that the results of the exposure-response analysis of the Louisville cohort shown above indicate a "*dose-response trend*" between chloroprene exposure and liver cancer mortality (US EPA 2010b). As shown in the table, statistical tests of trend by increasing exposure metrics including duration of chloroprene exposure, average intensity of chloroprene exposure, and cumulative chloroprene exposure were performed and were consistently not-statistically significant. Moreover, none of the risk estimates based on exposure-response metrics appeared to have a monotonic, or consistent, positive relationship with liver cancer risk based on statistical tests of trend. The interpretation of these results provided in the 2010 Review is in stark contrast to the interpretation provided by the UPitt study authors: "*Although RRs for the cancer sites and exposure measures considered were elevated in many non-baseline categories due to the low baseline rates, we observed no consistent evidence that RRs were positively associated with increasing exposure in any of the study plants*" (Marsh et al. 2007b).

The not statistically significant elevation in RRs observed from the UPitt exposure-response analysis for liver cancer among the Louisville cohort can be attributed largely to the fact that the lowest exposure groups for each exposure metric, which served as the baseline category for the calculation of the RRs, had unusually low mortality rates of liver cancer. These inordinately low baseline rates are demonstrated by the large deficits in lung cancer mortality when each of the exposure groups is compared to the regional population. Specifically, the SMRs among the least exposed, or baseline groups, in terms of

duration of chloroprene exposure, average intensity of chloroprene exposure, and cumulative chloroprene exposure, were 0.61, 0.62, and 0.43, respectively. These inordinately low mortality rates in the baseline category create the impression of large excesses in risk among persons in the non-baseline categories. For example, the 5.1-fold elevation in liver cancer risk for workers in the third highest cumulative exposure category (7 deaths, RR=5.10, 95%CI=0.88-54.64) reflects the fact that persons in that exposure category had a moderate, not statistically significant 1.62 fold rate of liver cancer (SMR = 1.62, 95% CI=0.65-3.33) compared with the regional standard population, and these workers were compared with workers in the baseline category who had a 57% deficit in liver cancer mortality based on the regional comparisons (SMR = 0.43, 95% CI=0.05-1.55). Thus, an internal comparison of these two groups results in an apparent but misleading greater than five-fold excess in liver cancer mortality.

Internal comparisons are an effective method of addressing healthy worker bias, which particularly affects risks of death from non-malignant causes such as cardiovascular disease or all-cause mortality. However, as illustrated above, risk estimates obtained from internal comparisons must be interpreted with caution as they may produce misleading estimates of mortality risk if workers in the baseline exposure category used to calculate internal RRs have an inordinately low (or high) risk of mortality compared with workers in the non-baseline groups. This phenomenon was addressed in a 2007 publication regarding this study, and has been observed and discussed in other cohort studies of workers exposed to acrylonitrile and formaldehyde (Marsh et al. 2007b; Marsh et al. 2001; Marsh et al. 2014). However, this explanation of the elevated RRs obtained from the exposure-response analysis was not discussed within the 2010 Review. It is also worth mentioning that this internal comparison analysis was conducted only among liver cancer cases from the Louisville cohort (n=17), and number of deaths in each of the exposure categories ranged from only 2 to 7. The small sample size evaluated within this portion of the analysis resulted in imprecise risk estimates as shown by the wide confidence intervals. The 2010 Review thus should not have given such large weight to unremarkable and not statistically significant results obtained from a limited exposure-response analysis of liver cancer conducted in only one study site in the UPitt study.

V. EPA'S MISINTERPRETATION OF DUPONT EMPLOYEE INTERNAL COMPARISONS AND HEALTHY WORKER EFFECT IN UPITT STUDY

In 2007, Leonard et al. published the results of an internal mortality analysis comparing chloroprene-exposed workers from the Louisville and Pontchartrain facilities to regional and national samples of DuPont workers along with the series of publications regarding the UPitt study. There were no statistically significant elevations in liver cancer mortality among the Louisville workers compared to other DuPont workers regionally (SMR=1.21; p>0.05) or nationally (SMR=1.27; p>0.05) (Leonard et al. 2007). Again, because no cases of liver cancer were observed among workers in the Pontchartrain facility, risk estimates for this outcome could not be determined.

The 2010 Review highlighted statistically significant elevations in all-cancer and respiratory cancer mortality that were observed when comparing workers from the Louisville cohort to a national sample of DuPont workers. When compared to DuPont workers regionally, only SMRs for all-cause mortality and lung cancer mortality remained significantly elevated in this cohort. The increase in SMRs observed in these specific analyses was not unexpected. Some of the increase in SMRs can be attributed to regional variation, while a reduction in healthy worker bias also likely played a role, particularly in regard to the all-cause mortality outcome. However, the health worker effect is unlikely to have influenced the results related to malignant causes such as lung and liver cancers due to their relatively sudden onset, short survival time, and high case-fatality rate (Enterline 1976). Ultimately, these results provide evidence that workers may more strongly reflect their local and regional populations rather than a more widely dispersed population of workers in terms of their mortality experience.

Interestingly, the 2010 Report does not mention that exposure-response SMRs for all-cancer and lung cancer were also calculated comparing the Louisville cohort to DuPont workers regionally, and the results were, with few exceptions, not statistically significant. Instead, evidence suggesting that there was no clear consistent positive trend across the increasing exposure groups was ignored by the 2010 Review. It is also worth mentioning that 48 effect estimates were reported in the Leonard et al. paper, which should be considered within the context of the series of six epidemiological publications that reported results of

the UPitt study. These results were not adjusted based on the fact that multiple statistical comparisons were made as part of this investigation. Therefore, it is misleading for the EPA to put such weight on these few statistically significant estimates comparing the Louisville workers to DuPont workers nationally when the vast majority of results obtained from this study were consistently null.

VI. CRITIQUE OF EPA CONCLUSIONS BASED ON BODY OF EPIDEMIOLOGICAL LITERATURE

a. Application of Bradford Hill Causal Criteria

According to the 2010 Review, Bradford Hill causal criteria were utilized to assess the body of epidemiological literature as recommended by the EPA Guidelines for Carcinogenic Risk Assessment (Hill 1965; US EPA 2005). The EPA, however, did not apply the Hill criteria to the epidemiological studies of chloroprene exposure in a uniform or consistent way, rather their selective application of Hill criteria was misleading and overstated the evidence of a relationship between chloroprene and cancer mortality. A description is provided below of the selective Hill criteria with which US EPA misrepresented the epidemiological evidence or inappropriately inflated the results (strength of association, consistency, specificity, and biological gradient).

Strength of Association

When describing the strength of association between chloroprene exposure and liver cancer mortality, the 2010 Review predominately relied upon risk estimates reported from the methodologically flawed studies described within section 1.2 of this critique (Bulbulyan et al. 1998; Bulbulyan et al. 1999; Leet et al. 1982; Li et al. 1989). The authors of the 2010 Review ignored the results from the UPitt study suggesting that there was no elevated risk among chloroprene-exposed workers compared to national or regional reference populations within this section of the 2010 Review. Instead, the authors discussed the not statistically significant elevation in risk among select exposure groups when workers with higher levels of exposure were compared to those with low exposure levels as though they were statistically significant.

As discussed in Section 1.2.1 of this critique, only 17 deaths from liver cancer were observed among the Louisville cohort and were therefore included in the exposure-response analysis. In fact, some of the exposure subgroups discussed by the US EPA authors comprised only two individuals, which resulted in imprecise risk estimates and wide confidence intervals (Marsh et al. 2007b). Further, as noted above in Section 1.2.1 the elevated RRs observed in this analysis were primarily driven by the fact that the individuals in the lowest exposure or baseline groups had exceedingly large deficits in liver cancer mortality compared to what would be expected in the general regional population. Therefore, the EPA's argument that the epidemiological evidence demonstrates a strong association between chloroprene exposure and liver cancer is flawed due to its reliance on biased studies and the misinterpretation of UPitt study results.

Consistency and Specificity

The US EPA authors also incorrectly asserted that the epidemiologic evidence of a consistent and specific relationship between chloroprene exposure and liver cancer was observed among four independent epidemiological studies (Bulbulyan et al. 1998; Bulbulyan et al. 1999; Leet et al. 1982; Li et al. 1989). First, the effect estimates calculated within these limited studies vary tremendously with some of the significant estimates only identified in sub-analyses of small groups with the highest exposure (Li et al. 1989) or only among participants of one gender (Bulbulyan et al. 1998). Next, the Leet and Selevan study is not independent of the UPitt study, and therefore, should not be considered in the evaluation of the epidemiological literature as a whole. Lastly, the UPitt study included more person-years of observation than the four prior studies combined, and consistently reported no evidence of an association between chloroprene exposure and liver cancer among four worker cohorts. For these reasons, it is inaccurate for the EPA to say that there is consistent evidence of an association between chloroprene exposure and liver cancer.

Biological Gradient

When describing the epidemiological evidence of a biological gradient, or exposure-response relationship, between chloroprene exposure and liver cancer, the US EPA cites the 1999 Bulbulyan study, which conducted only a crude exposure assessment, did not account for confounding factors, and ultimately did not find a statistically significant trend of increased liver cancer risk among those with the highest chloroprene exposure (Bulbulyan et al. 1999). The US EPA authors also cited the UPitt study, claiming that elevated risks among the individuals with the highest exposures were reported. Again, contrary to the EPA's conclusions, there were no statistically significant elevations in liver cancer risk among any of the exposure groups. Furthermore, the highest risk estimates were not even among the individuals in the highest exposure groups (RR=3.85 for 10-19 years exposure vs. RR=1.75 for 20+ years exposure) indicating that a consistent trend between greater chloroprene exposure and increased liver cancer risk was not observed.

b. Failure to Address Peer Review Comments

Our observation that the 2010 Review greatly exaggerated the epidemiological evidence of an association between chloroprene exposure and liver cancer 2010 Review is echoed by the reviewer comments to the US EPA's original draft of the 2010 Review. Specifically, Dr. Herman Gibb, an epidemiologist who served on the peer review panel, stated in his comments to the EPA that the "*document overstates the human evidence*" and that the 2010 Review is not "*transparent in its reasoning that there is a risk of liver cancer*" in regards to the epidemiological data (US EPA 2010a). The epidemiologic evidence of chloroprene carcinogenicity remains overstated and in many cases misrepresented in the final version of the 2010 Review. Due to the nature of the peer review process utilized by the EPA, the US EPA authors were not required to incorporate all reviewer comments and suggestions prior to publication. Therefore, it appears as though concerns, such as Dr. Gibb's, were left unaddressed within the final 2010 Review. In particular, the EPA did not change its conclusion that the epidemiological data provides evidence of a dose-response relationship in different cohorts in different continents, which Dr. Gibb stated "*grossly misrepresents the evidence*" (US EPA 2010a).

VII. CONCLUSION

In conclusion, we maintain strongly that there is no consistent or credible epidemiological evidence of chloroprene carcinogenicity in humans. It is clear that the EPA based their conclusion on evidence from substantially flawed studies and a misinterpretation of the more rigorous UPitt study. Not only does the body of epidemiological literature not support this conclusion, but it is also not consistent with the International Agency on Cancer Research (IARC), which has classified chloroprene as "*possibly carcinogenic to humans*" (IARC 1999). In their 1999 monograph, IARC determined that there was *inadequate evidence* of the carcinogenicity of chloroprene in humans. This classification was determined even before the definitive UPitt study reported that there was definitively no evidence of a relationship between chloroprene exposure and cancer mortality across four worker cohorts.

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> MS, Biostatistics, University of Pittsburgh, 1974
> BS, Mathematics, University of Pittsburgh, 1973

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> Fellow of the American College of Epidemiology

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Summary of Experience

Gary M. Marsh, Ph.D., F.A.C.E. is a Consulting Senior Science Advisor for Epidemiology for Cardno ChemRisk. Dr. Marsh is also a Professor of Biostatistics, Epidemiology, and Clinical and Translational Science, and the Director of the Center for Occupational Biostatistics and Epidemiology at the University of Pittsburgh, Graduate School of Public Health. He is a Fellow of the American College of Epidemiology.

Dr. Marsh directs occupational epidemiologic studies to investigate the long-term health effects of exposure to such agents as man-made mineral fibers, formaldehyde, acrylamide, acrylonitrile, arsenic, chloroprene, tungsten carbide with cobalt binder, petrochemicals, aromatic amines and pharmaceuticals. In addition, he conducts environmental epidemiologic studies of communities exposed to industrial pollutants or to hazardous waste site materials and is involved in basic methodological research related to longitudinal data analysis and quantitative risk assessment.

Dr. Marsh has more than 250 publications in the areas of biostatistics, occupational/ environmental epidemiology, quantitative risk assessment, statistical computing and health services evaluation. He is the senior author of the computer software packages, OCMAP (Occupational Cohort Mortality Analysis Program), which is used as a standard analytic tool by more than 150 domestic and 40 foreign institutions involved in occupational health research, and RACER (Rapid Assessment and Characterization of Environmental Risks). Dr. Marsh is also developer of the original Mortality and Population Data System (MPDS), a repository and retrieval system for National Center for Health Statistics (NCHS) and U.S. Census Bureau data.

Dr. Marsh is an active member of the American College of Epidemiology, the American Statistical Association, the Biometric Society, the International Society for Environmental Epidemiology, the Society for Epidemiologic Research, the Society for Occupational and Environmental Health and the International Commission on Occupational Health.

Significant Experience

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Graduate School of Public Health

> Professor of Epidemiology (2010-present)
> Professor of Clinical and Translational Science (2010-present)
> Director and Founder, Center for Occupational Biostatistics and Epidemiology (2008-present)
> Interim Chairman, Department of Biostatistics (2007, 2009-2010)
> Professor of Biostatistics (1991-present)
> Associate Professor of Biostatistics (1984-1991)
> Assistant Professor of Biostatistics (1978-1984)
> Research Associate (1977-1978)

Center for Clinical and Translational Science

> Professor of Clinical and Translational Science (2010-present)

Center for Environmental Epidemiology

> Assistant Director (1983-1985)

School of Health Related Professions

> Adjunct Assistant Professor of Health Related Professions (1981-1983)

University of Minnesota School of Public Health

> Faculty, Graduate Summer Session in Epidemiology (1984)

Wesley Institute, Bethel Park, Pennsylvania

> Mathematics Instructor (1974-1975)

Consulting Experience

Litigation Support

Dr. Marsh has provided litigation support as both a testifying and consulting expert to in-house and outside counsel on a variety of matters including:

> Railyard work and brain cancer
> Cosmetic talc and mesothelioma
> Non-occupational asbestos exposure and mesothelioma
> Asphalt adhesive and reactive airway dysfunction syndrome (RADS)
> Fiberglass and idiopathic pulmonary fibrosis
> Ethylene oxide and breast and lympho-hematopoietic tissue cancer
> Diesel exhaust and lung cancer
> Railyard work and hemaphagocytic lympohistiocytosis (HLH)
> Firefighters and kidney cancer
> Formaldehyde in hair straightening products and lung cancer
> Electric power plant occupational exposures
> Coal preparation workers and exposure to acrylamide
> FEMA trailer residents and risks from formaldehyde exposure
> Asbestos related diseases among workers and the community near an Italian manufacturing facility
> Evaluation of possible association between PFOA exposure and adverse health outcomes
> Worker exposure to amorphous silica
> Risk of mesothelioma for brake workers
> Evaluation of occupational exposures to hydroquinone and various cancer outcomes
> Evaluation of occupational exposure and adverse effects from carbonless copy paper
> Evaluation of risk of CML in workers exposed to benzene
> Evaluation of ATSDR health studies in Libby, MT

- Evaluation of community health issues associated with waste contamination near McCullom Lake, IL
- Health effects in workers exposed to ortho-toluidine
- Risk of respiratory health effects from exposure to fibrous glass in school buses
- Risks associated with occupational exposure to formaldehyde
- Advise on cases involving latex gloves and allergies
- Evaluation of case involving anophthalmia/microphthalmia in a child with potential exposure to Benomyl

Consulting Projects in Epidemiology and Biostatistics, and Advisory Positions

Dr. Marsh has been retained by numerous private sector clients to assist and advise in the evaluation of health effects associated with a wide variety of chemical, radiological and other exposures. He also has assisted managed care organizations with evaluations of health care delivery systems. Specific examples include:

- City of St. Louis, St. Louis, MO (2015-present)
  - Expert witness on case involving city firefighter
- Monsanto, St. Louis, MO (2015)
  - Member of expert scientific panel to review and critique epidemiological studies of persons exposed to glyphosate
- American Chemistry Council, Washington, DC (2015)
  - Review of epidemiological studies of persons exposed to ethylene oxide
- inXsol, Phoenix, AZ (2012-2013)
  - Statistical evaluation of smartphone application for measuring airborne chemical exposures
- Confidential Chemical Company, PA (2011-2012)
  - Advised on epidemiological study of brain cancer among workers at a chemical manufacturing facility
- Arnold & Porter, LLP, Washington, DC (2011)
  - Advised on response to NAS report on health effects of formaldehyde
- Hollingsworth, LLP, Washington, DC (2011)
  - Presentation and discussion of formaldehyde epidemiology
- ENVIRON International Corporation, Boston, MA (2010-2012)
  - Member of advisory board to evaluate manuscript reviewing association between formaldehyde exposure and lympho-hematopoietic malignancies
  - Member of advisory board to prepare comments on EPA's draft toxicological review of chloroprene
- Confidential Specialty Chemical Company, OH (2010-2011)
  - Advised on epidemiological evidence for association between formaldehyde exposure and cancer
  - Prepare presentations for NAS meeting on formaldehyde
- Confidential Heavy Duty Vehicle Manufacturer, IL (2010-2011)
  - Advised on epidemiological evidence for association between diesel exhaust exposure and lung cancer

- Review and critique of epidemiological studies of metalworking fluids exposure and cancer outcomes

> Confidential Biotechnology Company, MO (2009-2010)
- Designed probability sample to evaluate usage patterns of Botox

> North American Insulation Manufacturers Association, Alexandria, VA (2009)
- Wrote updated review of health effects associate with exposure to man-made vitreous fibers
- Presentation at NTP meeting on health effects of man-made vitreous fibers

> International Truck and Engine Corporation, Chicago, IL (2007-2011)
- Advised on epidemiological evidence for association between diesel exhaust exposure and lung cancer

> Geyer Pathology Services, LLC, Pittsburgh, PA (2007)
- Developed sampling design for selecting lung tissue for analysis

> Burdock Group Consultants, Vero Beach, FL (2006)
- Member of expert panel to review safety status of aspartame as a non-nutrative sweetener

> Energy Networks Association, London, UK (2006)
- Member of expert panel to review epidemiological literature on health effects of EMF exposure

> CEFIC AISBL European Chemical Industry Council, Brussels, Belgium (2006)
- Reanalysis of data from NCI cohort study of formaldehyde workers

> Gateway Health Plan, Pittsburgh, PA (2005-2009, 2013-2014)
- Design and analysis of health care delivery evaluations

> Confidential Construction Equipment Manufacturer, IL (2005-2010)
- Design and analysis of epidemiology study to evaluate association between welding exposures and Parkinson's Disease

> Confidential Chemical Manufacturer, PA (2005-2007)
- Advised on community studies to evaluate potential health effects of chromium exposure
- Design and analysis of epidemiological study to evaluate suspected link between working in paint production plant and testicular cancer

> FormaCare -European Chemical Industry Council (CEFIC), Brussels, Belgium (2005-2007)
- Performed various re-analyses of data from the NCI cohort study of formaldehyde exposed workers

> Formaldehyde Council Inc., Washington, DC (2004-2010)
- Advised on various studies evaluating health effects from formaldehyde exposure

> Pressley Ridge Child Care Services, Pittsburgh, PA (2004-2006)
- Designed probability sample to evaluate effectiveness of child care services

> Semi-Conductor Industry Association, Washington, DC (2003-2010)
- Member of expert scientific panel to advise on design, analysis and operational aspects of industry-wide study of semi-conductor workers

> Academy for Educational Development, Washington, DC (2003-2008)

- Advised on design and analysis of educational effectiveness studies

> Confidential Petroleum Refining Company, IL (2003)
- Design and analysis of a refinery cohort study to evaluate cancer mortality risks

> Formaldehyde Council Inc., Washington, DC (2002-2009)
- Performed various re-analyses of data from the NCI cohort study of formaldehyde exposed workers

> W.R. Grace Company, Leesburg, VA (2002)
- Advised on Libby, MT zonolite health issue

> NIOSH, Cincinnati, OH. (2001-2007)
Follow-up Investigations of Suspected Health Effects of Exposure to Effluents from a Copper Smelter, Copperhill, TN (2001-2007)

> Confidential Pharmaceutical Manufacturer, NJ (2001-2005)
- Design and analysis of epidemiological studies of pharmaceutical production workers

> Coordinated Care Network, Monroeville, PA (2001-2002)
- Statistical evaluation of coordinated care program for persons without traditional health insurance

> Confidential Aerospace Company, CT (2001-2002)
- Advised on feasibility of conducting large-scale cohort study of jet engine manufacturing workers

> The Acrylonitrile Group, Washington, DC (2001)
- Advised on plans for AN scientific conference

> Dow Chemical Co., Midland, MI (2000-2013)
- Statistical analysis of Dow benzene cohort data
- Member of scientific advisory board for epidemiological research program

> Confidential Metal Mining Company, UT (2000-2001)
- Advised on epidemiological studies of copper and zinc smelter workers
- Review and critique of protocol to evaluate association between smelter emissions and multiple sclerosis

> The Sapphire Group, Inc., Beachwood, OH (2000)
- Third-party review and critique of ethylene oxide risk assessment draft

> New Jersey Department of Health and Senior Services, Trenton, NJ (1999-2003)
- Advised on community studies to evaluate potential health effects of residing near Toms River, NJ chemical site
- Advised on design and evaluation of mail survey of chemical exposures

> University of Texas, Houston/Baylor Medical College, Houston, TX (1999-2003)
- Member, Research Advisory Committee-advised on proposed bladder cancer screening and medical surveillance program

> Confidential Chemical Manufacturing Company, MO (1999)
- Review and critique of mortality surveillance program

> Confidential Petrochemical Company, IL (1999-2002)
- Advised design and analysis of epidemiological studies of workers exposed to acrylonitrile and nitrogen products

- Orthopedic & Reconstructive Center, Oklahoma City, OK (1999-2001)
  - Advised on study protocol to evaluate treatments for carpal tunnel syndrome
- Confidential Chemical Company, PA (1999)
  - Review and critique of studies evaluating association between plasticizers and childhood asthma
- TERRA Inc., Tallahassee, FL (1998-2003)
  - Advised on various studies evaluating health effects of chemical exposures
- Confidential Chemical Company, NJ (1998)
  - Advised on possible cancer cluster study related to company. workers
- Confidential Specialty Chemical Company, NY (1998)
  - Review and provided written critique of UAB, Tom's River Plant cohort study
- The Acrylonitrile (AN) Group, Washington, DC (1997-2005)
  - Performed reanalyses of data from NCI cohort study of acrylonitrile-exposed workers
- Dow Chemical Company & Dow Corning Corporation, Midland, MI (1999)
  - Presented seminar on application of Occupational Cohort Mortality Analysis Program (OCMAP) developed by G. Marsh
- Consultant, Chemical Industry Institute of Toxicology, Research Triangle Park, NC (1998-2002)
  - Advised on reanalyses of cohort studies of formaldehyde exposed workers
- National Academy of Sciences, Institute of Medicine, Medical Follow-Up Agency, Washington, DC (1998-2002)
  - Advised on statistical analysis of large scale cohort studies
- Health Canada, Ottawa, CA (1998)
  - Participant in workshop on health effects of formaldehyde exposure
- Highmark Blue Cross Blue Shield, Pittsburgh, PA (1997-1998)
  - Design and analysis of health care delivery evaluations
- American Industrial Health Council, Washington, DC (1997)
  - Reviewed and critiqued epidemiological studies of chemical production workers
- Confidential Chemical Manufacturing Company, NJ (1996-2012)
  - Design and development of Company Mortality Registry
  - Design and analysis of cohort study of formaldehyde exposed workers
  - Design and analysis of cohort study of kidney cancer among workers exposed to acrylonitrile
  - Design and analysis of cohort study of workers exposed to acrylamide
  - Design and analysis of proportional mortality study of aerospace materials workers
  - Development of vital status tracing protocol for non-US workers
- Confidential Building Products Manufacturer, PA (1996-2007)
  - Developed mortality surveillance program with periodic proportional mortality analyses
  - Statistical analysis of mesothelioma deaths
- Electric Power Research Institute, Palo Alto, CA (1996-2006)
  - Advised on design, analysis and operational aspects of large cohort study of electrical power workers

- Member of advisory board to develop manuscript reviewing health effects studies of persons exposed to electromagnetic fields

> Chemical Manufacturers Association, Washington, DC (1996-2001)
- Reviewed health studies of chemical production workers

> Confidential Petrochemical Company, OH (1996-2001)
- Design and analysis of historical cohort study of workers exposed to acrylonitrile

> Showa Denko America, New York, NY (1996-1997)
- Member, Research Advisory Committee-advised on health studies of persons afflicted with eosinophilia myalgia syndrome (EMS)

> Confidential Petrochemical Company, PA (1996)
- Review and critique of Beaver Valley expanded mortality study
- Reviewed health studies of refinery workers

> International Center for Health Services Research, Verona, PA (1996)
- Designed sampling plan for hospital imaging services study

> Group Health Plan, St. Louis, MO (1995-1996)
- Design and analysis of health care delivery evaluations

> Ecology and Environment, Buffalo, NY (1994-2003)
- Advised on design of health survey in Kuwait

> Consultant, HealthAmerica, Pittsburgh, PA (1990-1995)
- Design and analysis of health care delivery evaluations

Research Experience

University of Pittsburgh

Graduate School of Public Health

Since the early 1980s, Dr. Marsh has directed an academic research program focused on occupational/environmental biostatistics and epidemiology, and health services evaluation. He has received research funding from a number and variety of sources, including federal and state government, foundations, trade organizations and corporations. Specific examples include:

> Cytec Aerospace Materials, Inc. (2015-present)
- Historical cohort study of aerospace adhesive materials

> Eli Lilly and Company (2015-present)
- Update of cohort mortality study of pharmaceutical production workers

> Research Foundation for Health and Environmental Effects (2013-2015)
- Additional reevaluation of the National Cancer Institute Formaldehyde Cohort Data
- Commentary on methodological and interpretational issues in the National Cancer Institute Formaldehyde Worker Cohort Study

> Eli Lilly and Company (2013-2014)

- Feasibility study of historical cohort study of pharmaceutical production workers at the Cosmopolis, Brazil site

> INEOS Nitriles, Inc. (2012-2015)
- Historical cohort study of workers exposed to acrylonitrile and nitrogen products

> International Institute of Synthetic Rubber Producers (2011-2013)
- Use of human exposure and epidemiology data in a physiologically based kinetic modeling risk assessment for chloroprene

> The Acrylonitrile Group (2011-2013)
- Statistical methods for adjusting risk estimates for potential confounding by smoking
- Analysis of pooled data from the NCI and DuPont acrylonitrile worker cohort studies

> Mining Awareness Resource Group (2011-2012)
- Evaluation of uncertainty factors in NCI-NIOSH diesel exhaust in miners study exposure assessment and their impact on risk estimates and exposure-response relationships

> North American Insulation Manufacturers Association (2010)
- Literature review of health effects from exposure to man-made vitreous fibers

> Pennsylvania Department of Health/International Tungsten Industry Association (2007-2017)
- International historical cohort and case-control studies of workers exposed to tungsten carbide with cobalt binder

> Pratt & Whitney (2002-2013)
- Historical cohort mortality and incidence studies of jet engine manufacturing workers

> International Institute of Synthetic Rubber Producers (2000-2005)
- Historical cohort study of workers exposed to chloroprene

> Owens Corning (2000-present)
- Mortality surveillance and epidemiological support program

> Highmark Blue Cross Blue Shield (1999-2014)
- A program of biostatistical support for the quality improvement department

> Solutia, Inc. (1999-2002)
- A collaborative program of biostatistical and epidemiological support

> Pennsylvania Department of Health (1998-1999)
- Evaluation of the community health project

> The Acrylonitrile Group (1997-2004)
- A program of epidemiological and biostatistical support

> Eli Lilly and Company (1996-2009)
- Historical cohort and nested case-control studies of pharmaceutical production workers

- Health America of Pittsburgh (1994-1996)
  - A program of biostatistical support for research and clinical audit activities
- Agency for Toxic Substances and Disease Control/Arizona State Health Department (1991-1995)
  - A population based case-control study of lung cancer in Arizona smelter towns
- DuPont Company (1991-1994)
  - Enhancement, modification and update of an occupational and ecological Mortality and Population Data System
- Chemical Manufacturers Association (1991-1992)
  - Identifying and responding to human disease clusters: a practical guidance document
- DuPont Company (1991-1992)
  - A Model Program for Assessing Health Risks among Communities Near Hazardous Waste Sites
- The Formaldehyde Institute (1989-1991)
  - A reanalysis of the national cancer institute study on mortality among industrial workers exposed to formaldehyde
- The U.S. Environmental Protection Agency (1989-1991)
  - A mortality update and case-control study of workers exposed to arsenic in a copper smelter
- Chemical Manufacturers Association (1989)
  - A review and critique of ecologic analyses as an epidemiologic research method
  - Development of decision and quality control criteria for conduct of pilot and epidemiology studies by ATSDR and SARA Section 110
- American Cyanamid Company/Cytec Industries, Inc. (1987-2007)
  - Historical cohort and case-control studies of workers exposed to formaldehyde
  - Historical cohort study of workers exposed to acylamide
- Pennsylvania Department of Health/NIOSH (1986-2006)
  - Bladder cancer screening program for former workers of the Drake-Kilsdonk chemical plant exposed to beta-naphthalmine
- North American Insulation Manufacturers' Association (1985-1999)
  - Historical cohort and nested case-control studies of fiberglass and rock wool production workers
- Shell Oil Company (1983-1987)
  - Historical cohort study of refinery workers
- Smelter Environmental Research Association (1981-1986)
  - Factors associated with mortality among copper and zinc smelter workers
- Development of Occupational Cohort Mortality Analysis Program (OCMAP) (1980-present)
- Development of Mortality and Population Data System (MPDS) (1980-present)

- Monsanto Company (1980-84)
  - Historical cohort study of workers in plastics producing plant
- U.S. National Cancer Institute (1980-1982)
  - Cancer in arsenic exposed populations

Service Activities

University of Pittsburgh

Biostatistics Department

- Member, PhD Admissions Committee (2015-present)
- Member, Pittsburgh Cancer Institute (1990-present)
- Member, PhD Student Admissions Committee (2015-present)
- Faculty Associate, Center for Social & Urban Research (2000-present)
- Member, Faculty Search Committee, Department of Epidemiology (2014-2015)
- Member, Curriculum Committee (2010-2016)
- Founder & Director, Center for Occupational Biostatistics and Epidemiology (2008-present)
- Interim Chairman, Department of Biostatistics (2007, 2009-2010)
- Member, Dean's Cabinet (2007, 2009-2010)
- Chair, Committee to Evaluate Departmental Biostatistics Consulting Practicum (2006-2007)
- Chair, Committee to Evaluate Master's Comprehensive Examination (2004-2005)
- Member, Health Sciences Library Advisory Committee (1997-2003)
- Member, Faculty Advancement, Promotion and Tenure Committee (1999-2001)
- Chair, Ad Hoc Search and Appointment Committees for Associate Professor and Director Occupational Medicine, Department of Environmental & Occupational Health (1996)
- Member, Budget Policies Committee (1995-1998)
- Member Fact-finding Committee for the Performance Review of Dean Mattison (1995-1996)
- Member, International Committee to Review Graduate Program of the Civil & Environmental Engineering Department (1995)

Graduate School of Public Health

- Member, Faculty Search Committee, Department of Epidemiology (2014-2015)
- Departmental Representative, Faculty Advancement, Promotion, Tenure Committee (2012-2016)
- Departmental Chair Representative, Planning and Budget Policy Committee (2009-2010)
- Member GSPH Council (2007, 2009-2010)
- Member, Committee to Evaluate MMPH Program (2005-2006)
- Member, Committee to Develop MPH Comprehensive Examination (2000-2001)
- Member, Search Committee for Dean (1999-2000)

- Member, Search Committee for Chair of EOH Department (1999-2000)
- Member, Faculty Advancement Committee (1999)
- Member, Recruitment Committee (1997)
- President, Faculty Senate (1992-1994)
- Chair, Faculty Senate Executive Committee (1992-1994)
- Member, Strategic Planning Committee (1992-1994)
- Representative, Accreditation Committee (1992-1993)

United States and International Government

- Invited Charter Member, U.S. Environmental Protection Agency, Science Advisory Board, Asbestos Panel, Washington, DC (2008)
- Invited Member, Butadiene Risk Assessment Expert Panel, Sciences International Inc., Alexandria, VA (2006)
- Invited Member, Electromagnetic Field (EMF) Risk Assessment Expert Panel, Energy Networks Association, Edinburgh, Scotland (2006)
- Invited Member, Expert Panel to Assess Health Effects of Artificial Sweetener, Burdock Group, Washington, DC (2006)
- Member, NIOSH Scientific Advisory Panel, Proposed NIOSH Study of Health Effects of Exposure to Electromagnetic Fields (EMF), Cincinnati, OH, May 4, 2001 (2001-2003)
- Member, CDC Scientific Advisory Panel to Review Protocol for Study of Long-Term Health Effects Following Administration of Anthrax Vaccine, Atlanta, GA, May 14-15 (2002)
- Invited Member, International Agency for Research on Cancer (IARC), Working Group to Re-evaluate the Carcinogenicity of Man-Made Vitreous Fibers, Lyon, France, October 9-16 (2001)
- Invited Peer Reviewer, External Peer Review Workshop on Hazard Assessment and Dose-Response Characterization for the Carcinogenicity of Formaldehyde by Route of Inhalation. Health Canada and the U.S. Environmental Protection Agency, Ottawa, Canada, March-December (1998)
- Invited Member, Site Visit Team, Veterans Health Administration, Office of Public Health and Environmental Hazards, Environmental Epidemiology Service, March 1997, Washington, DC (1997)
- Invited Member, Committee to Review the Health Consequences of Military Service During the Persian Gulf War, National Academy of Sciences, Institute of Medicine, Medical Follow Up Agency (1994-1996)
- Guest Editor, "The First International Conference on the Safety of Water Disinfection: Balancing Chemical and Microbial Risks". International Life Sciences Institute, Health and Environmental Sciences Institute (1992-1993)
- Reviewer, "Draft Health Assessment on Inorganic Arsenic", Health and Welfare Canada, May (1992)
- Invited Participant, Workshop on Environmental Epidemiology, National Research Council, National Academy of Sciences, Washington, DC, June (1992)
- Invited Participant, Advisory Committee on ATSDR Sponsored Project, "Community Health Effects of a Hazardous Waste Incinerator", The University of South Carolina, Columbia Campus (1991-1992)

- Invited Member, Study Section on Safety and Occupational Health, Centers for Disease Control/National Institute for Occupational Safety and Health (1989-1992)
- Invited Member, National Scientific Advisory Committee, CDC, Center for Environmental Health, Atlanta, GA (1987-1991)

Professional Honors/Awards

- B.S., Cum Laude (1973)
- Adolf G. Kammer Merit in Authorship Award - Best Publication in Field of Occupational Health, American Occupational Medical Association (1981)
- Delta Omega, Public Health Honorary Society (1985)
- Tenure, University of Pittsburgh, Department of Biostatistics (1986)
- Outstanding Teacher Award, Graduate School of Public Health (1994)
- Biographical Entry in *Who's Who in Science and Engineering* (1997)
- Fellowship, American College of Epidemiology (1997)
- 50 at 50 Award, Graduate School of Public Health (selected as one of 50 outstanding contributors in field of public health in 50 year history of school) (1999)
- Biographical Entry in *Who's Who in Medicine and Healthcare* (2002)
- Biographical Entry in *2000 Outstanding Scientists of the 21st Century* (2003)
- Biographical Entry in *Who's Who in America* (2004)
- Biographical Entry in *Who's Who in American Education* (2005)
- University of Pittsburgh Innovator Award for work on OCMAP software package (2006, 2008, 2009, 2013)
- Albert Nelson Marquis Lifetime Achievement Award, Marquis *Who's Who*

Membership and Service to Professional Societies

- American Statistical Association (1974-present)
  - Secretary, Vice President, President – Pittsburgh Chapter (1979-1982)
  - National Council Representative (1981-1982)
- Biometric Society (1974-Present)
- Society for Occupational and Environmental Health (1978-present)
  - National Governing Council (1986-1989)
- Society for Epidemiological Research (1979-present)
- Pennsylvania Public Health Association (1986-1995)
  - Member, Board of Directors (1989-1992)
- International Society for Environmental Epidemiology (1988-present)
- International Commission on Occupational Health (1996-present)
- American College of Epidemiology (1997-present)
  - Fellowship (1997)
- British Occupational Hygiene Society (2001-2010)

Publications

Journal Articles

- Liu, Y., G.M. Marsh, and V.L. Roggli. 2018. Asbestos fiber concentrations in the lungs of brake repair workers: An updated analysis using several regression methods to handle non-detectable measurements. J Occup Env Med. Advance online publication, March 30, 2018. doi: 10.1097/JOM.0000000000001320.
- Marsh, G.M., A.S. Riordan, K.A. Keeton, and S.M. Benson. 2018. Response to: 'Reanalysis of non-occupational exposure to asbestos and the risk of pleural mesothelioma' by Finkelstein. Occup Env Med. Advance online publication, March 24, 2018. doi: 10.1136/oemed-2018-105020.
- Duke, T.J., P.S. Ruestow, and G.M. Marsh. 2018. The influence of demographic, physical, behavioral, and dietary factors on hemoglobin adduct levels of acrylamide and glycidamide in the general U.S. population. Crit Rev Food Sci Nutr. 58(5):700-710.
- Finley, B.L., S.M. Benson, and G.M. Marsh. 2018. Response to letters regarding "Cosmetic talc as a risk factor for pleural mesothelioma: A weight of evidence evaluation of the epidemiology." Inhal Tox. Advance online publication, Feb. 21, 2018. doi: 10.1080/08958378.2018.143850.
- Svartengren M, Bryngelsson IL, Marsh GM, Buchanich J, Zimmerman S, Kennedy K, Esmen N, Westberg H. 2017. Cancer incidence among hard metal production workers: the Swedish cohort. Journal of Occupational and Environmental Health, 59:e365-e373.
- Marsh GM, Buchanich JM, Zimmerman S, Liu Y, Balmert L, Graves J, Kennedy KJ, Esmen NA, Moshammer H, Morfeld P, Erren T, GroB J, Yong M, Svartengren M, Westberg H, McElvenny DM, Cherrie J. 2017. Mortality among hard metal production workers: Pooled cohort analysis. J Occ Environ Health, 59:e324-e364.
- Marsh, GM, A Riordan, KA Keeton and SM Benson. 2017. Non-Occupational Exposure to Asbestos and Risk of Pleural Mesothelioma: Review and Meta-Analysis. Occ Environ Med. 74:838-846, 2017.
- Westberg H, I Bryngelsson, GM Marsh, K Kennedy, J Buchanich, S Zimmerman, N Esmen and MSvartengren. 2017. Mortality among hard metal production workers: Swedish measurement data and exposure assessment. J Occ Environ Health, 59:e327-e341.
- Dabass A, Talbott E, Rager J, Marsh GM, Venkat A, Holguin F. 2018. The Association of Systemic Inflammatory Markers Associated with Cardiovascular Disease and Acute and Chronic Exposure to Fine Particulate Matter Air Pollution (PM2.5) among US NHANES Adults with Metabolic Syndrome. Environmental Research, 161:485-491.
- Finley, BL, SM Benson, and GM Marsh. 2017. Cosmetic talc as a risk factor for pleural mesothelioma: A weight of evidence evaluation of the epidemiology. Inhal Tox. 29(4):179-185.
- Benson, SM, P Ruestow, KA Keeton, RM Novick, GM Marsh, and DJ Paustenbach. 2017. The 2014 crude 4-methylcyclohexanemethanol chemical release and birth outcomes in West Virginia. Arch Env Occup Health. Advance online publication, July 10, 2017. doi: 10.1080/19338244.2017.1350132..

- Summers WK, RL Martin, Y Liu, B Pea and GM Marsh. 2017. Complex Antioxidant Single Blind Study for Memory. Aging Clinical and Experimental Research, In Press.
- McElvenny, DM, LA MacCalman, A. Sleeuwenhoek, A Davis, BG Miller, C Alexander, JW Cherrie, KJ Kennedy, NA Esmen, SD Zimmerman, JM Buchanich, GM Marsh. 2017. Mortality among Hard Metal Production Workers: U.K. Historical Cohort and Nested Case-Control Studies. Journal of Occupational and Environmental Health, 59:e275-e281.
- Westberg, H, IL Bryngelsson, GM Marsh, JM Buchanich, SD Zimmerman, KJ Kennedy, NA Esmen, M Svartengren. 2017. Mortality among hard metal production workers: Swedish Historical Cohort and Nested Case-Control Studies. Journal of Occupational and Environmental Health, 59:e263-e274.
- Morfeld, P, J Gross, T Erren, B Noll, M Wei, K Kennedy, N Esmen, SD Zimmerman, JM Buchanich, GM Marsh. 2017. Mortality among hard metal production workers: German Historical Cohort Study. Journal of Occupational and Environmental Health, 59:e288-e296.
- Kennedy, KJ, NA Esmen, SD Zimmerman, JM Buchanich, GM Marsh. 2017. Mortality among hard metal production workers: Occupational Exposures. Journal of Occupational and Environmental Health, 59:e297-e305.
- Wallner, P, M Kundi, H Moshammer, SD Zimmerman, JB Buchanich, GM Marsh. 2017. Mortality among hard metal production workers: Austrian Historical Cohort Study. Journal of Occupational and Environmental Health, 59:e282–e287.
- Marsh, GM, JM Buchanich, SD Zimmerman, Y Liu, L Balmert, NA Esmen, KJ Kennedy. 2017. Mortality among Hard Metal Production Workers: U.S. Historical Cohort and Nest Case-Control Studies. Journal of Occupational and Environmental Health, 59:e306-e326.
- Marsh, G. and S. Benson. 2017. Response to: 'Pleural mesothelioma and occupational and non-occupational asbestos exposure: A case-control study with quantitative risk assessment' by Ferrante et al. Occup Env Med. 74:156-157.
- Acquavella, JF, D Garabrant, GM Marsh, T Sorahan, D Weed. 2016. Glyphosate Epidemiology Expert Panel Review: A Weight of Evidence Systematic Review of the Relationship Between Glyphosate Exposure and Non-Hodgkin's Lymphoma or Multiple Myeloma. Critical Reviews in Toxicology. 46(Sup1):28-43.
- Williams, G, M Aardema, JF Acquavella, C Berry, D Brusick, M Burns, J De Camargo, D Garabrant, H Greim, L Kier, D Kirkland, GM Marsh, K Solomon, T Sorahan, A Roberts, D Weed. 2016. Glyphosate: Carcinogenic Potential – A Critical Review Using Four Expert Panels. Critical Reviews in Toxicology. 46(Sup 1):3-20.
- Hutter, HP, P Wallner, H Moshammer, GM Marsh. 2016. Dust and cobalt levels in the Austrian tungsten industry: workplace and human biomonitoring data. International Journal of Environmental Research and Public Health the 13:931.
- Starr, T, Marsh GM. 2016. Commentary: Methodological Challenges in the Statistical Analysis of Epidemiology Studies: Use of Average Exposure Metrics in Historical Cohort Designs. Open Medicine Journal 3:238-242.
- Dabass, A, E Talbott, R Bilonick, J Rager, A Venkat, GM Marsh, D Chunzhe and T Xue. 2016. Using Spatio-Temporal Modeling for Exposure Assessment in an Investigation of Fine Particulate Air Pollution and Cardiovascular Mortality. Environmental Research, 151:564-572.

- Dabass, A, EO Talbott, A Venkat, J Rager, GM Marsh, RK Sharma and F Holguin. 2016. Association of exposure to particulate matter (pm2.5) air pollution and biomarkers of cardiovascular disease risk in adult NHANES participants (2001–2008). International Journal of Hygiene and Environmental Health 219(3): 301-310.
- Buchanich J, Balmert L, Pringle, J, Williams K, Burke D, Marsh GM. 2016. Patterns and trends in accidental poisoning death rates in the US, 1979-2013. Preventive Medicine, Apr 13. pii: S0091-7435(16)30062-7. doi: 10.1016/ j.ypmed.2016.04.007.
- Balmert L, Buchanich J, Pringle J, Williams K, Burke D, Marsh GM. 2016. Pennsylvania patterns and trends in accidental poisoning deaths, 1979-2014. PLoS One. Mar 10;11(3):e0151655. doi: 10.1371/journal.pone.0151655. eCollection.
- Benson, SM, EO Talbott, LL Brink, WC Wu, RK Sharma and GM Marsh. 2016. Environmental lead and childhood blood lead levels in US children: NHANES, 1999-2006. Arch Env & Occ Health, DOI:10.1080/19338244.2016.1157454.
- Brink, LL, EO Talbott, GM Marsh, R Sharma, SM Benson, WC Wu and C Duan. 2016. Revisiting nonresidential environmental exposures and childhood lead poisoning in the US: Findings from Kansas, 2000–2005.J Env Public Health. http://dx.doi.org/10.1155/2016/8791686.
- Marsh, GM, P Morfeld, SD Zimmerman, Y Liu and LC Balmert. 2016. An updated re-analysis of the mortality risk from nasopharyngeal cancer in the National Cancer Institute formaldehyde worker cohort study. J Occ Med Tox, 11:8 DOI 10.1186/s12995-016-0097-6.
- Gathuru, I, D. Dolan, J Buchanich, GM Marsh. 2015. Health Hazards in the Pharmaceutical Industry: A Review of the Literature. Pharmaceutical Regulatory Affairs, http://dx.doi.org/10.4172/2167-7689.1000145.
- Ferguson, AA, RA Bilonick, JM Buchanich, GM Marsh, and AL Fisher. 2015. How well do raters agree on the development stage of caenorhabditis elegans? PLoS One 10(7):e0132365.
- Johnson, RM, T Johnson, SD Zimmerman, GM Marsh, and O Garcia-Dominic. 2015. Outcomes of a seven practice pilot in a pay for performance (P4P)-Based program in Pennsylvania. J Racial Ethn Health Disparities 2(1):139-148.
- Marsh, GM, and SD Zimmerman. 2015. Mortality among chemical plant workers exposed to acrylonitrile: 2011 Follow-Up. J Occup Environ Med 57(2):134-145.
- Zimmerman, SD, GM Marsh, AO Youk, and E Talbot. 2015. Evaluation of potential confounding by smoking in the presence of misclassified smoking data in a cohort study of workers exposed to acrylonitrile. J Occup Environ Med 57(2):146-151.
- Allen, BC, C Van Landingham, Y Yang, AO Youk, GM Marsh, N Esmen, PR Gentry, HJ Clewell, 3rd, and MW Himmelstein. 2014. A constrained maximum likelihood approach to evaluate the impact of dose metric on cancer risk assessment: application to beta-chloroprene. Regul Toxicol Pharmacol 70(1):203-213.
- Marsh, GM, P Morfeld, JJ Collins, and JM Symons. 2014. Issues of methods and interpretation in the National Cancer Institute formaldehyde cohort study. J Occup Med Toxicol 9:22.

> Talbott, EO, LL Brink, RK Sharma, GM Marsh, and JR Rager. 2014. Ecological study of the potential association between county-level air lead and childhood blood lead levels: county-based results. . Journal of Environment and Public Health 2013:1-8, http://dx.doi.org/10.1155/2013/278042.

> Brink, LL, EO Talbott, RK Sharma, GM Marsh, WC Wu, JR Rager, and HM Strosnider. 2013. Do US ambient air lead levels have a significant impact on childhood blood lead levels: results of a national study. J Environ Public Health 2013:278042.

> Kennedy, KJ, NA Esmen, RP Hancock, SE Lacey, GM Marsh, JM Buchanich, and AO Youk. 2013. Long-term health experience of jet engine manufacturing workers: VII: occupational exposures. J Occup Environ Med 55(6):676-689.

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- Marsh, G.M. 1981. Proportional mortality among chemical workers exposed to formaldehyde. Technical Report submitted to the Monsanto Company, May 15.
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- Marsh, G.M. and M.E. Preininger. 1981. *OCMAP: Occupational Cohort Mortality Analysis Program-User Manual, Version September, 1980*. Pittsburgh, PA: University of Pittsburgh.

> Marsh, G.M. 1979. Final report on the Monsanto Company Indian Orchard plant mortality study. Technical Report submitted to the Monsanto Company, December 21.

Presentations

> "Nasopharyngeal Cancer and Formaldehyde Exposure: What We Know from the Epidemiology", American Chemistry Council Conference on Health Effects from Formaldehyde Exposure, Chapel Hill, North Carolina, October 10-11, 2017.
> "The Mineralogy and Mesothelioma Epidemiology of Cosmetic Talc", The Monticello Conference, Charlottesville, VA, October17-19, 2017.
> "Mini-Symposium on the Epidemiology of Tungsten Carbide with Cobalt Binder", Coordinator and Presenter, EPICOH 2017 Conference, Edinburgh, Scotland, August 28-31, 2017.
> "Preliminary Results from the International Historical Cohort Study of Workers in the Hard-Metal Industry", Cobalt Development Institute Scientific Meeting, Kristiansand, Norway, April 19, 2016.
> "An international historical cohort study of workers in the hard-metal industry." 2014. EPICOH Conference, Chicago, IL, June 23-26.
> "Evaluating health effects of exposure to acrylonitrile: A comprehensive research program at the University of Pittsburgh." 2013. EPICOH Conference, Utrecht, Netherlands, June 18-21.
> "An international historical cohort study of workers in the hard-metal industry." 2013. EPICOH Conference, Utrecht, The Netherlands, June 18-21.
> "Formaldehyde and nasopharyngeal cancer- What do we know from the epidemiology studies?" 2012. Formaldehyde International Science Conference, Madrid, Spain, April 18-19.
> "Training workshop: Rapid assessment and characterization of environmental risk (RACER)." 2010. CDC National Environmental Public Health Tracking Conference, New Orleans, LA, April 24-26.
> "Does formaldehyde cause leukemia? Opposing viewpoint." 2010. University of Pittsburgh, Department of Epidemiology Tipping Point Seminar Series, December 2.
> "Rapid assessment and characterization of environmental risk (RACER)." 2009. CDC National Environmental Public Health Tracking Conference, Washington, D.C., February 24-26.
> "Rapid assessment and characterization of environmental risk (RACER)." 2008. Centers for Disease Control, Public Health Information Network (PHIN) Annual Meeting, Atlanta, GA, August 25.
> "An epidemiological study of mortality among a cohort of jet engine manufacturing workers." 2008. Society for Neuro-Oncology Annual Meeting, Las Vegas, NV, November 19-22.
> "A new software tool: Rapid assessment and characterization of environmental risks (RACER)." 2007. Presented at the Environmental Summit, sponsored by the GSPH Department of Epidemiology, Pittsburgh, PA, April 18.
> "Formaldehyde and human cancer risk understanding the nasopharyngeal cancer excess in Plant 1 of the NCI study." 2007. Formaldehyde International Science Conference, Barcelona, Spain, September 20-21.

- "EMF-ELF exposure potentials among magnetic particle inspections workers." 2006. International Workshop to Evaluate Future Needs of Occupational ELF Epidemiology, Edinburgh, Scotland, September 14-15.
- "Sampling, statistics and Iraq: Review and critique of two surveys conducted to estimate deaths in Iraq since 2003." 2006. GSPH Doctoral Student Association Invited Seminar, Pittsburgh, PA, December 10.
- "Mortality patterns among workers exposed to chloroprene and other substances." 2005. British Occupational Hygiene Society Annual Meeting, Manchester, England, April 19.
- "Mortality among industrial workers exposed to chloroprene and other substances: I. Methods and issues." 2005. International Symposium on Butadiene and Chloroprene, Charleston, SC, September 20.
- "Mortality among industrial workers exposed to chloroprene and other substances: II. Results." 2005. International Symposium on Butadiene and Chloroprene, Charleston, SC, September 20.
- "Overview of formaldehyde epidemiology." 2005. Toxicology Forum Annual Meeting, Brussels, Belgium, November 8.
- "Pharyngeal cancer mortality among workers exposed to formaldehyde." 2004. Toxicology Forum, Washington, DC, February 2.
- "Mortality patterns among pharmaceutical production workers at one U.S. site." 2004. British Occupational Hygiene Society Annual Meeting, Stratford England, April 20.
- "Bladder cancer among chemical workers exposed to nitrogen products and other substances." 2003. British Occupational Hygiene Society Annual Meeting, London, England, April 8.
- "Does fiber glass pose a respiratory cancer risk in man? Findings from the Latest update of the U.S. cohort study of man-made vitreous fiber workers." 2001. Ninth Inhaled Particles Conference, British Occupational Hygiene Society, Robinson College, Cambridge, UK, September 2-6.
- "Census 2000: Scientifically and politically correct?" 2000. Symposium Panel Member and Discussant, University of Pittsburgh, Graduate School of Public Health, May 5.
- "Industrial inorganic fibres: Assessing and controlling the risk to public health." 2000. Presented at the 26th International Congress on Occupational Health (ICOH): Mini-Symposium on Fibres-State of the Art, Singapore, August 28.
- "Historical cohort study of U.S. fiber glass production workers. I. Initial findings of 1992 Follow-Up." 2000. Presented at the 26th International Congress on Occupational Health (ICOH), Singapore, August 29.
- "Staying healthy in an unhealthy world: Occupational and environmental health." 2000. Presented at the "Mini-Medical School" Seminar Series of the University of Pittsburgh, School of Medicine, December 5.
- "A program of biostatistical support for the research and quality improvement activities of Highmark Blue Cross Blue Shield." 1999. Presented at the Annual Meeting of the Pennsylvania Public Health Association, Pittsburgh, PA, October 25.
- "The role of epidemiology in an integrated workplace surveillance program." 1999. Presented at the Eli Lilly & Co. Annual Health Fair, Indianapolis, IN, September 19.

- "Mortality surveillance program for the United States man-made mineral fiber workers cohort: Mortality patterns among rock/slagwool workers 1989 Update." 1995. Presented at the Symposium on the Health Effects of Fibrous Materials (excluding asbestos), Sydney, Australia, October 31.
- "A population-based case-control study of lung cancer mortality in four Arizona smelter towns." 1995. Presented at the ATSDR International Congress on Hazardous Waste: Impact on Human and Ecological Health, Atlanta, GA, June 6.
- "OCMAP-PLUS: A new occupational cohort mortality analysis program for multifactor work history and exposure-based analysis." 1994. Presented at the IARC Conference on Retrospective Assessment of Occupational Exposures in Epidemiology, Lyon, France, April 13-15.
- "An expert computer system to accompany the model standardized risk assessment protocol for use with hazardous waste sites." 1993. Presented at the ATSDR International Congress on the Health Effects of Hazardous Wastes, Atlanta, GA, May 3.
- "Drake Chemical Company superfund site. Notification and medical surveillance of workers at high risk of developing bladder cancer." 1993. Presented at the ATSDR International Congress on the Health Effects of Hazardous Wastes, Atlanta, GA,
- "A preliminary evaluation of new fiber and co-exposure data for the U.S. man-made vitreous fiber worker cohort." 1993. Presented at the 10th International Congress on Occupational Health (ICOH), Nice, France, September 25.
- "The University of Pittsburgh studies of man-made mineral fiber workers." 1992 Presented at the 1992 Toxicology Forum, Washington, DC, February 18.
- "Additional analysis of the National Cancer Institute study on mortality among industrial workers exposed to Formaldehyde." 1991. Presented at the American Industrial Hygiene Conference and Exposition. Salt Lake City, UT, May 23.
- "The impact of exposure misclassification and confounding on the mortality experience of U.S. man-made vitreous fiber workers." 1991. Presented at the 8th International Congress on Occupational Health (ICOH)- Epidemiology in Occupational Health, Paris, France, September 12.
- "Long-term mortality studies of man-made mineral fiber exposure." 1991. Presented at the ICOH/Congrex Symposium on Health Aspects of MMMF. Rotterdam, Netherlands, September 13.
- "Evaluating health risks in a multi-exposure environment: The case of formaldehyde." 1992. Presented at the Annual Meeting of the American Occupational Health Conference, Washington, DC, May 8.

Peer-Reviewer

- American Industrial Hygiene Association Journal
- American Journal of Epidemiology
- American Journal of Public Health
- Annals of Epidemiology
- Archives of Environmental Health
- Cancer Causes and Control
- Chemico-Biological Interactions
- Critical Reviews in Toxicology

- Epidemiology
- Journal National Cancer Institute
- Journal of Exposure Analysis and Environmental
- Journal of Occupational and Environmental Hygiene
- Journal of Occupational and Environmental Medicine
- Lancet
- Occupational and Environmental Medicine (U.K.)
- Open Epidemiology Journal
- Regulatory Toxicology and Pharmacology
- Risk Analysis

Editorial Review Boards

- Associate Editor, Open Access Epidemiology (2013-present)
- Associate Editor, Epidemiology Research International (2009-present)
- Associate Editor, Journal of Environmental and Public Health (2008-2017)
- Associate Editor, Cancer Informatics (1995-present)

Natalie Suder Egnot, DrPH

Current Position
Health Scientist I

Discipline Areas
> Epidemiology
> Global Health
> Microbiology
> Program Evaluation
> Public Health Policy

Years' Experience
1

Joined Cardno
2017

Education
> DrPH, Epidemiology, University of Pittsburgh Graduate School of Public Health, 2014-2017
> MPH, Infectious Diseases and Microbiology, University of Pittsburgh Graduate School of Public Health, 2012-2014
> BS, Biology, Pennsylvania State University, 2008-2012

Summary of Experience

Dr. Natalie Suder Egnot is a Health Scientist with Cardno ChemRisk in the Pittsburgh, PA office. She completed her undergraduate studies at the Pennsylvania State University, and obtained both a Master's of Public Health in Infectious Diseases and Microbiology and a Doctor of Public Health in Epidemiology from the University of Pittsburgh Graduate School of Public Health. Her master's thesis research examined the association between herpesvirus coinfection and non-Hodgkin's lymphoma among men living with HIV. Dr. Egnot's dissertation work utilized novel statistical methods and imaging techniques in order to evaluate the role of inflammation in the development and progression of atherosclerotic cardiovascular disease. During her time at the University of Pittsburgh, Dr. Egnot also obtained certificates in Program Evaluation and Global Health.

Significant Projects

Epidemiology & Biostatistics

Performed statistical analysis modeling a variety of health outcomes using techniques such as multivariable regression, linear mixed effects modeling, mediation analysis, principle component analysis, and structural equation modeling. Frequently utilized statistical analysis software including SAS, SPSS, and STATA.

Conducted systematic reviews of epidemiologic literature and has contributed regularly to published manuscripts.

Litigation Support

Reviewed and summarized case materials related to occupational and para-occupational exposure to asbestos. Reviewed and interpreted epidemiologic literature related to asbestos exposure in preparation of expert reports and testimony.

Program Evaluation

Led evaluation of non-profit fellowship program in order to measure the impact of participation in the program among current and past fellows utilizing both quantitative and qualitative analysis methods. Detailed evaluation results in a final report for the fellowship program administrators and presented findings to fellowship program's board of directors.

Public Health Policy

Systematically reviewed and interpreted literature regarding strategies aimed at reducing drug overdose mortality among individuals who were recently incarcerated. Discussed existing policies with local stakeholders and developed actionable recommendations. Synthesized findings and recommendations into a white paper that was presented to local policymakers.

Professional Honors/Awards

> National Heart, Lung and, Blood Institute T32 Pre-Doctoral Trainee (2014-2017)
> Environmental Fellow, The Pittsburgh Albert Schweitzer Fellows Program (2013-2014)

Membership and Service to Professional Societies

> American Heart Association, 2014- Present

Publications

Peer-Reviewed Publications

> Hsu, S, DE Rifkin, MH Criqui, NC Suder, P Garimella, C Ginsberg, AM Marasco, BJ McQuaide, EJ Barinas-Mitchell, MA Allison, CL Wassel and JH Ix. 2017. Journal of Vascular Surgery. In Press.
> Wassel, CL, AM Ellis, NC Suder, E Barinas-Mitchell, DE Rifkin, NI Forbang, JO Denenberg, AM Marasco, BJ McQuaide, NS Jenny, MA Allison, JH Ix and MH Criqui. 2017. Femoral Artery Atherosclerosis is Associated with Physical Function Across the Spectrum of the Ankle-Brachial Index: The San Diego Population Study. Journal of the American Heart Association. July 20;6(7).
> Wukich, DK, KM Raspovic and NC Suder. 2017. "Patients with Diabetic Foot Disease Fear Major Lower-Extremity Amputation More than Death" Foot and Ankle Specialist. Feb 1.
> Wukich, DK, TL Sambenedetto, NM Mota, NC Suder and BL Rosario. 2016. "Correlation of SF-26 and SF-12 Component Scores in Patients With Diabetic Foot Disease" Journal of Foot and Ankle Surgery. Jul-Aug; 55(4): 693-6.
> Wukich, DK, KM Raspovic and NC Suder NC. 2016. "Prevalence of Peripheral Arterial Disease in Patients with Diabetic Charcot Neuroarthropathy" Journal of Foot and Ankle Surgery. Jul-Aug; 55(4):727-31.
> Sadoskas, D, NC Suder and DK Wukich. 2016. "Perioperative Glycemic Control and the Effect of Surgical Site Infections in Diabetic Patients Undergoing Foot and Ankle Surgery" Foot and Ankle Specialist. Feb; 9(1): 24-30
> Wukich, DK, W Shen, KM Raspovic, NC Suder, DT Baril and E Avgerinos. 2015. "Noninvasive Arterial Testing in Patients With Diabetes: A Guide for Foot and Ankle Surgeons" Foot and Ankle International. Dec; 36(12): 1391-9.
> Wukich, DK, BR Mallory, NC Suder and BL Rosario. 2015. "Tibiotalocalcaneal Arthrodesis Using Retrograde Intramedullary Nail Fixation: Comparison of Patents With and Without Diabetes Mellitus" Journal of Foot and Ankle Surgery. Sep-Oct; 54(5): 876-82.
> Wukich, DK, JW Dikis, SJ Monaco, K Strannigan, NC Suder and BL Rosario. 2015. "Topically Applied Vancomycin Powder Reduces the Rate of Surgical Site Infection in Diabetic Patients Undergoing Foot and Ankle Surgery" Foot and Ankle International. Sep; 36(9): 1017-24.
> Suder, NC and DK Wukich. 2012. "Prevalence of Neuropathy in Patients Undergoing Foot or Ankle Surgery" Foot and Ankle Specialist. Apr; 5(2):97-101.

Presentations

Oral Presentations

> "Associations of Biomarkers of Inflammation and Coagulation with Plaque in the Femoral Artery" American Heart Association EPI/Lifestyle Conference Trainee Session. Portland, Oregon. March 2017.

> "Recommendations for Reducing Morbidity and Mortality due to Heroin Overdose in Allegheny County" Presented to members of the Allegheny County Health Department on behalf of Health Policy and Management 2133: Law in Public Health Practice

Lectures

> "Introduction to Mentored Grant Writing" Epidemiology 2152: Student Workshop in Cardiovascular Disease Epidemiology, University of Pittsburgh Graduate School of Public Health

> "Social Determinants of Health" Health Policy: 90-861, Carnegie Mellon University Heinz College

> "Overview of Grant Writing" Epidemiology 2182: Design and Conduct of Clinical Trials, University of Pittsburgh Graduate School of Public Health

Poster Presentations

> Suder, N, E Barinas-Mitchell, M Allison, M Criqui, J Ix, N Jenny and C Wassel. "Associations of Biomarkers of Inflammation and Coagulation with Plaque in the Femoral Artery" American Heart Association EPI/Lifestyle Conference. Portland, Oregon. March 2017

> Suder, N, E Barinas-Mitchell, M Allison, M Criqui, J Ix, N Jenny and C Wassel. "Higher Levels of C-reactive Protein and Interleukin 6 are Associated with Femoral Artery Plaque Burden, but not Plaque Characteristics: The San Diego Population Study" Presented at the American Heart Association Fellows Research Day 2017

> Creppage, K, N Suder and L Torso. "A Legal Analysis of Laws Governing the Use of Naloxone (Narcan) in the United States and Pennsylvania" Presented at the Graduate School of Public Health Dean's Day 2016.

> Creppage, K, N Suder and L Torso. "Interventions to Reduce the Risk of Opioid Overdose upon Release from Jail or Prison: A Review of the Literature" Presented at the 2016 Health Disparities Poster Competition, University of Pittsburgh.

> Suder, N. "Knowledge Empowers: Communicable Disease Prevention in Abused and Neglected Children" Presented at IDM Research Day 2013, University of Pittsburgh Graduate School of Public Health. Poster based on Albert Schweitzer Fellowship and public health practicum experience.

> Suder, N. "Communicable Disease Prevention in Abused and Neglected Children Living in Beaver County, Pennsylvania" Presented at the Annual Infectious Disease Public Health Forum 2013, University of Pittsburgh Graduate School of Public Health. Poster based on proposed public health practicum.

Exhibit G

Request for Reconsideration
Denka Performance Elastomer LLC

FINAL

REVIEWER COMMENTS

External Peer Review Meeting on the *Toxicological Review of Chloroprene* (CAS No. 126-99-8)

Prepared for:
Allen Davis, M.P.H.
National Center for Environmental Assessment
U.S. Environmental Protection Agency
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Prepared by:
Versar, Inc.
Contract No. EP-C-07-025
Task Order 69

Peer Reviewers:
Herman J. Gibb, Ph.D., M.P.H.
Dale Hattis, Ph.D.
Ronald L. Melnick, Ph.D.
John B. Morris, Ph.D.
Avima M. Ruder, Ph.D.
Richard B. Schlesinger, Ph.D.

January 26, 2010

TABLE OF CONTENTS

I. INTRODUCTION

The Integrated Risk Information System (IRIS) is an EPA database containing Agency consensus scientific positions on potential adverse human health effects that may result from chronic (or lifetime) exposure, or in select cases less-than-lifetime exposures, to chemicals in the environment. IRIS currently provides health effects information on over 500 chemical substances. IRIS contains chemical-specific summaries of qualitative and quantitative health information in support of two steps of the risk assessment process, i.e., hazard identification and dose-response evaluation. IRIS information includes a reference dose (RfD) for noncancer health effects resulting from oral exposure, a reference concentration (RfC) for noncancer health effects resulting from inhalation exposure, and an assessment of carcinogenicity for both oral and inhalation exposures. Combined with specific situational exposure assessment information, the health hazard information in IRIS may be used as a source in evaluating potential public health risks from environmental contaminants.

The IRIS program developed a Toxicological Review of Chloroprene, an assessment which has not previously appeared in IRIS. Chloroprene was nominated for IRIS assessment in 1999. The draft document contains a chronic inhalation reference concentration (RfC) and a cancer inhalation unit risk.

Peer Reviewers:

Herman J. Gibb, Ph.D., M.P.H.
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Chapel Hill, NC 27514

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National Institute for Occupational Safety and Health (NIOSH)
Cincinnati, OH 45226

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Pace University
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II. CHARGE TO THE REVIEWERS

The U.S. Environmental Protection Agency (EPA) is seeking an external peer review of the scientific basis supporting the human health assessment of chloroprene that will appear on the Agency's online database, the Integrated Risk Information System (IRIS). IRIS is prepared and maintained by the EPA's National Center for Environmental Assessment (NCEA) within the Office of Research and Development (ORD). Currently an IRIS assessment of chloroprene does not exist on the database.

The draft health assessment includes a chronic reference concentration (RfC) and a carcinogenicity assessment. Below are a set of charge questions that address scientific issues in the assessment of chloroprene. Please provide detailed explanations for responses to the charge questions.

General Charge Questions:

1. Is the Toxicological Review logical, clear and concise? Has EPA clearly synthesized the scientific evidence for noncancer and cancer hazards?

2. Please identify any additional studies that should be considered in the assessment of the noncancer and cancer health effects of chloroprene.

Chemical-Specific Charge Questions:

(A) Oral Reference Dose (RfD) for Chloroprene

1. An RfD was not derived for chloroprene. Has the scientific justification for not deriving an RfD been clearly described in the document? Please identify and provide the rationale for any studies that should be selected as the principal study.

(B) Inhalation Reference Concentration (RfC) for Chloroprene

1. A chronic RfC for chloroprene has been derived from an inhalation toxicity study (NTP, 1998) investigating non-cancer effects in multiple organ systems. Please comment on whether the selection of this study as the principal study is scientifically justified. Please identify and provide the rationale for any other studies that should be selected as the principal study.

2. An increase in the incidence of degenerative nasal lesions in male rats, characterized by olfactory epithelial atrophy and/or necrosis with increasing severity, was selected as the critical effect. Please comment on the scientific justification for combining the incidence of atrophy and necrosis and for selecting this endpoint as the critical effect. Please identify and provide the rationale for any other endpoints that should be considered in the selection of the critical effect.

3. Benchmark dose (BMD) modeling was used to define the point of departure (POD) for the derivation of the RfC. The POD was based on increased incidence of degenerative nasal lesions in male rats at a benchmark response (BMR) of 10% extra risk. Has the BMD approach been appropriately conducted? Is the BMR selected for use in deriving the POD (i.e., 10% extra risk of degenerative nasal lesions of less than moderate severity) scientifically justified? Please identify and provide the rationale for any alternative approaches (including the selection of the BMR, model, etc.) for the determination of the POD and discuss whether such approaches are preferred to EPA's approach.

4. Please comment on the rationale for the selection of the uncertainty factors (UFs) applied to the POD for the derivation of the RfC. If changes to the selected UFs are proposed, please identify and provide a rationale(s).

(C) Carcinogenicity of Chloroprene

1. Under the EPA's 2005 *Guidelines for Carcinogen Risk Assessment* (www.epa.gov/iris/backgr-d.htm), the Agency concluded that chloroprene is *likely to be carcinogenic to humans* by all routes of exposure. Please comment on the cancer weight of evidence characterization. Is the cancer weight of evidence characterization scientifically justified?

2. A two-year inhalation cancer bioassay in B6C3F1 mice (NTP, 1998) was selected as the basis for derivation of an inhalation unit risk (IUR). Please comment on whether the selection of this study for quantification is scientifically justified. Please identify and provide the rationale for any other studies that should be selected as the basis for quantification.

3. A mutagenic mode of carcinogenic action is proposed for chloroprene. Please comment on whether the weight of evidence supports this conclusion. Please comment on whether this determination is scientifically justified. Please comment on data available for chloroprene that may support an alternative mode(s) of action.

4. Data on hemangiomas/hemangiosarcomas (in all organs) and tumors of the lung (bronchiolar/alveolar adenomas and carcinomas), forestomach, Harderian gland (adenomas and carcinomas), kidney (adenomas), skin and mesentery, mammary gland and liver in B6C3F1 mice were used to estimate the inhalation unit risk. Please comment on the scientific justification and transparency of this analysis. Has the modeling approach been appropriately conducted? Please identify and provide the rationale for any alternative approaches for the determination of the inhalation unit risk and discuss whether such approaches are preferred to EPA's approach.

5. Lung tumors have been alternatively treated as systemic or portal-of-entry effects in the modeling of cancer endpoints. Please comment on the scientific justification for this modeling approach. Please comment on whether the rationale for this decision has been transparently and objectively described. Please comment on data available

for chloroprene that may support an alternative method for modeling the observed lung tumors in mice.

6. An oral slope factor (OSF) for cancer was not derived for chloroprene. Is the determination that the available data for chloroprene do not support derivation of an OSF scientifically justified?

III. GENERAL IMPRESSIONS

Herman J. Gibb

In general, the document lays out its arguments well. The discussion of the epidemiology, however, should be more transparent and perhaps could be better organized (studies of a facility where cohorts overlap or could overlap discussed together). Elaboration on the transparency is provided in my response to Question C1. The epidemiologic studies should be evaluated more rigorously.

Dale Hattis

Overall, the judgments made in the draft IRIS document for chloroprene are sound. However the modeling of the cancer risk can be improved by taking into account the existing evidence for partial saturation of metabolic activation of chloroprene in the dose range studied in the NTP cancer bioassay. Using a simple Michaelis Menten dose response equation to model this approach to saturation indicates that low dose cancer risks in both the male and female mouse bioassays are likely to be 2-3 fold greater than the risks indicated by application of a straight linear dose response model, as was done using the Weibull equation in the current cancer slope factor analysis. For the final assessment it would be desirable either to incorporate the Michaelis-Menten saturating form into the Weibull model or (less desirably) to multiply the Weibull model result by a factor derived from the Michaelis-Menten analysis of the lifetime tumor incidence information. The former approach is preferable because it will simultaneously take into account the time-to-tumor information and the apparent saturation of activating metabolism indicated by the incidence data.

Ronald L. Melnick

The draft document is a well-written, comprehensive review and assessment of published studies on the health effects of chloroprene in humans and in experimental animals. The information is clearly presented and the conclusions are generally scientifically justified and consistent with EPA policy. One exception is the rationale for the selection of 10% extra risk for the benchmark response. Specific areas for improvement of this review are described below in my response to the “chemical-specific charge questions.”

John B. Morris

From my perspective as an inhalation toxicologist with expertise in rodent studies, the Toxicological Review of Chloroprene provides an in depth review of the toxicological literature on this compound. In many ways it is quite clear and thorough. The available database appears to be presented accurately and objectively. The overall conclusion, that chloroprene is an animal carcinogen whose mechanism(s) may include genotoxicity and mutagenesis, appears well founded. In some aspects, the document is confusing and perhaps lacks transparency. For example, information is provided in the summary and synthesis sections that have not been discussed previously. There are some apparent

contradictions in interpretive approaches, for example the potential for systemic blood delivery for the pulmonary but not nasal effects. The importance of some findings has gone unrecognized. For example, the extraordinarily high pulmonary metabolism rates in the mouse calls into question the relevance of this species with respect to pulmonary injury. Overall, the fundamental conclusions appear sound; however, the document could be significantly improved with respect to clarity and interpretive issues.

It is interesting that there are no charge questions relating to the toxicokinetics of chloroprene. Since the mode of action includes activation to an epoxide as the first step, the toxicokinetics becomes an issue of great importance. The toxicokinetic section describes the available information, but could provide much more information. Moreover, the toxicokinetic data is not adequately synthesized in the overall mode of action relative to potential species differences and extrapolation to man. PBPK modeling would be a highly appropriate way to incorporate kinetic data into the risk assessment. The published model of Himmelstein may provide a useful structure. Because it includes both nasal and tracheobronchial airway compartments the styrene model of Sarangapani may be a superior approach.

Avima M. Ruder

I can only validate accuracy for the section I compared to the original papers, that on human epidemiology. There are some key relevant references that were not cited and some points that should have been discussed (latency, age at diagnosis, etc.) that were not touched on (see 2.1).

The conclusions about the human hazard potential do not evaluate the role of genetic polymorphism in genes coding for glutathione *S*-transferases, epoxide hydrolase, and other metabolic enzymes in clearing epoxide metabolites from the body. Approximately half the human population is clears those metabolites at a much slower rate [Musak, et al. 2008], presumably making them more vulnerable to exposure. The conclusion also should point out that the noncancer effects (page 6-1, lines 24-33) were observed at levels lower than the current Permissible Exposure Limit.

The statements of conclusions in section 6 are less clear than those in section 4.7. It is appropriate to include all relevant caveats about the conclusions, and all the details of the studies that support those conclusions, but the conclusions themselves should be succinctly stated.

Richard B. Schlesinger

The background information that is provided to support the selection of the key studies is clearly and accurately presented. However, the derivation of some of the quantitative factors, as noted in subsequent comments in this document, could be made more transparent. In general, the overall conclusions appear to be sound.

IV. RESPONSE TO CHARGE QUESTIONS

General Charge Questions:

1. Is the Toxicological Review logical, clear and concise? Has EPA clearly synthesized the scientific evidence for noncancer and cancer hazards?

Herman J. Gibb

In general, the Toxicological Review is logical, clear and concise. A more rigorous and transparent evaluation of the epidemiologic studies and an objective evaluation of how the epidemiologic studies integrate with the rest of the data should be performed, however. The descriptor of "likely to be carcinogenic to humans" is justified based on the animal and genotoxicity information, but the document overstates the human evidence.

Dale Hattis

Generally, yes. I have some reservations and suggestions for incremental improvement, as will be apparent below. But the overall evaluation in the proposed IRIS document is sound.

Ronald L. Melnick

While the Toxicological Review is clear and comprehensive, it is not obvious why a particular dose response model was selected for the determination of the benchmark dose for noncancer hazards, if more than one model provided an adequate fit to the data. The rationale for the selection of 10% extra risk for the benchmark response for non-cancer effects is not adequately justified.

Based on the animal data, mechanistic findings, and "the reasonably consistent" evidence of increased risk of liver cancer mortality "among workers exposed to chloroprene in different cohorts in different continents," it is not clear why consideration was not given to the conclusion that chloroprene is "carcinogenic to humans."

John B. Morris

In many ways, the toxicological review is logical and clear; however, the document could be significantly improved in this regard. See my specific comments (below) for more detail on this concern.

Avima M. Ruder

The review is logical but less clear and concise than it could be. In the section on human carcinogenicity, the discussion should have been consolidated by population and recommendations for additional analyses (by age at onset/death, with lags) and substudies (nested case-control) should have been included. Such analyses should be done as very

early age at cancer onset/death has been associated with occupational exposure [Kreuzer, et al. 1999; Ward, et al. 1988] and lagged analyses focus on exposure in time periods that are most relevant for the development of solid tumors [Villeneuve and Steenland 2010]. All the studies on the Louisville plant should have been discussed together. The original study includes ages at death from lung cancer for 16 workers, including four who died in their forties [Pell 1978], but no analysis of whether the ages at onset were earlier than expected (in another chloroprene cohort, earlier ages at onset among exposed workers were reported [Li, et al. 1989]). The NIOSH walk-through survey of the plant, which was not referenced in the Toxicological Review, provides useful details on plant history, processes, and personnel, noting that "there is a complete pre-employment physical" plus periodic re-examinations (presumably those who did not meet some standard of health were excluded from employment; no details were presented on how the periodic re-examinations impacted continued employment [Jones, et al. 1975]. The NIOSH re-analysis of DuPont demographic data included recommendations for improving the epidemiologic studies by including all plant employees from 1942 on [Leet and Selevan 1982]. Blood draws from 846 of the workers employed in 1977 were compared for biochemical and hematological markers, with no significant differences in age-adjusted analyses [Gooch and Hawn 1981] and workers and plant sites were monitored for exposure, and workers interviewed [McGlothlin, et al. 1984](neither referenced in the Toxicological Review).

One of the more recent University of Pittsburgh papers (not referenced in the Toxicological Review), presents SMRs for the Louisville cohort using the DuPont worker mortality database; these are significantly elevated for all causes of death, all cancers, respiratory cancers, and liver cancer [Leonard, et al. 2007]. Kentucky cancer mortality is significantly higher than U.S. national cancer mortality [U.S. Cancer Statistics Working Group 2009], and the incidence of lung cancer in both Jefferson county and all of Kentucky is almost 50% higher than the U.S. rate [Kentucky Institute of Medicine 2007], so comparisons of a working population to the population at large will show a pronounced healthy worker effect. Presumably an employment-based database would control for the healthy worker effect to some extent. The most recent studies are more comprehensive but could have included additional analyses by age at diagnosis/death, lagged analyses, comparisons with the DuPont employee mortality database, and inclusion of the pre-1949 PYAR [Marsh, et al. 2007a; Marsh, et al. 2007b]. Some discrepancies should be explored; for example, Jones stated that approximately 8000 hourly and 1000 salaried (one-third foremen) employees had been employed to the time of the 1975 visit and over 1000 workers were employed in 1975; the Marsh analysis includes 5507 employees 1949-2000 [Jones, et al. 1975; Marsh, et al. 2007a].

Some discrepancies between the report of a 1985 NIOSH walk-through of the Pontchartrain, Louisiana, plant (neoprene production from 1968, 1264 workers to 1985) and the recent epidemiologic studies (chloroprene from 1969, 1258 workers to 2000) also need to be resolved [Fajen and Ungers 1985; Marsh, et al. 2007a; Marsh, et al. 2007b].

The studies of the plant in Grenoble, Isère, France, should also have been assessed together [Colonna and Laydevant 2001; Marsh, et al. 2007a; Marsh, et al. 2007b].

As to possible human health hazards other than cancer, the two medical studies at the Louisville plant [Gooch and Hawn 1981; McGlothlin, et al. 1984] and the recent study of chromosomal aberrations [Musak, et al. 2008] should be included. Apparently there are no studies of possible human reproductive effects more recent than Sanotskii's in 1976.

Richard B. Schlesinger

In general, the Review is well written and the toxicology of chloroprene is well synthesized.

General Charge Questions:

2. Please identify any additional studies that should be considered in the assessment of the noncancer and cancer health effects of chloroprene.

Herman J. Gibb

The NIOSH reports by Fajen and Ungers (1985) and by McGlothin et al (1984) should be included as background on the Pontchartrain and Louisville plants, respectively. Copies were provided to the peer reviewers by Avima Ruder subsequent to the peer review meeting on January 6, 2010 and are attached. Dr. Ruder also described references of Jones et al. (1975), Gooch and Hawn (1981), and Leonard et al. (2007) in her comments. Jones et al. (1975) and Gooch and Hawn (1981) describe conditions and the population at the Louisville plant and should be added as background information on that facility. The Leonard et al. paper apparently presents mortality analyses of the Louisville cohort using a Dupont worker mortality database. These papers should be reviewed to determine what insights they may offer to the mortality analyses by Pell (1978), Leet and Selevan (1982) and Marsh et al. (2007a, 2007b).

I am not aware of any additional original studies or reports that should be considered. The following reviews by Acquavella and Leonard (2001) and Bukowski (2009) should at least be given consideration although they need not necessarily be referenced. The review by Acquavella and Leonard (2001) appeared in the same journal as the review by Rice and Boffetta (2001) which is cited in the current Toxicological Review.

Acquavella JF, Leonard RC. 2001. A review of the epidemiology of 1,3-butadiene and chloroprene. Chemico-Biological Interactions 135–136 (2001) 43-52.

Bukowski JA. 2009. Epidemiologic evidence for chloroprene carcinogenicity: review of study quality and its application to risk assessment. Risk Analysis 29(9):1203-16.

Dale Hattis

Probably the most significant omission is an analysis by Dr. DeWoskin of EPA of the potential to use a PBPK model for estimation of human vs. mouse and rat delivered doses in modeling cancer dose response relationships for chloroprene. Its omission from the list of references is surprising. The abstract of this paper I retrieved from a MEDLINE search is:

PBPK models in risk assessment--A focus on chloroprene.

DeWoskin RS.

Chem Biol Interact. 2007 Mar 20;166(1-3):352-9. Epub 2007 Feb 8.

US EPA/NCEA (National Center for Environmental Assessment), Mail Drop B243-01, Research Triangle Park, NC 27711, USA. dewoskin.rob@epa.gov

Mathematical models are increasingly being used to simulate events in the exposure-response continuum, and to support quantitative predictions of risks to human health. Physiologically based pharmacokinetic (PBPK) models address that portion of the continuum from an external chemical exposure to an internal dose at a target site. Essential data needed to develop a PBPK model include values of key physiological parameters (e.g., tissue volumes, blood flow rates) and chemical specific parameters (rate of chemical absorption, distribution, metabolism, and elimination) for the species of interest. PBPK models are commonly used to: (1) predict concentrations of an internal dose over time at a target site following external exposure via different routes and/or durations; (2) predict human internal concentration at a target site based on animal data by accounting for toxicokinetic and physiological differences; and (3) estimate variability in the internal dose within a human population resulting from differences in individual pharmacokinetics. Himmelstein et al. [M.W. Himmelstein, S.C. Carpenter, P.M. Hinderliter, Kinetic modeling of beta-chloroprene metabolism. I. In vitro rates in liver and lung tissue fractions from mice, rats, hamsters, and humans, Toxicol. Sci. 79 (1) (2004) 18-27; M.W. Himmelstein, S.C. Carpenter, M.V. Evans, P.M. Hinderliter, E.M. Kenyon, Kinetic modeling of beta-chloroprene metabolism. II. The application of physiologically based modeling for cancer dose response analysis, Toxicol. Sci. 79 (1) (2004) 28-37] developed a PBPK model for chloroprene (2-chloro-1,3-butadiene; CD) that simulates chloroprene disposition in rats, mice, hamsters, or humans following an inhalation exposure. **Values for the CD-PBPK model metabolic parameters were obtained from in vitro studies, and model simulations compared to data from in vivo gas uptake studies in rats, hamsters, and mice. The model estimate for total amount of metabolite in lung correlated better with rodent tumor incidence than did the external dose.** Based on this PBPK model analytical approach, Himmelstein et al. [M.W. Himmelstein, S.C. Carpenter, M.V. Evans, P.M. Hinderliter, E.M. Kenyon, Kinetic modeling of beta-chloroprene metabolism. II. The application of physiologically based modeling for cancer dose response analysis, Toxicol. Sci. 79 (1) (2004) 28-37; M.W. Himmelstein, R. Leonard, R. Valentine, Kinetic modeling of beta-chloroprene metabolism: default and physiologically-based modeling approaches for cancer dose response, in: IISRP Symposium on Evaluation of Butadiene & Chloroprene Health Effects, September 21, 2005, TBD--reference in this proceedings issue of Chemical-Biological Interactions] propose that observed species differences in the lung tumor dose-response result from differences in CD metabolic rates. The CD-PBPK model has not yet been submitted to EPA for use in developing the IRIS assessment for chloroprene, but is sufficiently developed to be considered. The process that EPA uses to evaluate PBPK models is discussed, as well as potential applications for the CD-PBPK model in an IRIS assessment.

In reading the document, I don’t recall coming across an explanation for why the implications of this model for cancer risk were not explored. It seems to me that the high dose saturation effects that are apparent in the tumor data could be explained in part by even a basic application of this kind of model. Explaining the high dose saturation of the

metabolic activation would, I think, (1) avoid the need to eliminate the high dose for some data sets and (2) lead to an increase in the estimate of the linear coefficients for the cancer dose response model. The PBPK model may well be considered not sufficiently tested against human data for un-caveated application to human risk projection, but I think its implications should at least be explored for sensitivity analyses.

Ronald L. Melnick

No additional studies were found that would significantly impact the overall assessment.

John B. Morris

I am aware of no additional toxicity studies relative to chloroprene. The mouse bronchiolar airway lesions are reminiscent of those induced by naphthalene and styrene. In this regard, comparisons to these compounds might provide some useful perspectives.

Avima M. Ruder

Two recent studies of genetic damage in workers exposed to chloroprene are relevant to this review.

Heuser VD, de Andrade VM, da Silva J, Erdtmann B. 2005. Comparison of genetic damage in Brazilian footwear-workers exposed to solvent-based or water-based adhesive. Genet Tox Environ Mutat/Mutat Res 583(1):85-94.

This study compared Comet assay results for unexposed workers, workers using water-based adhesives, and workers using solvent-based adhesives containing polychloroprene (and, presumably, some chloroprene as a contaminant), with a significantly higher damage index among the solvent-based adhesive users than either the unexposed or workers using water-based adhesives.

It was not entirely clear from the article whether the solvent-based adhesive group used adhesives (and other compounds), as stated on page 90, or produced the polychloroprene (page 91). In either case, there are a number of additional exposures which might have been associated with the chromosome damage. Other than the chromosome results no health effects were reported.

Musak L, Soucek P, Vodickova L, Naccarati A, Halasova E, Polakova V, Slyskova J, Susova S, Buchancova J, Smerhovsky Z and others. 2008. Chromosomal aberrations in tire plant workers and interaction with polymorphisms of biotransformation and DNA repair genes. Mutat Res 641(1-2):36-42.

This study compared lymphocyte chromosome aberrations among smoking and nonsmoking tire workers (exposed to butadiene) and controls. In addition, participants were genotyped for polymorphisms in genes encoding metabolic enzymes. "Chromosomal aberrations were higher in subjects with GSTT1-null (2.4 ± 1.7%) than in

those with GSTT1-plus genotype (1.8 ± 1.4%; F = 7.2, P = 0.008)." In light of the papers on diene (butadiene, chloroprene, isoprene) metabolism that indicate that the detoxification of a mutagenic metabolite goes through the GST pathway [Himmelstein, et al. 2004a; Himmelstein, et al. 2004b; Munter, et al. 2007; Munter, et al. 2003], this result is significant. It means that the fifty percent of the human population that is GST-null may be at higher risk from exposure; any exposure-associated carcinogenicity could be higher in this susceptible subpopulation.

Other studies to consider:

Fajen JM, Ungers LJ. 1985. DuPont de Nemours and company, Pontchartrain Works, LaPlace, LA, IWS-147-31. LA, LaPlace: NIOSH, Cincinnati, OH. 1-18 p.

Jones JH, Young RJ, Selevan S. 1975. du Pont de Nemours and Company, Inc., Louisville, Kentucky, IWS-87-10. KY, Louisville: NIOSH, Cincinnati, OH. 1-9 p.

McGlothlin JD, Meyer C, Leet TL. 1984. E.I. DuPont De Nemours And Company, Louisville, KY, HETA-79-027-1459. KY, Louisville: NIOSH, Cincinnati, OH. 1-28 p.

These NIOSH site visits provide concise histories of processes and chemicals at the plants, as well as descriptions of records and medical monitoring (Fajen and Jones reports) and a Health Hazard Evaluation (McGlothlin).

Leonard RC, Kreckmann KH, Lineker GA, Marsh G, Buchanich J, Youk A. 2007. Comparison of standardized mortality ratios (SMRs) obtained from use of reference populations based on a company-wide registry cohort to SMRs calculated against local and national rates. Chem Biol Interact 166(1-3):317-22.

This study calculated SMRs for the Louisville and Pontchartrain chloroprene plants using the DuPont employee database as a reference population, rather than the U.S. national or local population. For the Louisville plant, "…the SMRs based on the total U.S. DuPont worker mortality rates for all causes of death (1.13), all cancers (1.11), and respiratory cancers (1.37) are statistically significantly increased. The SMR for liver cancer (1.27), although elevated, is not statistically significant."

Richard B. Schlesinger

There are none that I am aware of.

Chemical-Specific Charge Questions:

(A) Oral Reference Dose (RfD) for Chloroprene

1. An RfD was not derived for chloroprene. Has the scientific justification for not deriving an RfD been clearly described in the document? Please identify and provide the rationale for any studies that should be selected as the principal study.

Herman J. Gibb

The scientific rationale for not deriving an RfD has been clearly described.

Dale Hattis

Yes. But such a derivation would be possible if the PBPK model (or some suitable range of models derived from sensitivity analyses) were used.

The principal study selected for analysis is fine.

Ronald L. Melnick

Yes, the lack of an adequate multiple-dose oral toxicity study on chloroprene that could be used for a dose-response analysis and the lack of information on the disposition of chloroprene after inhalation or oral exposure that would enable a reliable route-to-route extrapolation justify not deriving an RfD for this chemical. Because of a likely large first-pass liver effect after oral exposure, the systemic distribution of parent compound and reactive metabolites could be very different after oral or inhalation exposures.

John B. Morris

An oral RfD was not derived for chloroprene. The current database is clearly described. The rationale for the decision to not derive an oral RfD is clearly and concisely described. The scientific justification is appropriate and the decision is well founded.

Avima M. Ruder

As the document states, there are no human data on oral exposure and only one lifetime animal study, so clearly the justification for not deriving an RfD exists.

Richard B. Schlesinger

The decision not to derive an RfD is clearly justified in the document as based upon the lack of appropriate datasets for oral exposure.

(B) Inhalation Reference Concentration (RfC) for Chloroprene

1. A chronic RfC for chloroprene has been derived from an inhalation toxicity study (NTP, 1998) investigating non-cancer effects in multiple organ systems. Please comment on whether the selection of this study as the principal study is scientifically justified. Please identify and provide the rationale for any other studies that should be selected as the principal study.

Herman J. Gibb

The selection of this study is justified. The document states that the Trochimowicz et al. study was not chosen as the principal study "primarily due to the lack of observed effects at similar exposure levels as the NTP (1998) study"(page 4-39, lines 19-20; page 5-2, lines 26-29). That doesn't seem as strong an argument as the high mortality in the low dose animals which were suffocated by the ventilation system (page 5-2, lines 13-16, 29-31).

Dale Hattis

The principal study selected for analysis is fine.

Ronald L. Melnick

The selection of the NTP chronic inhalation toxicity study as the principal study for the derivation of an RfC for chloroprene is scientifically justified. This was a well designed and conducted study, which identified several non-cancer effects in multiple organs of rats and mice exposed to a wide range of concentrations of chloroprene. A major strength of this study is the multiple histopathological reviews of lesions identified in rats and mice. The study clearly demonstrates the toxicity of chloroprene in multiple species and the data are suitable for dose-response analyses.

John B. Morris

The selection of the NTP inhalation study as the principal study is scientifically justified. It was well conducted and subject to peer review.

Avima M. Ruder

The data files for two human studies conducted at the Louisville plant [Gooch and Hawn 1981; McGlothlin, et al. 1984] might have some information on subchronic effects. Gooch and Hawn did biochemical and hematological assays on blood specimens from workers characterized by their duration of chloroprene exposure. McGlothlin and colleagues conducted medical interviews with workers who had been monitored for chloroprene exposure (personal zone air samples). The report does not present any tabular data on health effects. However, the lack of quantitative exposure data for Gooch

and Hawn and of quantitative medical data for McGlothlin et al. rule out their use as a principal study. Selection of the NTP study is justified.

Richard B. Schlesinger

This study is clearly the best one to use for derivation of the RfC. It has a range of exposure concentrations and examined two species and multiple organ systems. The other chronic bioassay of Trochimowicz et al. has a number of problems associated with it that in my mind preclude its use as the key study.

(B) Inhalation Reference Concentration (RfC) for Chloroprene

2. An increase in the incidence of degenerative nasal lesions in male rats, characterized by olfactory epithelial atrophy and/or necrosis with increasing severity, was selected as the critical effect. Please comment on the scientific justification for combining the incidence of atrophy and necrosis and for selecting this endpoint as the critical effect. Please identify and provide the rationale for any other endpoints that should be considered in the selection of the critical effect.

Herman J. Gibb

It seems reasonable to combine the incidence of epithelial atrophy and necrosis. The rationale for choosing degenerative nasal lesions over epithelial hyperplasia or splenic hematopoietic proliferation (page 5-10, lines 4-10) is reasonable.

Dale Hattis

I think there is no problem with the selection of these endpoints for RfC derivation.

Ronald L. Melnick

Combining the incidences of the degenerative nasal lesions, atrophy and necrosis, seems reasonable, but does not make much difference on the overall determination – the incidence of atrophy alone in the control and three dose groups of male rats was 6, 24, 94, and 98%, while the combined incidence of atrophy and necrosis was 6, 26, 96, and 98%; and the derived human equivalent POD values were essentially the same (1.1 mg/m^3 for atrophy and 1.0 mg/m^3 for the combined lesions, respectively).

Nasal degeneration is the appropriate effect for determination of the POD, because this was the most sensitive endpoint producing the lowest human equivalent POD. The document notes that candidate endpoints considered for the critical effect were those that were statistically increased in the lowest exposure concentration group. This limitation should not be imposed because it could result in exclusion of sensitive endpoints depending on the nature of the dose-response relationship. Other endpoints that should also be considered are renal tubule hyperplasia in male rats (single and step section data) and renal tubule hyperplasia in male mice. RfCs should also be derived and presented in Figure 5-1 for other endpoints, including olfactory effects in female rats, male mice, and female mice, and renal tubule hyperplasia in male rats, female rats, and male mice.

John B. Morris

Nasal degenerative lesions in the rat were selected as the critical response because the POD-HEC derived from these data was the most protective. Several concerns could be raised relative to this recommendation. First, the rationale for combining lesions and the precise way in which the data were combined is poorly described. In my view, the concept that necrosis may precede atrophy is quite straightforward. Numerous agents

induce nasal olfactory necrosis and atrophy (esters, styrene, and naphthalene to name a few); critical evaluation of this database will provide insights into the typical progression of lesions. The concept that atrophy precedes necrosis, however, is bewildering to me. I am not aware of a nasal toxicant in which it has been shown that atrophy results in subsequent necrosis. Such an example should be provided to support this concept. In the absence of such information, it is not reasonable, in my view, to assert that atrophy causes necrosis. I, therefore, do not concur with combining the lesions. I note that the difference in POD-HEC between combined and uncombined data is quite small; why invoke a poorly substantiated approach when it results in little difference? My other concerns focus on POD issues and are provided below. In my view, the POD should not be based on nasal lesions, making the issue of combination of lesions moot.

Avima M. Ruder

Combining the effects of atrophy and necrosis appears justified. Table 5-1 does not provide the p-values for trend in dose response for various endpoints. However, it appears that the trend might be stronger for the atrophy or necrosis, with percentages affected ranging from 6 to 98% with increasing doses, than for hematopoietic cell proliferation in the spleens of female mice, with percentages affected ranging from 26 to 78% with increasing doses.

Richard B. Schlesinger

A portal of entry effect was used as the critical effect, which is appropriate for this chemical. The justification provided for combining these two degenerative changes as the overall effect of interest is appropriate, even though it would be assumed that necrosis would precede atrophy. While it appears that the chloroprene while non reactive is metabolized in the upper respiratory tract to a reactive epoxide, there needs to be some explanation as to why the nasal changes themselves were selected over effects in the bronchial tree or alveolar region that were observed at the 12 ppm exposure level as well. An explanation does appear on page 5-7 following results of modeling, but there should have been some indication earlier on as to why the upper respiratory rather than the lower respiratory tract endpoint was selected in the first place.

(B) Inhalation Reference Concentration (RfC) for Chloroprene

3. Benchmark dose (BMD) modeling was used to define the point of departure (POD) for the derivation of the RfC. The POD was based on increased incidence of degenerative nasal lesions in male rats at a benchmark response (BMR) of 10% extra risk. Has the BMD approach been appropriately conducted? Is the BMR selected for use in deriving the POD (i.e., 10% extra risk of degenerative nasal lesions of less than moderate severity) scientifically justified? Please identify and provide the rationale for any alternative approaches (including the selection of the BMR, model, etc.) for the determination of the POD and discuss whether such approaches are preferred to EPA's approach.

Herman J. Gibb

The BMD approach is preferred to other approaches for the given data. The arguments made by one of the peer reviewers, Dr. Morris, to reconsider the calculation of the RfC with regard to blood borne delivery versus airborne delivery are reasonable, and I would recommend that the Agency evaluate both approaches prior to performing dosimetric adjustment. If atrophy/necrosis is eventually selected as the endpoint, a BMR of 10% extra risk is reasonable given the arguments on page 5-4 of the document.

Dale Hattis

The saturation of metabolism to the active metabolites could be clarified with the use of the PBPK model mentioned earlier. This could facilitate dose response modeling and perhaps lead to a somewhat lower point of departure for application of uncertainty factors.

At the peer review meeting an issue arose as to whether the 10% benchmark response level was appropriate in the light of the severity of the nasal lesions in some of the animals. If counts are available on the numbers of animals showing different levels of severity in relation to dose than this would seem to be a good case for the use of the EPA's categorical regression software. With that system it would be possible to take the severity information into account and estimate a somewhat lower BMDs and BMDLs corresponding to a 10% extra risk of mildly adverse effects.

In addition, EPA might consider a modifying the benchmark dose estimation to take into account the approach to saturation of metabolic activation derived from the cancer dose response information (see below).

Finally I agree with some of the other reviewers that the RfC should be derived using the procedures for a category 3 rather than a category 1 vapor.

Ronald L. Melnick

BMD modeling is the preferred approach to derive the POD because it uses all of the dose response data and is less impacted by the group size. Some discussion is needed on why a particular dose response model was selected for the determination of the POD in situations where more than one model provided an adequate fit to the data. If it is EPA's policy to select the model that yielded the lowest AIC value, then that rationale should be explicitly noted. The characterization of chloroprene as a Category 1 gas and the application of a dosimetric adjustment factor for portal-of-entry effects have not been adequately justified.

The NTP study that was used to derive the RfC did not achieve a NOAEL, and the severity of the nasal lesions was greater than minimal in the lowest exposure concentration group. In fact, several male rats in the low exposure group (12.8 ppm) were graded with moderate severity for olfactory atrophy and necrosis. The benchmark response of 10% extra risk is not a NOAEL and the estimated BMD_{10} used to derive the RfC is approximately 60% of the lowest concentration used in the chronic toxicity study of chloroprene. Because the NTP study included 50 animals per group, a BMR of 2% or 5% extra risk would likely provide a reliable estimate for the derivation of the POD without substantially increasing statistical uncertainty at the POD. Thus, I strongly recommend BMD modeling and derivation of the POD from the 2% or 5% extra risk response; if that is not done then an additional uncertainty factor of 3 to 10X would need to be applied to the human equivalent POD.

John B. Morris

I do not concur with the approach used to derive the POD-HEC. Multiple POD-HEC values were derived for differing lesions and the most sensitive was then selected. I note that the POD values (prior to DAF correction) for all the lesions are virtually identical, spanning 2.1-8.3 mg/m3 range. The only reason the POD-HEC is lower for the nasal lesions is that the DAF is so low. Thus, the selection of the nasal lesions as the most sensitive response is simply an artifact of the DAF (RGDR) calculation and not based on the primary experimental observations.

My concerns relative to the RGDR are described below. Essentially they are: 1) the RGDR calculation is theoretically flawed and discordant with the inhalation dosimetry database, and 2) there is no basis to conclude that airborne rather than blood-borne chloroprene induces nasal olfactory lesions. The absence to consider blood-borne delivery is particularly confusing in light of the fact that the possibility of blood-borne delivery relative to pulmonary lesions received much attention. Why this was ignored for the nose is perplexing. The distribution of lesions (olfactory, but no respiratory mucosal damage) could certainly be reflective of a critical role for blood borne delivery and/or in situ metabolic activation. The absence of nasal respiratory injury suggests the parent compound and/or direct reactivity of the parent compound are not likely involved. Commonly a strong anterior/posterior gradient in respiratory mucosal injury is seen for vapors which are directly reactive. This is not the case for chloroprene, in fact, no respiratory mucosal lesions were seen. Were blood borne delivery considered I believe

the RDGR would be 1. In my view, the assumption that chloroprene is a category 1 gas is also flawed (see below). Given that numerous compounds produce nasal olfactory injury following parenteral administration, the observation of nasal olfactory injury cannot be used in support of a category 1 assignment. The partition coefficient of chloroprene is quite small (10) from a nasal dosimetric view. It is difficult, if not impossible, to envision a scenario in which nasal backpressure does not influence dosimetry and/or that nasal deposited chloroprene does not penetrate to the depth of the blood. In my view, chloroprene is a category 3 gas.

At best, the assignment of category 1 status and the exclusion of blood-borne delivery mechanisms represent a weakness of the RfC derivation. An alternate approach would be to select the POD on a parameter closely associated with the collected data rather than to pick a value subject to artifact from the RGDR approach. Were this done, a differing critical lesion would be selected – likely alveolar epithelial hyperplasia and/or hematopoietic proliferation. Given that the subsequent text includes considerable discussion of the possibility of blood borne delivery relative to pulmonary injury, the selection of an inhalation based DAF of 2.3-4.1 would need to be critically discussed and supported were lung lesions selected as the critical effect. For the cancer risk extrapolation both inhalation based and blood-borne based DAF values were used. Why not use both approaches for the non cancer endpoints as well? The lack of consistency is striking.

I am supportive of using a BMD approach as the database appears sufficiently robust to allow for this calculation. An extra risk of 10% of mild lesions is an appropriate endpoint in my view. However, if moderate grade lesions were observed at exposure concentrations approximating the calculated BMD10, it would suggest the calculated value is too permissive. As noted above, I would recommend selecting the endpoint based on the observed data and then performing a single DAF-based calculation based on those data. Such an approach would minimize artifacts due to complexities associated with selection of the most appropriate DAF.

Avima M. Ruder

I don’t have the expertise in risk assessment to comment on whether the modeling and extrapolation from animal to human was appropriately conducted. However, a 10% increase in an effect appears to be a significant enough departure from good health to justify the calculation. Upon reflection, I agree with the argument made by Dr. Melnick that the proposed benchmark dose does not represent a NOAEL and that it might be better to look at a lower response level (2-5%). From the responses from EPA staff at the review meeting it appears that a 2-5% extra risk response level was considered in internal EPA discussions. I also think that the issues raised by Dr. Morris as to whether chloroprene is a category 1 gas or not need to be clarified.

Richard B. Schlesinger

The BMD approach is very well suited for the large data set of the principal study being used in this document and using chronic toxicity and carcinogenicity as endpoints. In general when using the BMD, a 10% level of acceptable risk is used. Thus, this document follows relatively standard procedures in this regard. However, based upon the data, this level may be too high and it is suggested that a lower level, perhaps 5%, be used in this case. The document could be clearer in showing the different stages in the development of the RfC. It does provide a formula on page 5-4 but does not show the use of the formula with actual numbers from the principal study. It would be helpful to the reader if such a step by step actual derivation was provided. For example, it would help to see the actual value for the PODadj (mg/m^3) that was used to derive the HEC.

(B) Inhalation Reference Concentration (RfC) for Chloroprene

4. Please comment on the rationale for the selection of the uncertainty factors (UFs) applied to the POD for the derivation of the RfC. If changes to the selected UFs are proposed, please identify and provide a rationale(s

Herman J. Gibb

The uncertainty factors seem reasonable.

Dale Hattis

I have no quarrel with the selection of uncertainty factors made in the document. The analysis seems very standard. The only area of modest controversy might be the choice of a database uncertainty factor of 3. This seems adequately justified by the absence of a two-generation reproductive study, although the negative findings for teratogenesis and dominant lethal effects could have been considered an adequate substitute.

Ronald L. Melnick

The selection of uncertainty factors of 10X for human variation, 3X for animal-to-human toxicodynamic uncertainty, and 3X for database insufficiencies are reasonable and consistent with EPA policy. However, it is not possible to know if the UFs selected for human variability and interspecies uncertainty adequately account for the extent of these variations. For example, human variability is greater than 10X for the activities of the enzymes involved in chloroprene metabolism (both activation of chloroprene and detoxification of the reactive epoxide intermediate). As noted in response #3 above, the BMD_{10} is a true effect level with several animals diagnosed with moderate lesion severity (i.e., the severity level just below marked). The EPA assumption that the BMD_{10} represents a minimal biologically significant change that was less than moderate severity is not correct. Thus, an additional uncertainty factor of 3-10X should be applied to the RfC derived from a BMD_{10}; alternatively, the POD should be derived from a BMR or 2% or 5% extra risk. An additional deficiency in the database includes lack of data on potential neurodevelopmental toxicity, or other long-term effects following perinatal exposure.

John B. Morris

The rationale for UF selection is clear and appears consistent with typical procedures. The discussion would be greatly enhanced by inclusion of discussion of the impact and uncertainty of selecting DAF factors based on airborne delivery. My concerns, in this regard, are provided above. In my view, it is important to recognize that the DAF calculation is subject to considerable uncertainty and, as such, should not be accepted as factually based. Discussion should also be included on the basis for inclusion of a database limitation uncertainty factor as a multi-generation study is available. It should be stated if this is policy-based rather than scientifically-based decision.

Avima M. Ruder

The uncertainty factors appear justified. As I commented above, there is probably considerable human variation in the metabolism of chloroprene, due to polymorphisms in the genes coding metabolic enzymes. However, as Drs. Schlesinger, Hattis, and Melnick suggested during the review (or as I understood them to suggest), it might be more appropriate to change the benchmark dose response, rather than the uncertainty factors. Their arguments should be considered.

Richard B. Schlesinger

The specific UFs chosen are well justified and appropriate for the data set used and follow standard USEPA guidelines.

(C) Carcinogenicity of Chloroprene

1. Under the EPA's 2005 Guidelines for Carcinogen Risk Assessment (www.epa.gov/iris/backgr-d.htm), the Agency concluded that chloroprene is likely to be carcinogenic to humans by all routes of exposure. Please comment on the cancer weight of evidence characterization. Is the cancer weight of evidence characterization scientifically justified?

Herman J. Gibb

The characterization is clearly justified based on the animal and genotoxicity data, but the argument for the epidemiologic data has been overstated.

The reported evidence of a liver cancer risk in the Louisville cohort studied by Marsh et al. (2007a, 2007b) summarized on page 4-18, lines 3-5 relies heavily on a purported dose response in 4 cumulative exposure categories. The document does not describe what the relative risks (and confidence limits) are in each of the four exposure categories but states that the probability of the trend is 0.09 (page 4-13, lines 13-17; page 4-71, lines 4-7)[1,2]. Furthermore, the document neglects to report what the overall SMR for liver cancer is in the Louisville cohort. Interestingly, the document concludes that there is no evidence of a dose response relationship for respiratory cancer yet describes the relative risks and confidence limits for respiratory cancer by all four cumulative exposure levels for all four facilities in the Marsh et al. study (page 4-14, Table 4-9). Why isn't the reader given that information for the liver cancer relative risks, at least for the Louisville cohort, since the document has gone to the point of suggesting that the data indicates that there is a liver cancer dose response? Furthermore, in the discussion of "biological gradient" on page 4-71, no mention is made of Table 4-11 on page 4-17 showing that two studies demonstrate evidence of a dose response for liver cancer, and two demonstrate *no* evidence of a dose response. The dose response in one of the studies (Leet and Selevan 1982) would not even exist if only deaths from liver cancer were included in the analysis since two of the three deaths from cancer of the liver and biliary passage in the high exposure category were due to gall bladder cancer. The other study in Table 4-11 that suggests a dose response is Bulbulyan (1999), but the relative risks in the high and low dose are not statistically different. The statement at the bottom of page 4-18 that there is evidence of a dose-response relationship in different cohorts in different continents (U.S., China, Russia, and Armenia) grossly misrepresents the evidence.

Known risk factors for liver cancer include Hepatitis B and C infection, aflatoxin ingestion, certain inherited metabolic diseases, cirrhosis due to alcohol abuse, obesity, and certain inherited metabolic diseases (American Cancer Society). None of these factors with the exception of alcohol consumption (page 4-69, lines 28-29) have been

[1] The document states on page 4-13, lines15-17, and page 4-13, lines 4-71, lines 5-6 the *range* for the *three* highest exposure levels was from 1.9-5.1 but doesn't state what the RR's for each of the four exposure levels are nor does it provide confidence limits on the RRs.
[2] If the p = 0.09 is calculated by the authors of the EPA document (as opposed to Marsh et al.), that should be indicated.

discussed in the review. It is interesting that in the Major Conclusions on page 6-2, lines 27-29, the document notes that "These associations (respiratory cancer) are not considered as strong as those with liver cancer due to the inability to control for confounding by smoking status, a strong indicator of lung cancer." What about the well-known risk factors for liver cancer? Were they considered in the various studies? On page 4-69, lines 28-29, the document indicates that the lack of data on alcohol consumption is a "key limitation." On lines 31-32, the document states that there is also a "high likelihood of co-exposures which may be confounders." Nonetheless, the document goes on to blithely state that "Despite this potential, there is little evidence of substantial exposure to liver carcinogens in these populations." How can such a statement be made if the study authors never considered the major risk factors?

Of particular note with respect to the Li et al. study is that the highest liver cancer rate in the world is China (as much as 10X that in the U.S.), primarily the result of Hepatitis B infection and aflatoxin ingestion. Given the considerable risk posed by these risk factors in a Chinese population and that there were only 6 liver cancer deaths in the entire cohort working in a facility where there were multiple chemical exposures, it is impossible to conclude that the study indicates an association between chloroprene and liver cancer.

The document indicates on page 4-8 that Bulbulyan et al. (1998) found 11 deaths due to cirrhosis. It is possible that these deaths could have been caused by chloroprene, but alcohol and hepatitis B/C infections are the most common causes of cirrhosis which should say something about the cohort. Liver cancer is about 50% higher in Eastern Europe than it is in North America, and alcohol consumption in Russia is reported to be almost double that of the U.S.

The analysis of the Bulbulyan (1999) study indicates that there was increasing incidence of liver cancer by duration of employment and by cumulative exposure. Presumably duration of exposure and cumulative exposure were not evaluated together in a multiple regression by the study authors (I do not have the original paper). Given that there was an increasing risk by duration of exposure, one cannot rule out that the increasing risk with cumulative exposure was not due to other exposures at the facility. Presumably, there was no analysis by intensity of exposure? If there was, what did it show?

The document should be more transparent in the presentation of the human data on liver cancer. For example:

- The liver cancer relative risks for all four exposure categories in the Louisville cohort studied by Marsh et al. should be reported.
- The SMR for liver cancer should be reported for the Louisville cohort studied by Marsh et al.
- Whether Marsh et al. (2007a, 2007b) and Leet and Selevan (1982) Louisville cohorts are independent should be addressed. If Leet and Selevan (1982) is a part of or the same as the Marsh et al. cohort (or even very similar), then use of the Leet and Selevan (1982) should not be described as providing independent results of dose

response, consistency, etc. The same is true of the Colonna and Leydavant (2011) and the Marsh et al. studies of the Pontchartrain facility.

- The confounding factors for liver cancer and whether studies addressed these risk factors should be discussed.
- The statement in the Major Conclusions on page 6-2, lines 19-20 that there was "some evidence" of liver/biliary passage cancer risk being associated with chloroprene exposure is followed by the statement on lines 22-23 that these measures of association were "strong, especially in the presence of healthy worker bias" is inconsistent.
- An association between liver cancer and chloroprene exposure being strengthened by the healthy worker effect as indicated in the Major Conclusions is not evident in the summary of the overall weight of evidence (some mention of HWE is made on page 4-69, lines 21-25 but does not indicate that the evidence is strengthened). Furthermore, a healthy worker effect for liver cancer? With such a short life expectancy following diagnosis, I would expect the healthy worker effect for liver cancer to be minimal if it even exists.
- The small number of liver cancer deaths/cases in the studies by Li et al., Bulbulyan (1998, 1999) and Leet and Selevan (1982) and the variability about such small numbers should be better described, particularly in light of the limitations of those studies with respect to calculation of the expected deaths, follow-up, etc.

As the document acknowledges on page 4-17, there is little if any evidence that chloroprene increases the risk of respiratory cancer. The limitations of the earlier studies (Li et al. 1989, Bulbulyan 1998, 1999) are significant with regard to whether or not they indicate an increased risk of liver cancer from chloroprene exposure. The largest and what appears from the document to be the best conducted study (Marsh et al., Louisville cohort) provides little if any evidence that a liver cancer risk exists. Furthermore, the document has not been transparent in its reasoning that there is a risk of liver cancer.

In summary, the descriptor of "likely to be carcinogenic to humans" is supported by the animal and genotoxicity data, but not by the human data. While the descriptor is appropriate, the document should not try to make more of the epidemiologic studies than is warranted.

Dale Hattis

Yes. The ample information on carcinogenesis in many sites in animals, the clear metabolism information to mutagenic metabolites, and the analogies to related chemical carcinogens with analogous metabolic pathways to DNA-reactive metabolites all combine to make this conclusion unequivocal. As suggested by Dr. Melnick, the final document should consider whether the available evidence warrants an upgrade of the classification to "carcinogenic to humans.

Ronald L. Melnick

Results from the NTP study demonstrating multiple organ carcinogenicity of inhaled chloroprene in both sexes of rats and mice are consistent with the EPA descriptor "likely to be carcinogenic to humans." Because the carcinogenicity of chloroprene is likely due to its epoxide metabolites, and because cytochrome P450-mediated epoxidation of chloroprene can occur in several organs including the liver, kidney, and lung, metabolism of absorbed chloroprene to a mutagenic intermediate can occur by any route of exposure. The systemic distribution of tumors in the NTP studies demonstrates that chloroprene can induce tumors beyond the sites of initial contact. Liver toxicity of chloroprene in rats after oral exposure (stomach tube) indicates the occurrence of oral absorption of this chemical. Chloroprene is absorbed by the skin (Hazardous Substances Data Bank; see page 3-1).

However, the descriptor "carcinogenic to humans" may be more appropriate based on the multiple tumor response in two species, the fact that chloroprene is activated by CYP2E1 to a DNA reactive intermediate (chloroethenyl oxirane) by rat, mouse, or human liver microsomes, the finding of a unique K-ras mutation (A→T at codon 61) in chloroprene-induced lung neoplasms in mice, and the relatively consistent evidence of an association between increased liver cancer mortality risk and occupational exposure to chloroprene. The EPA document does not adequately justify the characterization of chloroprene as "likely to be carcinogenic to humans" rather than "carcinogenic to humans," especially since many of the identified methodological limitations in the epidemiologic studies (e.g., exposure misclassifications, healthy worker effect) would result in an underestimate of risk. According to EPA's cancer risk assessment guidelines, the descriptor "carcinogenic to humans" may be applied when there is less than convincing epidemiologic evidence of a causal association between human exposure and cancer if there is strong evidence of carcinogenicity in animals, the MOA and precursor events have been identified in animals, and key precursor events in animals are anticipated to occur in humans and progress to tumors. These conditions have been demonstrated for chloroprene.

John B. Morris

I concur that the weight of evidence supports the concept that chloroprene may be carcinogenic by all routes of exposure. Multiple tumors were seen in two species in inhalation bioassays. Additionally some data suggesting increased tumor risks in humans is available. Tumors were seen in non-site of contact sites in the rodent studies. (In this regard respiratory tract as well as gastrointestinal tract tumors may be considered as site of contact because of preening activity.) Moreover, there is discussion of the possibility of a critical role blood-borne chloroprene relative to nasal and pulmonary lesions. If there is, indeed, a role for blood borne chloroprene, then the possibility of carcinogenicity after multiple routes of exposure is elevated because systemic absorption and blood-borne delivery to multiple targets is possible. (The document indicates dermal absorption may occur.) Importantly, a potential increase in liver tumors was noted in some occupationally exposed cohorts. In my view, these epidemiological data support the concept that chloroprene may represent a carcinogenic hazard to man.

Avima M. Ruder

The literature supports the likely carcinogenicity of chloroprene and the mutagenicity of its epoxide metabolites. The need for regulation of environmental (in addition to occupational) exposure to chloroprene is justified by a report on public health in the area where the Louisville DuPont plant and other industrial facilities, as well as residences, are co-located. In that report, the Agency for Toxic Substances and Disease Registry (ATSDR) stated that the volume of release of chemicals from the plants made it likely that soil and water (groundwater and the Ohio River) had been contaminated in the past; chloroprene air contamination was measured as 218 ppb or 789 $\mu g/m^3$ in 1956-7 downwind of the plants and 6 ppb or 2.68 $\mu g/m^3$ in 1988 at a monitoring station in downtown Louisville not downwind of the plants [Agency for Toxic Substances and Disease Registry 1998].

ATSDR provided a rationale for the greater vulnerability of children to toxic exposures: they are more likely to play outdoors and bring food into contaminated areas; are shorter and therefore closer to dust, soil, and contaminants; weigh less, resulting in higher doses per unit body weight; and are developing rapidly [Agency for Toxic Substances and Disease Registry 1998]. The EPA's use of age-adjustment factors seems appropriate.

Richard B. Schlesinger

While the *Guidelines for Carcinogen Risk Assessment* are being followed in the chloroprene assessment, even though there are limited to no data on exposure other than inhalation, it seems that the mode of action of the chemical is such that it may not be carcinogenic via all routes, e.g., dermal exposure. It is nonreactive chemically and relatively insoluble in water. The weight of evidence characterization is clear and justified. The animal toxicological data support the conclusion that it may likely be carcinogenic to humans. While the epidemiological evidence in this regard is equivocal, the conclusion is also supported by the fact that the MOA involves conversion to epoxides.

(C) Carcinogenicity of Chloroprene

2. A two-year inhalation cancer bioassay in B6C3F1 mice (NTP, 1998) was selected as the basis for derivation of an inhalation unit risk (IUR). Please comment on whether the selection of this study for quantification is scientifically justified. Please identify and provide the rationale for any other studies that should be selected as the basis for quantification.

Herman J. Gibb

The selection of this study is justified. The document states that the Trochimowicz et al. study was not chosen as the principal study "primarily due to the lack of observed neoplastic effects at similar exposure levels as the NTP (1998) study"(page 5-12, lines 5-8). As with the response to Question 1 for the RfC above, high mortality in the low dose animals (page 4-39, lines 19-20; page 5-2, lines 13-16, 29-31) would be a stronger argument for not choosing the Trochimowicz study than would differences in observed effects between studies. Differences in study results can occur regardless of how well the individual studies are conducted.

Dale Hattis

Choice of the two-year inhalation bioassay is beyond dispute. However, as indicated earlier, the dosimetry, in terms of active metabolite concentration AUC, could have been informed by application of a preliminary PBPK model.

Ronald L. Melnick

The selection of the NTP 2-year inhalation carcinogenicity study of chloroprene in B6C3F1 mice for derivation of an inhalation unit risk is scientifically justified. The NTP study was well designed and conducted, and identified carcinogenic effects in multiple organs of rats and mice exposed to a wide range of concentrations of chloroprene. A major strength of this study is the multiple histopathological reviews of lesions identified in rats and mice. As with the related human carcinogen, 1,3-butadiene, the carcinogenic potency of chloroprene was greater in mice than in rats.

John B. Morris

In my view, the selection of the two-year inhalation bioassay done by NTP as the critical study is appropriate. This study was well performed and peer reviewed. It is true that the Trochimowicz study provided contradictory results, but without substantive rationale the NTP study cannot be ignored. Inclusion of the mouse lung tumor data for dose-response evaluation may be scientifically problematic. As is commonly observed, the mouse metabolic activity for chloroprene is 50-fold higher (Table 3-4) than that in the human or the rat (in which lung tumors were not increased). This fact should be discussed. It is my view that the mouse lung data may overestimate the risk to humans. It is recognized that exclusion of these data may be problematic, but at a minimum a discussion of this

weakness should be provided. Because the metabolism rates in the rat appear similar to the human, the rat may offer a better species for prediction of human health risks. Certainly the document would be improved by an explicit discussion of the relevance of the mouse response considering its high metabolic capacity.

Avima M. Ruder

The text in section 5.4.4 explains the derivation of the inhalation risk but does not explain why inhalation in mice was chosen over inhalation in rats from the same study. I assume there are physiological differences which make mice a more suitable choice, but none were provided here.

Richard B. Schlesinger

The study selected for derivation of the IUR is well justified based upon the standard procedure used by USEPA in selecting the most sensitive animal model. However, they may want to consider the fact that metabolic activation rate in the rat is closer to that occurring in humans than is the situation in mice.

(C) Carcinogenicity of Chloroprene

3. A mutagenic mode of carcinogenic action is proposed for chloroprene. Please comment on whether the weight of evidence supports this conclusion. Please comment on whether this determination is scientifically justified. Please comment on data available for chloroprene that may support an alternative mode(s) of action.

Herman J. Gibb

The hypothesized epoxide metabolite mode of action is reasonable.

Dale Hattis

Yes. The ample information on carcinogenesis in many sites in animals, the clear metabolism information to mutagenic metabolites, and the analogies to related chemical carcinogens with analogous metabolic pathways to DNA-reactive metabolites all combine to make this conclusion unequivocal. I am not aware of any evidence that comparably supports any other mode of action.

Ronald L. Melnick

Based on the fact that the predominant pathway of chloroprene metabolism is via cytochrome P450-mediated oxidation to a DNA-reactive epoxide intermediate (chloroethenyl oxirane), which is mutagenic in multiple strains of Salmonella, and the finding of activating K-ras and H-ras mutations mutations in tumor tissues obtained from mice exposed to chloroprene, including unique K-ras mutations (A→T transversions in codon 61) in lung tumors, the proposed mutagenic mode of carcinogenic action is scientifically justified. This MOA is consistent with that of other epoxide-forming carcinogens, e.g., 1,3-butadiene and vinyl chloride. There is no scientific data supportive of any alternative mode of action. Recent experimental results presented to the Peer Review Panel by DuPont demonstrated the induction of changes in gene expression related to DNA damage in the lungs of mice exposed to 2.5 ppm or higher concentrations of chloroprene (Figure 8, page 79). These data also support a mutagenic mode of carcinogenic action for chloroprene.

John B. Morris

It should be stated that detailed assessment of mutagenic versus non-mutagenic modes of action is somewhat beyond my expertise. With this qualification, I concur with the proposed mutagenic mode of action of chloroprene. Chloroprene metabolite(s) are DNA reactive and mutagenic in some bacterial strains. Data presented by DuPont suggests the induction of DNA repair responses in chloroprene exposed animals. Mutations were observed in vivo in lung tumors of animals exposed to chloroprene. Were a purely cytotoxic mode of action proposed it would be important to show appropriate temporal and dose-response data supportive of this mode. I am aware of no such data. In my view there are insufficient data to exclude the possibility of a mutagenic mode of action. There

appears to be multiple lines of evidence in support of this mode of action and it, therefore, appears scientifically justified. If, however, it is concluded that a metabolite represents the ultimate toxic species, then the quantitative risk assessment should be discussed/validated in light of the large species differences in metabolism rate.

Avima M. Ruder

The metabolic pathways detailed in figure 3-1 (and in the toxicological literature from which this section is drawn) appear to justify this conclusion. The finding of increased chromosome aberrations among humans with variant metabolic enzymes that clear the epoxide metabolite more slowly [Musak, et al. 2008] also supports this conclusion.

Richard B. Schlesinger

There is much compelling evidence that chloroprene has a mutagenic mode of action due to metabolism into reactive epoxides. While this may not be the only MOA, it clearly is one of them.

(C) Carcinogenicity of Chloroprene

4. Data on hemangiomas/hemangiosarcomas (in all organs) and tumors of the lung (bronchiolar/alveolar adenomas and carcinomas), forestomach, Harderian gland (adenomas and carcinomas), kidney (adenomas), skin and mesentery, mammary gland and liver in B6C3F1 mice were used to estimate the inhalation unit risk. Please comment on the scientific justification and transparency of this analysis. Has the modeling approach been appropriately conducted? Please identify and provide the rationale for any alternative approaches for the determination of the inhalation unit risk and discuss whether such approaches are preferred to EPA's approach.

Herman J. Gibb

The rationale for combining risks from different tumor sites is reasonable given a mutagenic mode of action. It is interesting, however, that the inhalation unit risk estimate for chloroprene is an order of magnitude higher than the inhalation unit risk estimate for butadiene which is considered a structural analog and characterized by EPA as "carcinogenic to humans". A reality check on the unit risk for chloroprene by comparing it with an upper bound on the cancer risk in the Louisville cohort studied by Marsh et al. should be performed. The Louisville cohort has the best exposure information for this purpose. From the resulting comparison, it may be necessary to adjust the unit risk estimate.

Dale Hattis

The approach is transparent and reasonable as far as it goes. However, I think it is not ideal in that it fails to make explicit use of the information that there is likely to be high dose saturation of metabolic activation.

As an alternative, at the peer review meeting I presented a series of model fits using a dose response form that incorporates an assumption of saturating metabolism on a systemic level (applicable to all tumors in the same way) but different effective background rates and potencies for the causation of tumors at low doses:

$$P(d)_i = 1 - e^{-(q0_i + \frac{Vmax_i * d}{Km + d})}$$

where:

d is the external experimental concentration in ppm

$P(d)_i$ is the fraction of animals with at least one tumor for a specific tissue (i)

$q0_i$ is a parameter estimated from data that is related to the background (control group) lifetime incidence of tumors in that tissue

V_{max} is related to the maximum tumor yield over background for the specific tissue (i)

K_m is the external dose that produces half the maximal tumor yield over all tissues (based on an assumption that metabolic activation is systemic, rather than being effective for only one tissue due to local metabolism).

This is essentially a quick and easy but approximate substitute for doing a full PBPK model, but instead uses the tumor response nonlinearity at high doses for all the tumor sites to quantify the approach toward saturation of the activating metabolism. Compared to a PBPK modeling approach, this is not informative for the issue of interspecies projection, but it does provide information about the high-dose-to-low dose projection, assuming that the saturable activating metabolism is systemic and affects the tumor frequency in all tissues in the same way. This sort of treatment is warranted by the fact that, in nearly all tissues with an appreciable tumor yield in both male and female mice, the tumor incidence over background at the highest (80 ppm) chloroprene concentration is much less than double the tumor incidence at the next highest (32 ppm) concentration (see plots below). Contrasting the results for the high-dose saturable metabolic activation model with those for a straight linear model allows us to assess how large the change in estimated low dose cancer slope might be relative to a case where there is only a term that is linear in dose:

$$P(d)_i = 1 - e^{-(q0_i + q1_i d)}$$

To maintain parallelism with the EPA analysis as much as possible, I made this comparison excluding the anomalous high-dose point for hemangiosarcomas in female mice. Because of this same anomaly, I choose to begin the discussion of the modeling and the model results with the observations in male mice.

Figure 1 is a raw plot of the end of life tumor data for male mice used by EPA in its analysis (from a comment by Dr. Melnick, I understand that tumor results adjusted for mortality are also available in one of his papers; EPA should probably used those results for a more refined analysis.)

A difficulty with the raw plot the tumor data is that one might object that of course there is a flattening of the curve at higher doses and tumor incidences because no more than one tumor can be effectively detected and recorded in any specific tissue. Thus a more appropriate interpretation of the data is to say that each data point represents the fraction of animals that showed <u>at least</u> one tumor in each specific tissue studied. A more appropriate plot without the potential distortion due to multiple tumors per organ can be made by using a Poisson distribution formula

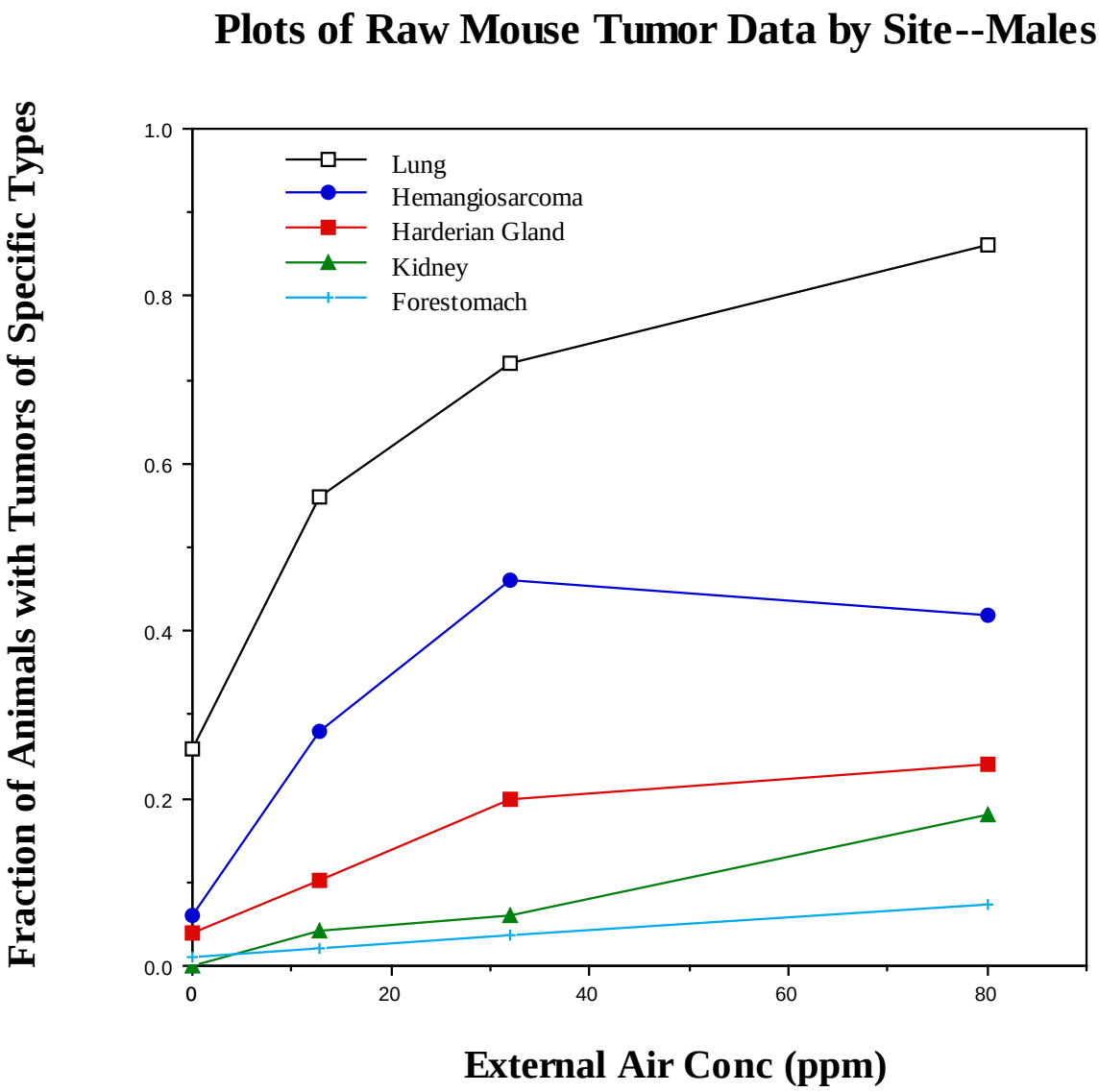
$$P_{0 \text{ tumors in an organ}} = 1 - \text{Fraction of Animals with at Least 1 tumor} = e^{-m}$$

where m = the mean number of tumor transformations per animal

:

.

Figure 1


Plots of Raw Mouse Tumor Data by Site--Males
Fraction of Animals with Tumors of Specific Types
1.0
0.8
0.6
0.4
0.2
0.0
Lung
Hemangiosarcoma
Harderian Gland
Kidney
Forestomach
0
20
40
60
80
External Air Conc (ppm)

Given this, we can solve for m to find

$$\text{mean number of tumor transformations per animal} = -\ln(1 - \text{fraction of animals with at least 1 tumor})$$

Figure 2 is a plot of the male mouse tumor data using this transformations/animal parameter as the dependent variable. It can be seen that even after removing the truncation of the tumors/animal results at 1 in this way, there is still a pronounced flattening of the curves at the higher dose levels, indicating some approach to saturation. This is reminiscent of the vinyl chloride angiosarcoma case where there was saturation of metabolic activation at the higher exposure levels.

One other advantage of the transformations/animal dependent variable is that we can add up the results for the different tumor sites. Figure 3 shows a revised plot of the male tumor data showing the sum of tumor transformations/animal at all five tumor sites. It can be seen that the sum of tumor transformations at all five sites still shows a pronounced convexity as one proceeds to the highest exposure levels.

The fitting of the saturable and linear models was accomplished in Microsoft Excel workbooks designed to incorporate likelihood calculations according to the basic structure published by Haas (1994).[*] Copies of the final workbooks themselves will be submitted to accompany this comment. I would be pleased to explain the detailed features and operation of the modeling system if any EPA personnel would like to pursue this. Basically, each workbook consists of 3 sheets: one for optimization of the maximum likelihood estimates and two for estimation of upper and lower confidence limits on the sum of transformations/animal at all tumor sites. The optimizations were all done with the Excel solver tool, generally with multiple runs of hundreds to thousands of iterations each. Because the maximum likelihood and confidence limit estimates are done on the sum of tumor transformations per animal for all tumor sites, no Monte Carlo post-processing analysis is needed to derive confidence limits on the total tumor risk, as was needed for the separate Weibull model analyses done by/for EPA for the individual tumor sites. On the other hand, a disadvantage of this modeling system is that it only incorporated total tumor incidences observed by the end of the bioassays; not the more detailed time-to-tumor information used in the Weibull model analysis.

Figure 4 shows the overall results of this fitting for both the saturable and linear models. In the case of the saturable model, the parameters estimated are a Vmax and background (zero dose) tumor risk for each organ, and a Km (external ppm needed to achieve half of the total saturated tumor yield) common to all organs—following the hypothesis of saturable metabolism at a systemic level followed by common exposure of all organs to the activated metabolite(s). It can be seen that the saturable model fit corresponds very well with the observations of total tumors per animal (the P value is 0.51, meaning that a difference between data and model predictions as large as that observed would be expected to be produced about half the time from chance sampling-error fluctuations).

[*] Haas, C. N. "Dose Response Analysis Using Spreadsheets" Risk Analysis 14:1097-1100 (1994).

Figure 2

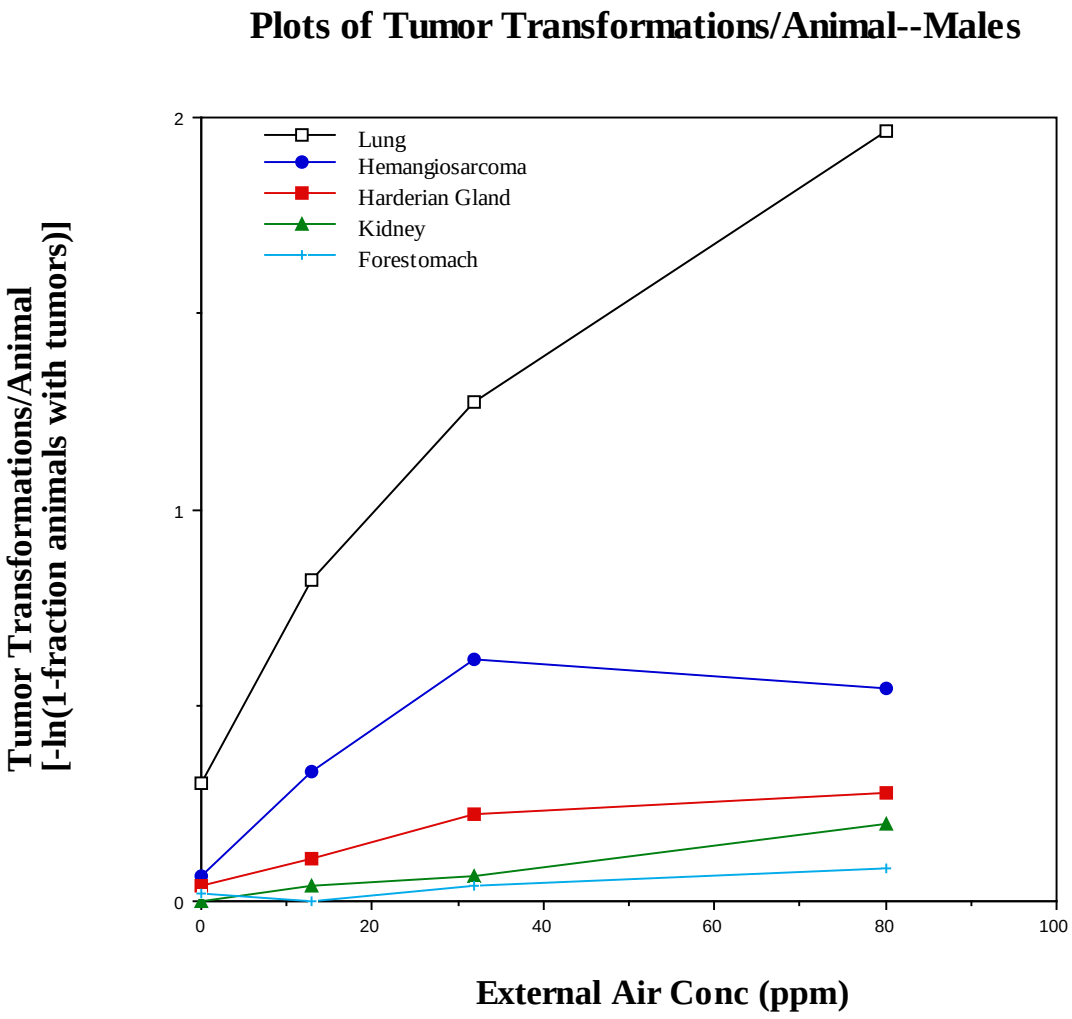

Plots of Tumor Transformations/Animal--Males
Tumor Transformations/Animal
[-ln(1-fraction animals with tumors)]
Lung
Hemangiosarcoma
Harderian Gland
Kidney
Forestomach
2
1
0
0
20
40
60
80
100
External Air Conc (ppm)

Figure 3

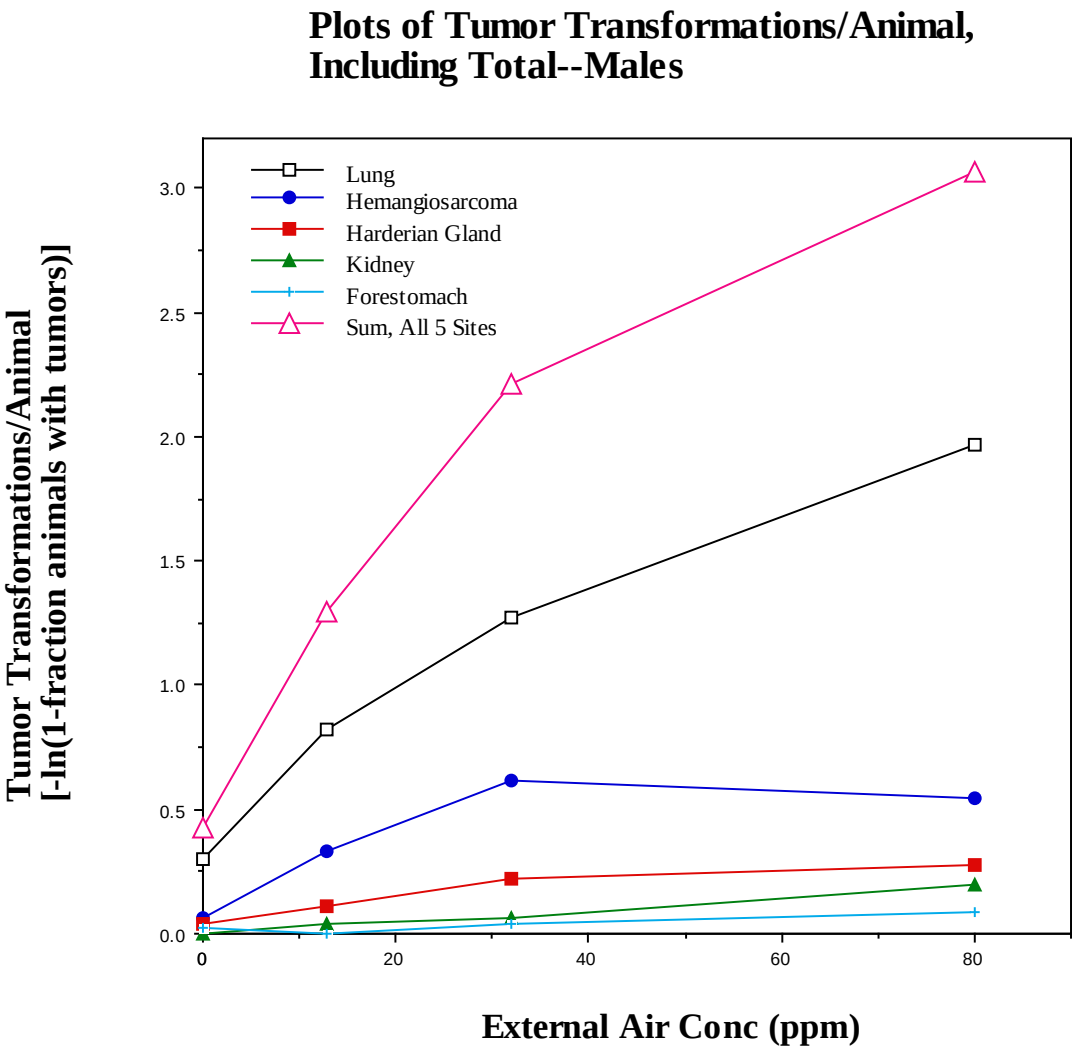
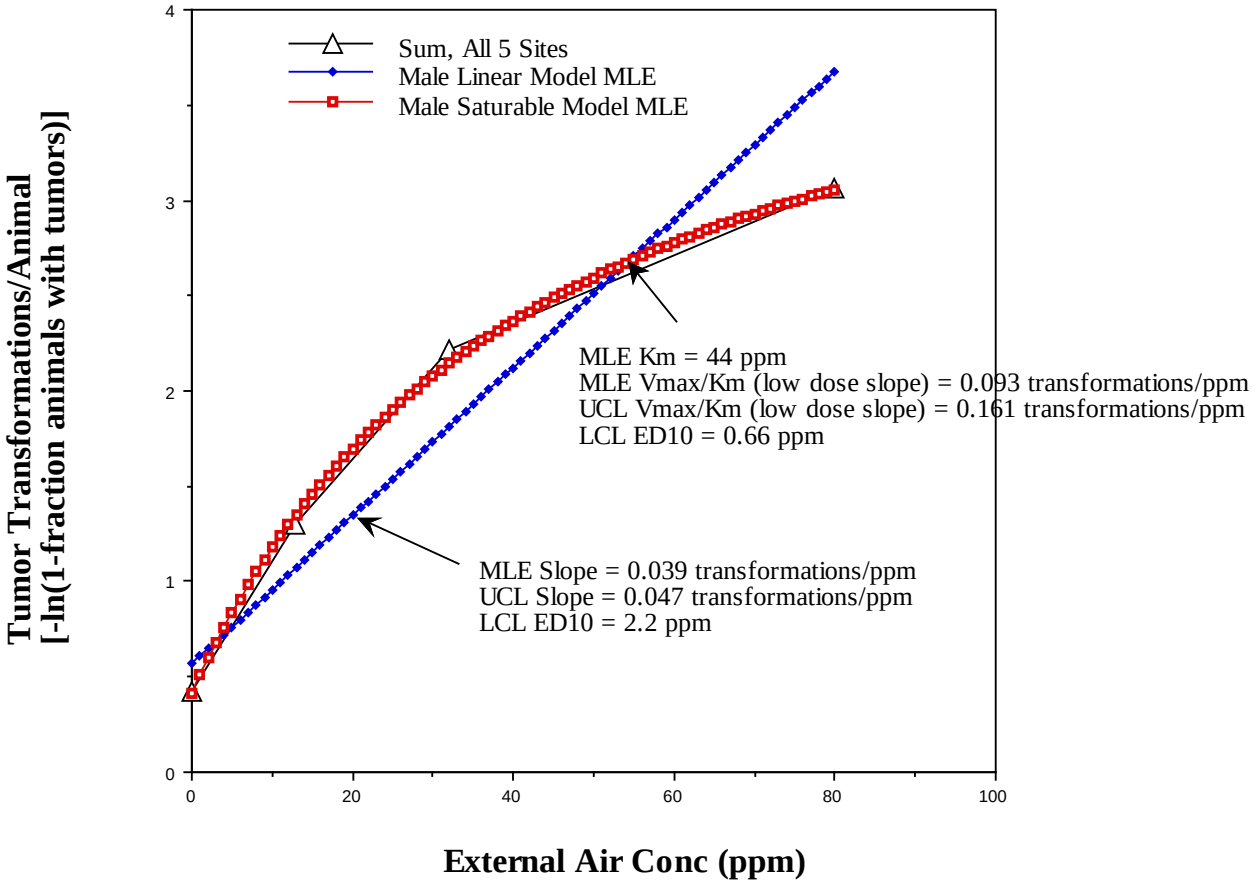

Plots of Tumor Transformations/Animal, Including Total--Males
Tumor Transformations/Animal [-ln(1-fraction animals with tumors)]
Lung
Hemangiosarcoma
Harderian Gland
Kidney
Forestomach
Sum, All 5 Sites
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
20
40
60
80
External Air Conc (ppm)

Figure 4

Comparison of Observed Tumor Transformations/Animal For All 5 Sites in Males with Maximum Likelihood Expectations for Linear and Saturable Models



The linear model fit somewhat less well at P = 0.06, although still barely within the conventional P = 0.05 criterion based on estimation of one fewer parameter (10, rather than 11, corresponding to a background rate and a transformations/ppm parameter for each tumor site).

The results in Figure 4 indicate a half saturation point (Km) of about 44 ppm, and an approximately 2-3 fold greater cancer potency at low doses for the saturable, compared to the linear model, depending on whether one makes the comparison based on MLE slopes or lower confidence limit ED10's. Thus the indication is that a simple linear formulation, as incorporated into EPA's Weibull model is likely to considerably understate the low dose potency indicated by the data for males.

Figure 5 shows a plot of the female tumor data comparable to Figure 2. The same tendency for flattening at high exposure levels is apparent. Figure 6 shows the results a similar comparison of saturable and linear model fits for the female tumor data (excluding, as did EPA, the high dose point for the hemangiosarcomas). The overall fit in this case is less successful than for the male tumor data, with a P value of about 0.02, but the saturable model still fits a great deal better than the linear model with a P value of about 9×10^{-5}. In this case the indicated Km is slightly lower (30 ppm) indicating a slightly greater effect of the indicated saturation of metabolic activation, and the saturable model again suggests a low dose cancer potency a few fold greater than expected with the linear model formulation.

In summary results lead me to five conclusions/recommendations:

- The tumor data are better fit by models incorporating systemic saturable metabolism.
- Saturable models lead to 2-3 fold increases in expected low dose risks compared to simple linear models.
- However, the current saturable models do not incorporate available time-to-tumor information.
- The best way forward would therefore be to add a saturable component to the Weibull time-to-tumor model.
- A second-best approach would be to multiply the expected ratio of saturable vs. linear model-predicted low dose risk by the existing Weibull linear model coefficient (or make a similar adjustment downward in the Weibull model estimated ED10 or LED10).

Figure 5

Plots of Tumor Transformations/Animal Excluding Hemangiosarcomas--Females

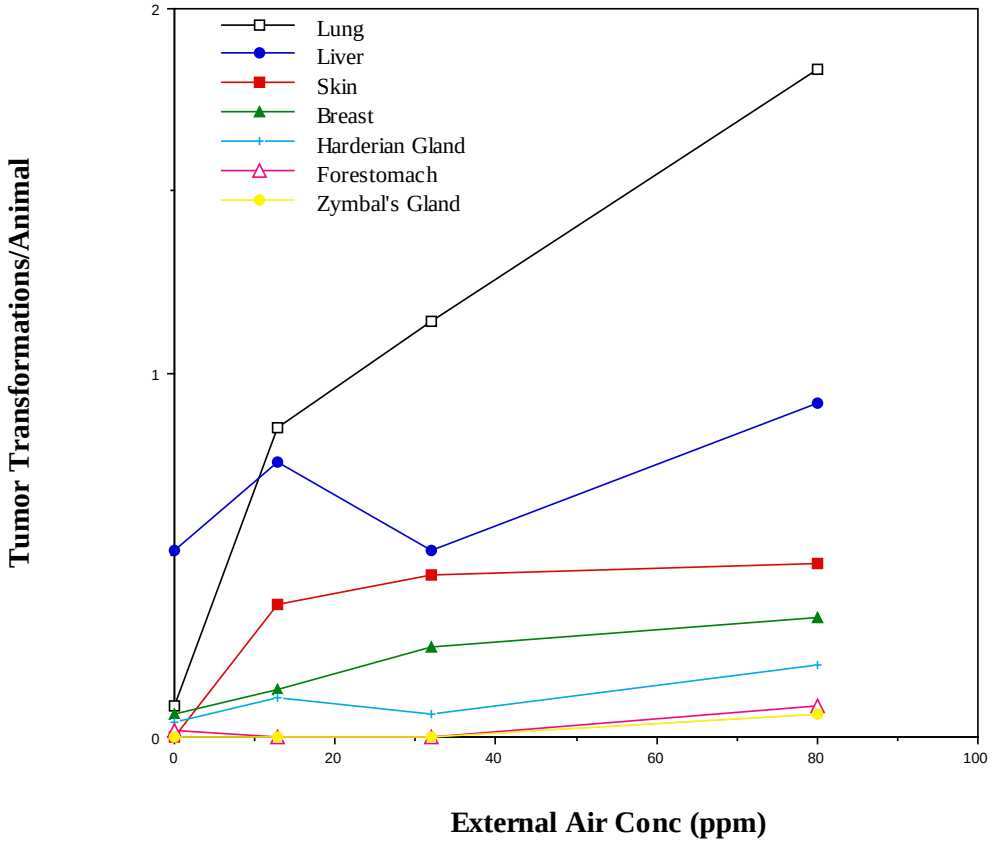
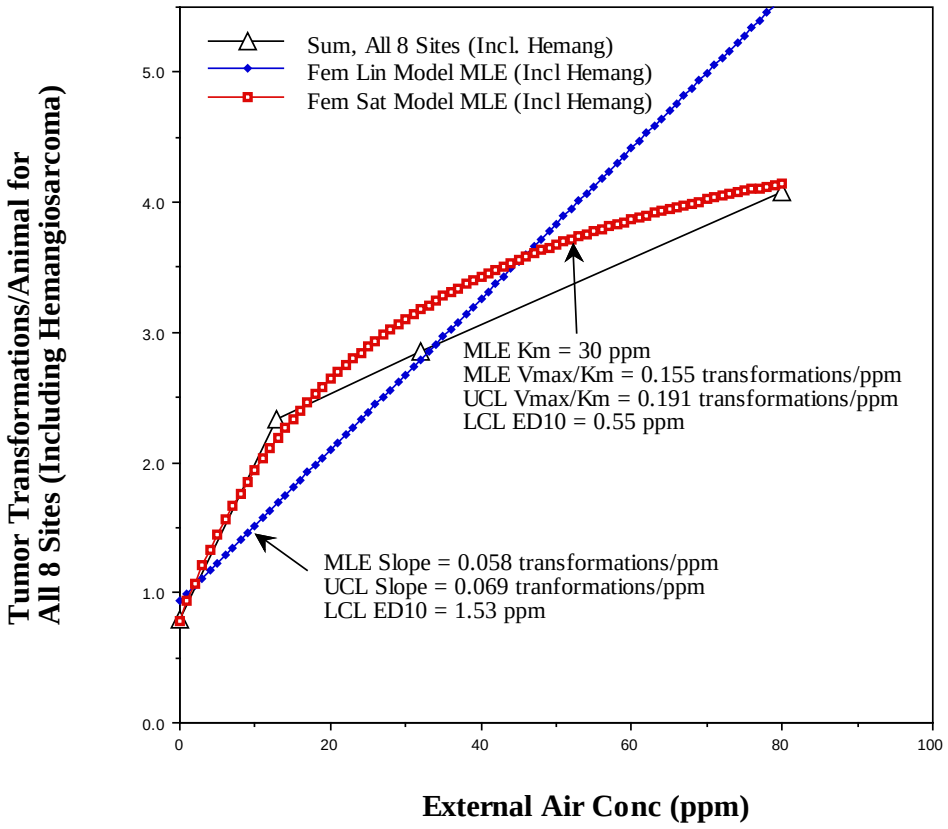


Figure 6

Comparison of Observed Tumor Transformations/Animal For All 8 Sites in Females with Maximum Likelihood Expectations for Linear and Saturable Models



Ronald L. Melnick

Yes, all of the induced tumor sites in mice should be used to estimate the inhalation cancer unit risk; an assessment based on separate modeling of each tumor type would underestimate the carcinogenic potency of chloroprene. Cancer potency estimates are increased only about 2-fold by combining all sites in the assessment compared to estimates based on only the most potent response in either male or female mice. Because of the reduced mortality of exposed mice due to induction of malignant tumors, a multistage Weibull time-to-tumor model that accounts for differences in survival among groups is most appropriate. The chloroprene document should provide discussion on why no uncertainty factor (other than early-life susceptibility) for human variability was applied to the cancer unit risk estimate. There are certainly substantial differences in human metabolism of chloroprene and its reactive epoxide metabolite and in human susceptibility to chloroprene-induced cancer.

The suggestion by Dale Hattis to apply a model that accounts for saturable metabolism of chloroprene to its epoxide intermediate should be pursued and incorporated into the estimate of the inhalation cancer unit risk. This analysis should use survival-adjusted tumor incidence values. The blood time-course data for chloroprene presented by DuPont (Figure B-1, page 99) to the Peer Review Panel clearly demonstrates saturable metabolism of chloroprene in mice at exposures between 13 and 90 ppm.

John B. Morris

The modeling approaches for the quantitative risk evaluation of chloroprene carcinogenicity were transparently described. Cancer unit risks are calculated individually for specific tumor types and an overall unit risk was calculated. Presumably the overall unit risk was calculated in concordance with accepted EPA procedures. It is beyond my expertise to comment on the generalized appropriateness of combining tumors in this way relative to overall cancer unit risk calculation. If tumors are to be combined then the human relevance of each tumor type must be considered. As noted above, in my view, some skepticism is appropriate relative to the quantitative importance of mouse bronchiolar tumors. The mode of action includes metabolic activation as the first step. The metabolic activation rates in the mouse exceed those in other species by 50-fold (Table 3-4). Clearly this is a critical observation relative to quantitative risk extrapolation. This pattern of mouse vs. human bronchiolar metabolism is certainly not unique to chloroprene. The large differences in mouse vs. human relative to pulmonary activation raise questions as to the relevance of the mouse lesions. At the very least, this issue needs to be discussed. Exclusion of the mouse lung tumors would influence the final overall unit risk estimate indicating this is not a trivial concern.

It should be noted that the epidemiological data suggests the liver at the primary target, although this may be the result of statistical issues related to the high incidence of lung tumors in humans obscuring a response. Nonetheless, a discussion of the site discordance would strengthen clarity of the text. I don’t know if it is possible, but some comparison of the unit risk versus the observed tumor risks in the worker populations would seem warranted. Is it possible to estimate an upper bound risk from the human data?

Alternatively, is it possible to project human occupational risks from the unit risk factor to determine if the unit risk factors are consistent with epidemiologic observations? I recognize that only crude comparisons could be made, but a large discordance would be a cause of concern.

Avima M. Ruder

The assumption of tumor independence (p 5-20), based on the National Research Council risk assessment document, appears justified. However, the results of the animal studies should be evaluated to determine if there is a distinction (genetic, epigenetic, or other) between animals which get one tumor versus those which get more than one.

Richard B. Schlesinger

The derivation of the IUR could be made somewhat clearer in the text.

(C) Carcinogenicity of Chloroprene

5. Lung tumors have been alternatively treated as systemic or portal-of-entry effects in the modeling of cancer endpoints. Please comment on the scientific justification for this modeling approach. Please comment on whether the rationale for this decision has been transparently and objectively described. Please comment on data available for chloroprene that may support an alternative method for modeling the observed lung tumors in mice.

Herman J. Gibb

It makes sense that lung tumors could develop from a systemic as well as a portal-of-entry effect. The extent that the lung tumors occur by systemic vs. portal of entry effects may not be possible to determine, but the text should provide more elaboration for the reader so that they can better understand the approach.

Dale Hattis

The early results for the saturation modeling described in section 4 above strongly suggest that the lung tumors for both male and female mice are completely compatible with the systemic saturable metabolic activation model with a half-saturation point similar to that derived with data for other tumor locations. Therefore, I think the lung tumors should not be treated as if they depended on local metabolism and other portal-of-entry specific processes.

Ronald L. Melnick

Both treatments of the lung tumor data are appropriate because these tumors may have arisen from metabolites formed in the lung, or in other organs, particularly the liver, and subsequently distributed to the lung. No data are available to distinguish the extent of these possibilities. The EPA document did note that the induction of tumors in multiple organs after inhalation exposure to chloroprene demonstrates the systemic distribution of carcinogenic metabolites by this route of exposure.

John B. Morris

The importance of portal of entry versus systemic delivery of chloroprene is not known. A reasonable approach would be to make estimates using both approaches and then make a determination of whether or not it is of quantitative importance. Naturally, the default approach would be to select the more health protective approach. In my view, the fundamental issue in this regard is actually based on the assignment of category 1 status to chloroprene. This assignment is not appropriate (see my other comments), and at the very least needs to justified. Chloroprene should be determined to be a category 3 vapor in my view. It is a low partition coefficient vapor that does not appear to be highly reactive. Indeed, were it highly reactive it would be impossible to measure a partition coefficient. Moreover, the pattern of nasal injury (olfactory but not respiratory mucosal

damage) is inconsistent with a highly reactive vapor. Finally the modeling efforts of Himmelstein would not have been successful were chloroprene highly reactive in tissues. True it is metabolized, but the provided data do not indicate it is metabolized to such an extent that it should behave as a category 1 vapor. If category 1 vapors do not penetrate to the blood in any sufficient degree and if they should be scrubbed very efficiently in the nose, then why are distal lung tumors and non-respiratory tract tumors observed? Were chloroprene to be determined to be a category 3 vapor, then I believe the whole issue of portal of entry versus system delivery will be moot because a DAF=1 would be assumed for both cases. The regional injury pattern in the respiratory tract (olfactory and bronchiolar injury) is suggestive for a critical role of local metabolic activation. It is possible however that active metabolite is formed in and then escapes from the liver.

Avima M. Ruder

If chloroprene is indeed rapidly absorbed in mice, it makes sense that a systemic effect from the metabolite as well as a portal-of-entry effect could occur. From the text (p 5-21) I could not determine whether it is postulated that the portal-of-entry effect is from the parent compound or the metabolite; this could be made clearer.

Richard B. Schlesinger

Since it is not clear, as noted in the Document, the extent to which chloroprene induces cancer via direct contact with the lungs or via systemic contact of lungs with metabolites, the approach used is valid. However, the application of this approach is not clear from the discussion in the document.

(C) Carcinogenicity of Chloroprene

6. An oral slope factor (OSF) for cancer was not derived for chloroprene. Is the determination that the available data for chloroprene do not support derivation of an OSF scientifically justified?

Herman J. Gibb

The determination is justified. There were no data on which to base an OSF and the PBPK model developed by Himmelstein (2004) (description on page 3-7) did not seem adequate to allow route-to-route extrapolation.

Dale Hattis

Not completely. With a PBPK model formulation, an oral slope factor could be estimated.

Ronald L. Melnick

Yes, the lack of an adequate multiple-dose oral carcinogenicity study on chloroprene and the lack of information on the disposition of chloroprene, including the AUC for the DNA-reactive epoxide intermediate, after inhalation or oral exposure that might enable reliable route-to-route extrapolation justify not deriving an oral slope factor for this chemical. Because of a likely large first-pass liver effect after oral exposure, the systemic distribution of parent compound and reactive metabolites could be very different after oral versus inhalation exposures.

John B. Morris

I concur with the determination that the available data do not support derivation of an oral slope factor.

Avima M. Ruder

As there are no quantitative data on effects of oral administration (p 5-1), the determination appears justified.

Richard B. Schlesinger

The lack of oral exposure data clearly justifies not deriving an OSF.

V. SPECIFIC OBSERVATIONS

Herman J. Gibb

Page 4-1, line 8: Delete "and"

Page 4-3, line 1: Delete "also"

Page 4-3, line 8: Delete "number"

Page 4-3, lines 8-9: Delete "of these"

Page 4-3, line 14: Delete the second "were"

Page 4-5, lines 1-2: The document indicates that a limitation of Li et al. is that only three years of local area data were used to estimate the expected numbers of deaths which may not be representative with regard to the period of follow-up of the cohort. An issue not considered is the stability of the expected rates based on local data.

Page 4-5, line 5: This discussion is unclear. If the general population had a higher mortality for a given disease during the periods not examined, then there would have been a higher number of expected deaths and the SMR for that disease would have been overestimated for the period of time that was considered, not underestimated. If the mortality was lower, then the SMRs would have been overestimated. In any case, the discussion is not clear.

Page 4-6, line 18: Change "1979-1993" to "1979 to 1993".

Page 4-6, line 22: Insert "the" before "general".

Page 4-8, line 19: Change "1979-1988" to "1979 to 1988".

Page 4-9, line 12: There is an inconsistency in how the SIR is reported on line 12 and in Table 4-6. Line 12 reports as 327 with 95% CI of 147 and 727; Table 4-6 reports as 3.27 with 95% CI of 1.47 and 7.27. The epidemiology section has several examples of changing back and forth between the convention of using the convention of multiplying by 100 and the ratio. Need to make consistent.

Page 4-9, line 23: Change "suggested" to "suggest"

Page 4-9, line 23: What are "highly exposed operators"? High cumulative exposure? Intensity of exposure? Duration of exposure? It makes a difference in the interpretation.

Page 4-10, line 29: Insert "in the group employed" before "prior". Presumably the author is describing those employed prior to 1977 and not those who developed cancer prior to 1977.

Page 4-10, line 33: The document states that "all of the SIRs exceeded 100" yet Table 4-7 indicates no SIR is over 100. Again, the authors need to use a consistent convention (report as a multiple of 100 or not report as a multiple of 100).

Page 4-11, line 10: Change "cancers" to "cancer"

Page 4-11, line 15: Is there any indication of how many workers died or left the area prior to 1979? Does the author have an idea of how much impact this would have on results or is it part of a laundry list of study faults? The power of the study was low regardless of whether workers died or left.

Page 4-14, lines 16-24 and Page 4-15, lines 1-3: It is not difficult to understand why Marsh et al. would conclude that their study provided no evidence of cancer risk associated with chloroprene exposures. Table 4-9 on page 4-14 shows little evidence of a dose response. It is inappropriate to conclude as is done in lines 1-3 on page 4-15 that Marsh et al.'s explanations are "not entirely consistent with the data presented". The authors of this document have chosen one interpretation; the authors of the study have chosen another interpretation.

Page 4-15, lines 24-35: Some of the criticisms are too harsh. For example, how often are causes of death verified by histological confirmation or review of medical records? Nice if it can be done, but the vast majority of mortality studies would fall in the same boat. Incomplete enumeration of incident cases is a criticism that could be leveled at many incident studies. The statement that despite the lack of quantitative exposure information, occupational studies are still able to contribute to the overall qualitative weight of the evidence considerations (lines 31-33) states the obvious, but the statement should not be used as license to draw conclusions on studies that have serious limitations.

Page 4-16, Table 4-10: All SMRs are reported as the multiple of 100 except for Bulbulyan et al. (1998). "Sullivan" should be "Selevan". It would be more logical to have the intermediate exposure column first, followed by the high exposure column, followed by the total cohort column.

Page 4-17, Table 4-11: The relative risk is reported as a multiple of 100 for the high and intermediate exposures in the Leet and Selevan (1982) study but not for the other studies. "Sullivan" should be "Selevan." It would be more logical to have the intermediate exposure column first, followed by the high exposure column, followed by the total cohort column.

Page 4-18, lines 7-8: The limited number of cases (one in each cohort) "precluding meaningful examination" states the obvious.

Page 4-18, line 19: "these cancers"? Should this be "an increased liver cancer risk"?

Page 4-19, line 8: "No workers experienced loss of hair." This is the first place where loss of hair is mentioned. Since that is an unusual effect, it would be better to report the results of the distillation workers after the results of the polymerization workers.

Page 4-63, line 13: What is "horizontal activity"?

Page 4-66, line 30: Delete "based on available data".

Page 4-67, Table 4-38: "Sullivan" should be "Selevan"

Page 4-69, lines 6-8: "Although not statistically significant, these findings were comparable to results (RR range 2.9-7.1) detected in two other studies for high and intermediate cumulative exposures (Bulbulyan et al., 1999, 1998)." Given that there could have been considerable differences in exposure, follow-up, duration of exposure, etc. between the studies, such a statement is not justified.

Page 4-69, lines 23-26: "only Bulbulyan et al. (1999) observed a statistically significant association between chloroprene exposure and liver cancer mortality." The preceding sentence suggests that this was done by an internal analysis, but the increase in liver cancer mortality was observed from an external analysis.

Page 4-69, lines 29-30: "….although there is no direct evidence that alcohol is related to the exposure of interest (i.e., chloroprene)." There may be no "direct evidence that alcohol is related to the exposure of interest"; there is no direct evidence that is not either. More convincing that alcohol did not play a confounding role would have been clear evidence of a dose response to chloroprene since it would be unlikely that alcohol consumption would correlate with chloroprene exposure. Evidence of a dose response, however, is equivocal (see Table 4-11 on page 4-17).

Page 4-70, lines 7-10: Criticizing mortality studies for not doing a medical record review or histological examination to confirm cause of death is extreme. Almost all mortality studies could be faulted for not doing that.

Page 4-71, lines 21-24: What "current understanding" allows one to state that specificity is "one of the weaker guidelines"? Reference?

Page 6-1, line 22: Replace "th" with "the".

Dale Hattis

1. Table 3.2 should express results in fraction of total metabolites rather than relative to butanol standard. Or it could be expressed in terms of absolute rates per unit time per unit microsomal protein. Recalculate?

2. p. 3-5, lines 5-7: "Estimates for V_{max} and K_m for oxidation of chloroprene in liver microsomes ranged from 0.068–0.29 μmol/hour/mg protein and 0.53–1.33 μM, respectively."

The meaning of the ranges should be described. If these are in fact the ranges of all observations, then the number of observations should be given; also, there should be some way of describing the dependencies of the estimates of V_{max} and K_m values.

3. Presentation of metabolic data in Table 3-4 is inadequate. No error bars or statements of how many animals tested independently (or pooled?), or more crucially, how many humans and how they differ in V_{max}/K_m for various organs (obtain original papers on metabolism).

Source: Himmelstein et al. (2004a).
Himmelstein, MW; Carpenter, SC; Hinderliter, PM. (2004a) Kinetic modeling of beta-chloroprene metabolism: I. In vitro rates in liver and lung tissue fractions from mice, rats, hamsters, and humans. Toxicol Sci 79(1):18–27..

4. Table 3.5: Again, no error bars or description of the number of animals studied or experimental errors.

5. p. 3-7, lines 4-5: "The clearance of these thioethers reached a threshold at 24 hours after dosing, indicating that elimination was rapid."

Use of the word "threshold" here is unclear and ill-advised. If what is meant is that there was no further increase in thioether excretion, then that should be said explicitly.

6. Table 3-6: Why are values not provided for the major physiological parameters (body weight, cardiac output, and alveolar ventilation)?

7. Epi data discussion: The authors do qualify the discussion of the epidemiological data with the healthy worker effect. However, they do not as yet include suitable caveats for the "internal" comparisons by mentioning the distortions expected from the healthy worker survivor" effect — that longer exposed workers with higher cumulative exposures have lower mortality than shorter term workers. This must be incorporated into the analysis. Some language I have adapted from prior work (Hattis and Goble 2007) is:

> "The "healthy worker survivor" effect is a known phenomenon that produces established distortions in relationships between measured risks and measures of cumulative exposure, as shorter term workers suffer greater mortality than workers who work at exposure-producing jobs for longer periods of time (Steenland et al., 1996; Kolstad and Olsen, 1999; Garshick et al. 2004; Siebert et al. 2001; Steenland and Stayner 1991). Adjustments for this effect are at the cutting edge of current practice for the treatment of human epidemiological data, but they are vital for achieving the best possible analysis of those data. Even if the data will not support the more complex analyses [and analyses of this sort are

notoriously complex (Robins 1986; Arrighi and Hertz-Picciotto 1996; Hertz-Picciotto, personal communication)], EPA could provide at least some discussion of how large the distortions might be by citing such previous cases as the cancer risks from diesel particles (Garshick et al. 2004; 2008) and the approach that California risk assessors (and possibly others) have taken to risk analysis where the healthy worker survivor effect is even more prominent than it may be in this case. (For diesel particulates, initial estimates of the relative risk vs. cumulative dose curve even had a negative, rather than a positive slope.)"

8. The discussions of both liver and lung cancer might benefit from some attempt at integrative meta-analysis, combining the effects of multiple studies for reasonably comparable levels of exposure. This, however, likely depends on obtaining some disaggregated data from the individual investigators, and that might not be possible. Even if the combination is somewhat speculative, it might be informative to make some attempt to combine the human evidence for comparison with the projections from animal studies.

9. Chronic NTP exposures: For later modeling, the authors should report integrated average exposures that were measured, rather than the nominal target exposures. The difference may well be small, as indicated in the discussion, but the measurements should be used in preference to the target levels in the dose response modeling which appears later in the document.

10. p. 4-54, lines 16-18: "Estimates for V_{max} and K_m for oxidation of chloroprene (into (1-chloroethenyl)oxirane) in liver microsomes ranged from 0.068–0.29 μmol/hour/mg protein and 0.53–1.33 μM, respectively."

Again, what is the meaning of these ranges? Simple ranges of all best estimates for all species? 5%-95% confidence limits? What is the number of experiments based on how many different individuals in which species, particularly for humans?

Undescribed ranges of this type are absolutely useless for understanding the uncertainty and variability of the data, or for drawing inferences for subsequent steps in the risk analysis.

11. p. 4-61, lines 5-7: "A comparative report of the carcinogenicity of these compounds highlights the qualitative and quantitative concordance of their tumorigenic effects (Melnick and Sills, 2001). The female mouse lung was the most sensitive site of carcinogenicity for both chloroprene and butadiene."

It would be useful to have some quantitative comparison of cancer potency in rodents for these compounds. The full abstract is:

Comparative carcinogenicity of 1,3-butadiene, isoprene, and chloroprene in rats and mice.

Melnick RL, Sills RC.

Chem Biol Interact. 2001 Jun 1;135-136:27-42.

National Institute of Environmental Health Sciences, National Institutes of Health, PO Box 12233, Research Triangle Park, NC 27709, USA. melnickr@niehs.nih.gov

1,3-Butadiene, isoprene (2-methyl-1,3-butadiene), and chloroprene (2-chloro-1,3-butadiene) are high-production-volume chemicals used mainly in the manufacture of synthetic rubber. Inhalation studies have demonstrated multiple organ tumorigenic effects with each of these chemicals in mice and rats. Sites of tumor induction by these epoxide-forming chemicals were compared to each other and to ethylene oxide, a chemical classified by the National Toxicology Program (NTP) and by the International Agency for Research on Cancer (IARC) as carcinogenic to humans. For this group of chemicals, there are substantial species differences in sites of neoplasia; neoplasia of the mammary gland is the only common tumorigenic effect in rats and mice. Within each species, there are several common sites of tumor induction; these include the hematopoietic system, circulatory system, lung, liver, forestomach, Harderian gland, and mammary gland in mice, and the mammary gland and possibly the brain, thyroid, testis, and kidney in rats. For studies in which individual animal data were available, mortality-adjusted tumor rates were calculated, and estimates were made of the shape of the exposure-response curves and ED10 values (i.e. exposure concentrations associated with an excess risk of 10% at each tumor site). Most tumorigenic effects reported here were consistent with linear or supralinear models. For chloroprene and butadiene, the most potent response was for the induction of lung neoplasms in female mice, with ED10 values of 0.3 ppm. Based on animal cancer data, isoprene and chloroprene are listed in the NTP's Report on Carcinogens (RoC) as reasonably anticipated to be a human carcinogen. Butadiene is listed in the RoC as known to be a human carcinogen 'based on sufficient evidence of carcinogenicity from studies in humans, including epidemiological and mechanistic information', with support from experimental studies in laboratory animals. Epidemiology data for isoprene and chloroprene are not considered adequate to evaluate the potential carcinogenicity of these agents in humans.

I believe the similarity of ED10s for lung tumors is potentially helpful for the reader, however, a more comprehensive summary of potencies for other and/or all tumors would provide important background for the quantitative cancer risk analysis. Table 4-37 should be supplemented with a table giving quantification of the indicated potency for multiple- and all sites.

12. p. 4-69, lines 13-19: "One of the strengths of several of the more recent epidemiologic studies was improved exposure assessment data. These studies utilized industrial hygiene information to determine which areas or jobs were most likely to have received higher chloroprene exposures. This allowed for examination of various exposure contrasts and helped reduce the potential for exposure misclassification. As such, valid internal analyses were conducted which were less impacted by bias due to the healthy worker effect. Despite these improvements, several study limitations added to the

uncertainty in addressing the weight of evidence of the epidemiologic data."

The discussion following this paragraph should include the healthy worker survivor effect.

13. Table 5-2: DAFs greater than 1 for lung and less than 1 for nasal epithelium deserve specific discussion.

14. Page 5-20, top: Variability (uncertainty?) in slope factors follows a normal distribution? Try lognormal.

15. Cancer modeling: In view of the saturation of the generation of active metabolite, and the need to drop high doses in some cases, there should be investigation of a Michaelis Menten transformation of dose, in lieu of a full PBPK model. Demonstrate results of this for the incidence of tumors in mice (without the Weibull factor for time dependent tumor observations).

References

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Garshick E, Laden F, Hart JE, Rosner B, Smith TJ, Dockery DW, Speizer FE. 2004. Lung cancer in railroad workers exposed to diesel exhaust. Environ Health Perspect. 112(15):1539-43.

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worker survivor effect in a cohort of workers in the construction industry. Occup Environ Med. 2001 Dec; 58(12):774-779.

Steenland K, Deddens J, Salvan A, Stayner L. 1996. Negative bias in exposure-response trends in occupational studies: modeling the healthy workers survivor effect. Am J Epidemiol. 143(2):202-210.

Steenland K, Stayner L. 1991. The importance of employment status in occupational cohort mortality studies. Epidemiology. 2(6):418-423.

Ronald L. Melnick

Page 3-2 to 3-5. The discussion on chloroprene metabolism is deficient in its consideration of species differences in glutathione conjugation, catalyzed by glutathione-S-transferase, in the detoxification of (chloroethenyl)oxirane.

Page 3-7 to 3-8. Discussion is needed on likely differences in chloroprene clearance among species. Factors influencing the clearance of chloroprene include fat:air partition coefficients, % of body weight as fat (mouse: 5%; rat: 7%; human 21%), metabolic elimination, etc.

Page 4-13. It seems odd that of the 652 cancer cases in the Louisville facility, only 1 case was unexposed (Table 4-8). This might suggest that a large percentage of individuals classified as exposed were essentially unexposed. The document should provide greater emphasis on the potential impact of exposure misclassifications.

Page 4-16 to 4-17. Use common units for SMR and RR values in Tables 4-10 and 4-11. On some cases the actual ratios are given, while in other cases the ratios are expressed as per cent.

Page 4-22. Contrary to the statement on lines 2-6, the data in Table 4-14 show incidences of ovarian or mammary tumors in control female rats.

Page 4-47, lines 5-7. Additional analyses are needed before dismissing the finding of increased resorptions in the 10 and 25 ppm exposure groups.

Page 4-60. Delete lines 12-15. The hypothesis that chloroprene would only produce tumors in directly exposed tissues has been disproved by the NTP studies which demonstrated the multiple organ carcinogenicity of this chemical.

Page 4-63, line a6. Severities were minimal to moderate, not minimal to mild.

Page 4-73, line 7. The document specifies a mutagenic MOA involving the reaction of epoxide metabolites formed at target sites. Until studies are conducted evaluating blood levels of epoxide intermediates it would not be appropriate to impose this target site

limitation. It is not known if epoxide formation occurs in all of the tumor target sites identified in the rodent carcinogenicity studies.

Page 5-19, Table 5-7. The unit risk value for hemangiosarcomas/hemangiomas is incorrect – it should be 2.8×10^{-5}, not 8.3×10^{-5}.

John B. Morris

Pages 3-1 - 3-6

The data on partition coefficient should be discussed more completely. It is true that it is possible to infer information on tissue distribution from such data. It is also possible to make inferences on regional respiratory tract absorption from these numbers. A vapor with a blood:air partition coefficient less than 10 is not likely to be scrubbed efficiently from the airstream in the upper airways. This is an important point because an inhalation cancer potency factor will be derived assuming category 1 status.

More detail should be provided on the metabolism kinetics for chloroprene. The information on elucidation of putative metabolites is clear and concise, but the data on kinetics is incompletely presented data and is very difficult to interpret fully. The information in Table 3-1 needs to be more fully described. Is this table cited in the text? Precisely how were these data obtained, what is the meaning of these data, particularly with respect to rodent-human extrapolations? The relative level of metabolite 1 in the humans was approximately 10-fold lower than the F344 rat and mouse. The level of metabolite in the Wistar rat and hamster was lower as well. Were these quantitative differences synthesized into a coherent explanation of species differences in response?

Similar issues could be related relative to Tables 3-4 and 3-5. The text should precisely indicate how the estimates for V_{max}/K_m for lung metabolism were obtained. The mouse – human comparison for lung metabolism is particularly important, a fact that was not adequately considered in the risk evaluation. The presented data indicate the activity in human lung is 50-fold lower than in mouse lung (Table 3-4). The liver activities in the mouse and man are much more similar. Since metabolic activation is the first step in the mode of action and lung tumors in mice drives the risk extrapolation, this comparison becomes particularly important. Exactly how was the value of 1.3 for V_{max}/K_m in the human obtained? What is the reliability of this number? Can it or can it not but used for quantitative species extrapolations? An explicit rationale for not using these data in the data synthesis sections needs to be provided. It should be noted that this type of species difference (mouse to human pulmonary metabolism) is hardly unique to chloroprene. For example, consider styrene.

Pages 4-1 - 4-18

The section on human exposures to chloroprene appears to be objectively and concisely presented. Epidemiology is not within my area of expertise. My only comment is the thought that it would be useful if as much information as possible on occupational exposure levels would be presented in the text. At least to me, information on exposure concentrations in addition to cumulative (ppm-year) would be of value. If available,

recent published reviews of the epidemiological data relative to chloroprene should be cited.

Page 4-25

Clarity would be enhanced if the table also provided information on the magnitude of injury in Table 4-16 and subsequent tables. A footnote might be adequate. Alternatively, the average injury score might be provided parenthetically in each column. The wording of the text infers there was no observed histopathological damage in the lungs of mice in the 16 day study. Clarity would be enhanced if this were explicitly stated.

Page 4-28

Clarity would be enhanced if it were explicitly stated that lesions were not observed in the nasal respiratory mucosa in the 13-week study. All lesions in Table 4-19 were in olfactory mucosa, the reader must make the inference that respiratory mucosa damage was absent. This is an important issue relative to data interpretation.

Page 4-29

Clarity might be enhanced if it is stated that preening behavior might have lead to direct gastrointestinal exposure to chloroprene. If this is not thought to be the case, then it should be explicitly stated.

Pages 4-30 - 4-43

It is noted that all nasal lesions in Table 4-16 are presented under the heading of "olfactory," implying that no nasal respiratory mucosal lesions were observed. This needs to be explicitly stated. The subsequent text is quite ambiguous in this regard. For example, in the absence of any respiratory mucosal lesions, why include speculation on the relative expression of CYP450 in olfactory versus respiratory mucosa of the rat nose? (I did a quick scan of the NTP report to confirm, at least superficially, the absence of respiratory mucosal lesions.) All subsequent descriptions of these data, e.g. chronic nasal inflammation (p5-2) should be qualified to state chronic nasal olfactory inflammation (if this is, in fact, true). Site specificity of nasal lesions is a critical aspect in the evaluation of nasal response.

Subsequent portions of the text refer to time to tumor data. Where are these data and derivation described? Should some discussion of maximum tolerated dose and whether it was exceeded be included in the text?

Clarity would be enhanced if the text provided more detail on how the survival adjusted neoplasm rates in Table 4-28 were calculated.

The description of the Trochimowicz et al. 1998 study indicates there was less chronic respiratory disease in exposed than controls. Perhaps more information should be

provided on the lesions that were present in control animals. This would seem to be a relevant issue with respect to interpretation.

Page 4-54

The text (line 20) indicates epoxide hydrolysis was faster for the human and hamster than rat or mouse. Where are these data presented?

Page 4-45

The test (lines 27-32) indicates "some activity" was observed in strains TA97A and TA98. Subsequently (p. 4-65), it is stated the epoxide mutagenicity is "positive in all strains." Are these two parts of the text concordant?

Page 4-61, Table 4-37

This table is very confusing. What was the basis for including data from the rat relative to "sites of increased incidence" of neoplasms? Listed are many sites in which statistically significant results were not enumerated in previous portions of the text. Obviously, clarity needs to be improved.

Pages 4-62 - 4-65

In general, this "synthesis" of the inhalation exposure data is not a synthesis but merely a reiteration of the results. Rather than repeat the results study by study, it might be much preferable to organize this section on the basis of target organ. It could, for example, discuss the olfactory lesion data in toto, followed by the liver, etc. On page 4-62 line 15, it is stated that chloroprene is associated with reproductive and developmental effects, yet the earlier portions of the text concluded otherwise.

Table 4-38

Table 4-38 is somewhat confusing. Why was lung cancer mortality listed under "rare tumors?" The table includes a reference to time to tumor, yet such data were not presented earlier in the text.

Page 4-72

Lines 11-12 include a listing of increased incidences of tumors, yet the basis for inclusion in this listing is unclear. Some organs are listed in which the tumor incidence was not significantly increased. The discussion of species differences (lines 27-31) should include reference to possible species differences in epoxide hydrolysis rates. Such data are presented earlier and its absence here is confusing. This section fails to include the most important species difference – the appearance of lung tumors in mice but not rats. An in situ pulmonary metabolic basis might be provided, given that the metabolic activation rate in mice appears to be 50-fold higher than the rat but that in the liver differs by only

2-fold (Table 3-4 and 3-5). This would also serve to emphasize the potential role of metabolism relative to carcinogenicity. Epoxide formation is thought to be important relative to the respiratory tract toxicity/carcinogenicity of naphthalene and styrene and the same species differences (lung tumors in mice but not in rats) is seen for these vapors. Line 32 includes a reference to Dong et al 1989; this study was not described previously.

Page 4-75

The statement that in vivo uptake of chloroprene involved the balance between epoxide formation and detoxification is confusing. Certainly the toxicity depends on the balance, but it is unlikely that uptake does. Uptake rates depend on the blood and tissue concentration of parent, downstream conversion of metabolite is not necessarily important in diffusion-based uptake. Greater clarity is needed.

Page 4-76

It is stated on lines 3-4 that there is remarkable similarities in the potency and shape of the dose response between butadiene and chloroprene. Such data are not presented in earlier portions of the text.

Page 4-77

It is stated that Melnick et al. (line 18) performed a 6 month exposure-6 month follow-up study. Where are these data presented?

Page 5-3, top

The text needs to clearly describe how the atrophy and necrotic data were combined. I am not certain there are any data indicating nasal olfactory atrophy leads to necrosis (as stated on lines 5-6). The concept that necrosis may lead to atrophy is quite straightforward however.

Page 5-5

In my view, chloroprene is not a category 1 gas (see also my comments above). Its partition coefficient is only 10, clearly backpressure in nasal tissues controls the uptake process. The presence of non-respiratory tract tumors clearly indicates it is absorbed into the bloodstream. This vapor does not possess the physical chemical characteristics required of category 1 gases; in my view, it is a category 3 gas. The text needs to rigorously support this conclusion with respect to the physical chemical characteristics of chloroprene relative to those required of category 1 gases. The presence of olfactory lesions is NOT evidence that the toxicant was delivered via the airstream. Numerous compounds produce selective olfactory injury after parenteral administration. Indeed, the presence of olfactory but not respiratory nasal mucosal injury might be considered to provide data in support of a blood-borne mechanism. Naphthalene is one example of this phenomenon. Importantly, the subsequent text describes in great detail how the lung

lesions may be due to blood-delivered rather than air-delivered chloroprene. The text needs to be consistent. Redistribution of chloroprene from fat stores during non-exposure periods is one potential mechanism for a role of blood borne chloroprene in inducing olfactory lesions.

The RfC methodology is fatally flawed with respect to RGDR calculation. The derivations of these equations are based on the faulty assumption that the mass transfer coefficient is uniform throughout the nose. Dosimetry predictions from RGDR-based evaluations are totally discordant with the data. For example, the RGDR-predictions are counter to the theoretically sound modeling and experimental data obtained for formaldehyde and vinyl acetate. The RGDR-based estimates of species differences in dosimetry are discordant with the database on acetaldehyde dosimetry in multiple laboratory animal species. While application of a flawed methodology may be consistent with EPA policy, it certainly is not consistent with the scientific state-of-the-art. Perhaps it is felt that chloroprene is truly a category 2 gas, but it is assigned category 1 status because of difficulty in implementing RGDR calculations for category 2 gases. If so, it should be explicitly stated. As noted above, its low partition coefficient and the existence of distal organ effects indicate chloroprene is likely a category 3 gas.

The mode of action is assumed to include metabolic activation to the epoxide. The RGDR of 0.28 indicates the humans will receive roughly 4-fold more toxicant (1/0.28) than the rat. Is it meant to imply that the metabolic activation rate in the human nose is 4-fold higher than the rat? Is there a single example of this being the case? The use of the RGDR needs to be discussed in light of the metabolically-based mode of action.

Page 5-8

I recognize that it may be policy to include a database limitation factor due to the lack of a two generation study, but I do not feel it is scientifically justified in this case. A multigeneration study does exist. The rationale for the selection of this uncertainty factor should include this study.

Table 5-3

Table 5-3 does not include a row in the consideration column for database limitation.

Table 5-4

This table provides time to tumor data, but such data have not been presented.

Page 5-21

Would it be possible to compare the tumor risk calculations with the human workplace experience? This might provide a useful “reality check.” Even if the occupational exposure levels were only crudely known, it might be possible to determine if the estimated cancer risks were at least somewhat reflective of reality.

Page 5-25

The cross-species scaling section is deficient in that it does not include consideration of metabolism rate. The first step in the mode of action is metabolic activation to an epoxide and the toxicokinetic data indicate the mouse lung activity exceeds that in the human by 50-fold (Table 3-4). Clearly, this is highly relevant. Moreover, magnitude of species difference in metabolism is not unique, consider styrene or naphthalene. One might convincingly argue that the enormous metabolic activation rate in the mouse coupled with the low epoxide hydrolysis rate renders this species inappropriate relative to extrapolation of lung tumors. The authors of the document may not agree, but a critical discussion and rationale for using the mouse data needs to be included.

Page 6-5

The sentence on lines 18-19 is confusing. Lesions were specific to the olfactory mucosa, what is the relevance of cytochrome P450 in respiratory mucosa in this regard?

Avima M. Ruder

Page 2-1 line 12. volume produced or volume used?

Page 2-1 line 18. Is Mg a million grams? Not in List of Abbreviations.

Page 2-1 line 22. Starting material for chloroprene synthesis is butadiene *in the U.S.*

Page 2-2 line 15. Suggest rewording to: The polymerization process has been discussed…

Page 3-2 line 5. Suggest inserting "that of" between "similar to" and "vinyl chloride"

Page 3-4 Figure 3-1 and caption. Why these numbers? Why not consecutive in key/caption? Why no 2, 3, 6, etc.?

Throughout section 4, SMRs and SIRs should consistently use base 1 or base 100, not vary (cf pp 4-10 and 4-11). The adjectives low-exposure and high-exposure are not consistently hyphenated (cf p 4-2 lines 18 and 19 versus line 25, p 4.7 table 4-4 title vs. header for column 3). Deaths can be in excess but cannot be elevated (cf p 4-3 line 13). SMRs can be elevated. Deaths in and of themselves cannot be statistically significant; SMRs can be (cf p 4-3 line 13). Mortality is a rate and therefore "Mortality rate" (cf page 4-6 line 22) is redundant. Check citations! Leet and Selevan becomes Leet and Sullivan in tables 4-10 and 4-11.

Page 4-1 line 2. occupationally exposed should not be hyphenated. "during" not "from" the period …

Page 4-1 line 8. delete "and" at beginning of line

Page 4-1 line 20. Need comma after 1957. Similarly page 4-3 lines 24-25, page 4-4 line 13, etc.

Page 4-2 line 14. Change "both internal…and" to "either internal…or"

Page 4-2 lines 24-25. Needs commas after SMR and liver.

Page 4-2 line 31. Lack of adjustment (data were available) or lack of ability to adjust (data were unavailable)?

Page 4-3 line 8. A total…*was* observed

Page 4-3 line 13. Suggest rewording to: "observed cancer deaths were also in excess (SMR = 140) but the SMR was not statistically significant…"

Page 4-3 line 14. Change last phrase to "and four deaths due to lung cancer"

Page 4-3 lines 15-17. Suggest rewording to: "With five observed cancers of the urinary system (3 bladder and 2 kidney) the SMR was significantly elevated (300 compared to the DuPont population and 250 compared to the U.S…."

Page 4-3 line 23. Suggest "accrued" instead of "worked for"

Page 4-3 line 24. Should be "*was* identified" (subject is "a cohort")

Page 4-4 line 3. Were exposures determined or estimated?

Page 4-4 lines 8-10. The sentence as written doesn't actually state that males had increased exposure. Suggest "Males had statistically significant ($p<0.005$) greater exposure to chloroprene than females based on…"

Page 4-4 line 11. Subgroup has not been defined.

Page 4-4 line 13. "their *dates* of death"

Page 4-4 line 15. Suggest "sixteen reported cancer deaths occurred among…"

Page 4-5 Table 4-2, row "researcher". All cause cell needs slash between 21 and 176.

Page 4-5 line 1. Suggest "One limitation of the Li et al. (1989) study was insufficient comparison mortality data"

Page 4-5 line 2. "years *were* not"

Page 4-5 line 4. "*time* periods"

Page 4-5 line 6. Suggest "…during the time periods with no rates available,…"

Page 4-5 line 8. "there *were* no data…"

Page 4-5 line 17. "age at death was 12.7 years *younger*"

Page 4-6 line 7. Not clear whether "lasting and making" is one or two departments

Page 4-6 line 10. Locations or departments?

Page 4-6 lines 11-12. Suggest: "year. They therefore devised a relative exposure system. Workers in the high-exposure departments were assigned…"

Page 4-6 lines 19-20. Suggest: "Thirty-seven percent of cohort members (female/male distribution was not provided) contributing 26,063 person-years…"

Page 4-6 line 22. Suggest: "Mortality of the general population of Moscow was used for comparison."

Page 4-6 line 24. Suggest "available only"

Page 4-6 line 25. "the *rate* of expected deaths"

Page 4-6 lines 29-31. Need to specify that SMRs were elevated, not just statistically significant. What are "cancer-specific SMRs for liver cancer and leukemia" as opposed to "SMRs for liver cancer and leukemia"?

Page 4-7 line 4. "low number". Is this a statistically significant decrease? Or provide expected.

Page 4-7 line 8. Delete comma after leukemia.

Page 4-4 Table 4-4 header. All cases or just high-exposure cases?

Page 4-7 lines 10-11. Suggest: "…analysis by categories of duration of employment in high-exposure jobs (1-9…"

Page 4-7 line 12. Need new paragraph starting with "The cumulative.."

Page 4-7 line 15. "Kidney cancer was increased in all categories…" Are these categories of duration of employment as in lines 10-11 or tertiles or quartiles of cumulative exposure?

Page 4-8 line 13. "Similar to *the* Li et *al.* study…"

Page 4-8 line 14. Suggest: "…values if *mortality during* these years *was* not representative…"

Page 4-8 line 20. "Death certificates were coded by using *the* ICD-9…"

Page 4-9 line 9. Suggest: "Cancer incidence data *were available for* 1979-1999…"

Page 4-9 line 10. "…were identified, with six liver.."

Page 4-9 line 13. "lung cancer *in* both the total…"

Page 4-9 line 20. "noted *in analyses* using…"

Page 4-9 lines 21-22. "…five cases in *the* highest cumulative exposure *category* of…"

Page 4-10 line 7. "adjusted for *in either* mortality…"

Page 4-10 line 12. "time" of employment—era of employment or time of first employment?

Page 4-10 line 23. "…estimated *daily* exposure…" ?

Page 4-10 lines 29-30 states that 32 cancers occurred prior to 1977. How is that possible if the registry began in 1979? Does this mean 32 cancers occurred among those exposed prior to 1977?

Page 4-10 line 32 states all SIRs exceeded 100. Table 4-7 presents SIRs using base 1. Page 4-11 Table 4-7 header 3rd column. Cases Exposed before 1977?

Page 4-11 lines 2-3. "lung cancers *occurred* in workers with >20 years of exposure…, 3 in *those with* 11-20 years…and 1 in *those with* $\leq$10…"

Page 4-11 line 10. "the lung *cancer* excess…"

Page 4-11 line 11. "…smoking and alcohol consumption *were*…"

Page 4-11 line 18. Suggest: "…using external regional rates and internal comparisons…"

Page 4-11 line 20. "…both chloroprene and a potential…"

Page 4-12 throughout. As done in some places, but not consistently, label data with plant initials instead of providing a string of numbers and then stating "respectively". For example, line 9, change "1.54 and 0.094 ppm, respectively" to "1.54 (L) and 0.094 (M)". Similarly in lines 11, 24, 25.

Page 4-12 lines 4-6. Suggest: "Kentucky, and Ponchartrain (P), Louisiana. The third one was the Maydown (M) plant in Northern Ireland and the fourth facility was the Enichem Elastomer plant in Grenoble (G), France."

Page 4-12 line 8. Suggest "occurred at" instead of "existed in"

Page 4-12 line 14. "cohorts" (as in line 10)

Page 4-12 line 23 states 266, 48, 12, 10 for lung cancer deaths; table 4-8 has these numbers for all respiratory cancer deaths. Were all respiratory cancer deaths lung cancers?

Page 4-12 line 26. Suggest: "deaths *than expected* from liver cancer were…"

Page 4-12 line 29. Suggest: "~~when~~ compared to expectations based on the general population. When…"

Page 4-13 line 2. "trends across quartiles of exposure were examined"

Page 4-13 line 14. "included" instead of "contained"

Page 4-13 line 23. Delete "the" at end of line

Page 4-14 line 4. "…work status *was* so highly…"

Page 4-14 line 7. "They found inverse *associations*…"

Page 4-15 lines 7-8. "cohorts had *fewer* than 1000 workers, while the remaining cohorts had *fewer* than 6000."

Page 4-17, line 8. "…Louisville, Kentucky, plant."

Page 4-18 line 16. "found in workers *who*…"

Page 4-18 line 32. "…cohorts *on* different…

Page 4-19 line 7. "…much *lower* numbers…" or "many fewer numbers"

Page 4-20 line 1. "…19-23 employed…"

(I did not read section 4.2 as closely as the preceding section; there may be errors and ambiguities I did not catch.)

Page 5-15 line 3. Delete period preceding 1st word in line

Page 5-17 line 26. "multis*t*age-Weibull…"

Page 5-21 line 21. EPA 1994A or EPA 1994B?

Page 7-3 lines 19-20. Only articles by the same author (which these are not) should be labeled 2001a and 2001b.

Page 7-5 line 33. "…*life* table analysis…"

Page B-2 Figure B-1. Abbreviations should be explained in a caption (similarly for other figures). What is the metric for the doses (horizontal axis)?

Richard B. Schlesinger

Section 4.6. The first paragraph of this section should have a subsection 4.6.1. Human Studies and the Animal Studies should be renumbered as 4.6.2.

Section 4.7. This section could be better organized. The summary in section 4.7.1 should probably be moved to the end of the entire section on carcinogenicity. The human data are discussed separately in an Evidence for Causality section, yet this is not provided for the animal studies. A true synthesis would discuss Evidence for Causality across studies in all species. This could be integrated with the discussion in Section 4.7.3.3 on Mode of Action to provide a stronger rationale for effects of chloroprene