REQUEST FOR RECONSIDERATION

RFC # 17002 (chloroprene)

Submitted on behalf of
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INTRODUCTION

In September 2010, the Environmental Protection Agency (EPA) released its Toxicological Review of Chloroprene ("2010 Review") for the Integrated Risk Information System (IRIS).[1] In the 2010 Review, EPA calculated a human cancer Inhalation Unit Risk (IUR) of 5 X 10^{-4} per $\mu g/m^3$ cancer risk for 70-years of exposure based on data from the female B6C3F1 mouse. Because of the large toxicokinetic differences between mice[2] and humans—differences which EPA did not account for in its calculation of the IUR—the IUR dramatically overstates the human cancer risks associated with chloroprene exposure.

The erroneous IUR has directly harmed Denka Performance Elastomer LLC (DPE) as the owner and operator of the only Neoprene[3] production facility in the United States. Moreover, if not corrected, the IUR may ultimately lead to the facility's closure. DPE therefore submitted a Request for Correction (RFC) on June 26, 2017 seeking to correct EPA's flawed conclusions on chloroprene human carcinogenicity. In its RFC, DPE submitted evidence showing that the IUR is approximately 156 times too high.

EPA denied the RFC in a letter to DPE's counsel dated January 25, 2018, and the letter included two attachments (together, the "Denial").[4] In the Denial, EPA for the most part did not address the scientific evidence DPE had presented in the RFC. EPA's explanation for not addressing DPE's scientific evidence was that the 2010 Review had undergone a review process that included external peer review, interagency review, and White House review. The Denial repeats nine times that its conclusions in the 2010 Review were supported by a peer review panel and "numerous" other review groups, including the White House and other federal agencies.

EPA's Denial, however, misstates the support of the peer review panel. In fact, several peer reviewers offered sharp criticisms of EPA's methods and conclusions in the 2010 Review. For example, peer reviewer Dr. Herman J. Gibb, an epidemiologist, commented that EPA had "grossly misrepresented" the epidemiological data on chloroprene exposure, and peer reviewer Dr. John B. Morris, a toxicologist, questioned the appropriateness of mouse data as a predictor of human response to chloroprene. EPA did not resolve these major issues in the final 2010 Review. Further, several sections of the final 2010 Review were never peer reviewed, as the peer review panel were not given the opportunity to review EPA's treatment of their critical responses, or the significant changes EPA made to its discussion of the epidemiologic data and the toxicokinetics of chloroprene in the draft 2010 Review.

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[1] EPA (Environmental Protection Agency). (2010). Toxicological Review of Chloroprene (CAS No. 126-99-8) In support of Summary Information on the Integrated Risk Information System (IRIS). Washington, DC. U.S. Environmental Protection Agency.

[2] For simplicity, all reference to "mice" or "the mouse" herein refer to the B6C3F1 mouse strain.

[3] Chloroprene is the base feedstock for Neoprene.

[4] A copy of the Denial is attached as Exhibit A.

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EPA's Denial similarly misstates both the quantity and strength of the support of the White House and "numerous agency review groups." In fact, only one federal agency and two White House offices supplied comments on the post-peer review draft of the 2010 Review, and the interagency and White House review together produced less than five pages of comments, many of which were actually critical of EPA's methodologies and peer review documentation. Comments from the Office of Management and Budget, for example, recommended a second round of peer review, given certain substantive changes EPA made to the draft 2010 Review after the completion of the peer review process. It does not appear, however, that any additional review, though warranted, ever occurred.

EPA therefore erred when it relied on the IRIS review process as its primary justification for denying the RFC. As this RFR will show, EPA wrongly presumed that the 2010 Review is correct because it survived the IRIS review process. Instead of denying the RFC on this basis, EPA should have thoroughly considered the arguments and evidence presented in the RFC demonstrating that EPA's scientific findings in the 2010 Review are unsound. This Request for Reconsideration ("RFR") is a plea to the agency to review the underlying science and either to correct the 2010 Review based on the best available science or to withdraw the 2010 Review pending reanalysis of the scientific evidence on chloroprene.[5]

Additionally, the RFC urged EPA to apply a physiologically-based pharmacokinetic (PBPK) model to adjust for the significant species difference between mice and humans. EPA, however, has concluded that the available PBPK models are inadequate and has thus refused to apply those models to improve its IUR calculation. Although DPE maintains that applying the published and peer reviewed PBPK models is scientifically appropriate, DPE is communicating with EPA regarding a new PBPK model that Ramboll has developed for chloroprene[6] to address EPA's concerns about earlier models.[7] DPE is hopeful that EPA will agree to cooperate in its endeavor to achieve a scientifically justifiable IUR value by participating in the proposed PBPK model workplan.

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[5] On March 6, 2018, Jones Walker LLP submitted two Freedom of Information Act (FOIA) requests to EPA seeking information related to the Denial. On May 9, 2018, Jones Walker submitted additional FOIA requests to the Office of Management and Budget, the Council on Environmental Quality, and the National Institute of Environmental Health Sciences. Jones Walker has not received any responses to either the March 6, 2018, or May 9, 2018, FOIA requests. DPE therefore reserves the right to supplement this RFR once that information is received.

[6] The new PBPK model confirms that the current EPA IUR for chloroprene is approximately 156 times too high.

[7] Counsel for DPE sent a letter dated April 6, 2018, to Dr. Jennifer Orme-Zavaleta enclosing a workplan for developing a new chloroprene PBPK model dated March 23, 2018, and generated by Ramboll. Counsel for DPE then sent a letter dated May 17, 2018, to Dr. Orme-Zavaleta providing an update on Ramboll's progress in developing the new model. On June 13, 2018, Dr. John Vandenberg with EPA responded to the PBPK workplan with several comments and suggestions to help guide Ramboll's continuing development of the model. Copies of the April 6, 2018, letter, the proposed PBPK workplan, the May 17, 2018, letter and EPA's comments of June 13, 2018, on the proposed PBPK workplan, are attached collectively as Exhibit B.

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BACKGROUND

I. Factual Background

DPE operates a Neoprene production facility (the "Facility") in LaPlace, Louisiana. DPE acquired the Facility from DuPont on November 1, 2015. On December 17, 2015, shortly after the acquisition, EPA published its 2011 National Air Toxics Assessment (NATA) study. The 2011 NATA study,[8] which applied the highly overestimated IUR for chloroprene from the 2010 Review in its risk calculations, associated DPE's facility with the highest offsite cancer risks of any chemical facility in the United States.[9] As a result of the NATA study, EPA, the Louisiana Department of Environmental Quality (LDEQ), the local and national press, and members of the local community have turned DPE's air emissions into an environmental *cause célèbre*.

Following the public release of the NATA study, EPA and 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, which EPA calculated based on the IUR in the 2010 Review, represents more than a four thousand-fold reduction in the currently applicable standard. While there is no agency rule or proposed rule requiring the attainment of the overly stringent 0.2 $\mu g/m^3$ target value, EPA has advised DPE, LDEQ, and the public that DPE should achieve this value.

DPE is an environmentally proactive company and is fully committed to complying with environmental requirements. Even though DPE has maintained a strong position that the 2010 Review and the erroneous IUR do not adhere to information quality standards, DPE has taken extraordinary steps to meet EPA's and LDEQ's emission reduction demands. In January 2017, DPE voluntarily entered into an agreement with LDEQ to reduce chloroprene emissions by approximately 85% as compared with the facility's 2014 emissions. To comply with this agreement, DPE has installed new, state-of-the-art emission reduction equipment at a cost of more than $30 million. DPE's new emission reduction system will cost DPE hundreds of thousands of dollars per year to operate and maintain.

Even though DPE has installed the most advanced air pollution controls available at great cost, DPE still will not be able to achieve the 0.2 $\mu g/m^3$ target value. In other words, if such a value were to become a formally required standard either by EPA, LDEQ, or otherwise, DPE's Neoprene production facility could be forced to shut down. However, for the reasons explained in this RFR, any requirement for DPE to meet the 0.2 $\mu g/m^3$ target value would be scientifically unreasonable and unjustified.

II. DPE Submits the RFC

Given the substantial degree to which the IUR overestimates the human risks of chloroprene exposure, as well as the considerable impact the IUR has had on DPE's operations,

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[8] The NATA study used 2011 emissions data.

[9] This finding was a result of the unusually high IUR value in combination with the facility's emission characteristics.

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on June 26, 2017, DPE submitted its RFC[10] of the 2010 Review and the erroneous IUR under the Information Quality Act (IQA)[11] and EPA's Information Quality Guidelines.[12] In the RFC, DPE showed that the 2010 Review fails to comply with the EPA Information Quality Guidelines for the following reasons:

- The 2010 Review (a) gave improper weight to poor quality epidemiological studies, (b) misinterpreted the leading epidemiological study, and (c) came to the erroneous conclusion that the epidemiological studies demonstrate an increased risk of liver and lung cancers among chloroprene-exposed workers (when in fact small deficits of these cancers were observed among exposed workers).

- The IUR was derived primarily from mouse data, without any adjustment for toxicokinetic differences between mice and humans. Because multiple lines of evidence demonstrate that the B6C3F1 mouse is significantly different from rats, hamsters, and humans in the way it metabolizes chloroprene, mouse data should not be used to predict human response to chloroprene without applying a PBPK model to compensate for these cross-species differences. As a result, the 2010 Review established an erroneous human IUR of 5×10^{-4} per $\mu g/m^3$ expected excess cancers per lifetime (70 years) of exposure—one of the highest IUR values ever derived by EPA, even for recognized human carcinogens.

- EPA calculated the final IUR by applying a series of default assumption—beginning with the default selection of the female mouse as representative of human response to chloroprene—that led to a dramatically overestimated risk value. The RFC identifies multiple areas of disagreement with the IUR calculation. One calculation error is obvious even to a non-scientist: EPA rounded-up its calculations twice.[13] This double rounding led to an arbitrary 20% increase in the calculated IUR. After correcting errors and applying the results of the most recent peer reviewed and published PBPK model, Ramboll calculated that EPA overestimated the IUR by a factor of 156.

In support of its RFC, DPE submitted a 123-page report generated by Ramboll on DPE's behalf titled "Basis for Requesting Correction of the US EPA Toxicological Review of Chloroprene" (the "Ramboll RFC Report").[14] The Ramboll RFC Report, prepared by experts in epidemiology, risk assessment, and toxicology, provided EPA with a detailed analysis of the

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[10] A copy of the RFC and exhibits is attached as Exhibit C.

[11] 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).

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

[13] EPA made a "multiple tumor adjustment" for an IUR calculation of 2.7×10^{-4}. EPA then rounded up to a value of 3×10^{-4}. Next, EPA multiplied this value by the age-dependent adjustment factor (ADAF) of 1.5, leading to a calculation of 4.5×10^{-4}. EPA then rounded up (again) to the IUR to 5×10^{-4}.

[14] A copy of the Ramboll RFC Report is included in Exhibit C as Exhibit 1 to the RFC.

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errors in the 2010 IRIS Review that require correction.[15] EPA refused to consider this information.

III. EPA Denies the RFC

On January 25, 2018, EPA denied the RFC with a letter and two attachments (together, the "Denial") asserting that the IRIS 2010 Review is "consistent with the EPA's Information Quality Guidelines." EPA's Denial is set out in three parts, consisting of:

1. A cover letter, dated January 25, 2018,

2. A ten-page response to the RFC arguments entitled "U.S. EPA's Response to 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)," dated January 2018 (referred to herein as "Attachment 1"), and

3. A forty-two page review of the scientific literature published since the 2010 Review, entitled "Systematic Review of Chloroprene [CASRN 126-99-8] Studies Published Since 2010 IRIS Assessment to Support Consideration of the Denka Request for Correction (RFC)," dated January 2018 (referred to herein as "Attachment 2").

Attachment 1 of the Denial did not address the merits of DPE's RFC. Instead, it repeats nine times, that its conclusions were supported by the "numerous" review groups and the peer review panel. In other words, the Denial concludes that there is no reason for EPA to reexamine its scientific findings from 2010, despite the detailed scientific evidence to the contrary provided in the RFC, simply because the 2010 Review had been externally reviewed.

In fact, EPA's 2010 Review essentially ignored the critical disagreement of EPA's own peer review panel with its epidemiological findings and its toxicological reliance on mouse data as representative of human response. EPA made a number of additions and revisions to the external peer review draft of the 2010 Review dated September 2009 ("the 2009 Draft Review") after the completion of the peer review; however, EPA did not follow key suggestions of the peer review panel—specifically, those related to EPA's misinterpretation of the epidemiological data and the inappropriateness of the mouse as a predictor of human response to chloroprene. The revised document was not submitted to the expert peer review panel for comment or approval. Further, the "White House review"[16] (Office of Management and Budget and Council on

[15] The Denial commented that the Ramboll RFC Report had not been peer reviewed. DPE disagrees that the evidence presented in the RFC and its attachments must be peer reviewed in order for EPA to consider whether the 2010 Review is flawed in light of that evidence. Notwithstanding this objection, DPE's consultants are moving forward to obtain peer review and publication of all key scientific papers supporting the RFC and this RFR. DPE would be pleased to coordinate these peer review activities with EPA.

[16] Copies of the comments generated by the inter-agency and White House review are attached collectively, as Exhibit D.

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Environmental Quality) actually criticized EPA's peer review process,[17] and the interagency and "White House review" together produced a mere five pages of (mostly critical) comments from just two White House offices and one federal agency.

Had EPA considered DPE's RFC on the scientific merits, EPA would have recognized that the 2010 Review does not represent the best available science, methods, or interpretations. EPA would have recognized that the epidemiological evidence does not provide any credible evidence of a link between chloroprene exposure in workers and increased risk of lung or liver (or any other) cancer mortality. EPA would also have recognized that EPA's IUR, based on the female B6C3F1 mouse, grossly overestimates potential human risks.

DPE also disagrees with the findings in Attachment 2, particularly its dismissal of two key new studies that support the application of a PBPK model to correct the chloroprene IUR, (Yang et al. (2012) and Allen et al. (2014)). However, as mentioned above, DPE's consultants have developed a PBPK model that DPE believes addresses EPA's concerns about currently available PBPK models for chloroprene.

Further, DPE contends that Attachment 2 contains new scientific information and essentially amounts to an update on the 2010 Review. As a result, attachment 2 should be subject to the IRIS review process, including external peer review.[18]

IV. DPE's RFR Should Be Granted

The following sequence of events shows that the 2010 Review requires correction and shows that this RFR should be granted:

- ***EPA Changes Peer Review Policy:*** Prior to 2010, EPA discontinued its peer review policy of requesting peer reviewers to provide a short follow-up letter review of changes to IRIS scientific documents in response to peer review comments.

- ***2010 Review Was Completed Prior to NAS Reform Initiatives:*** EPA formulated the 2010 Review in 2009 and 2010. Subsequently, the National Academy of Science ("NAS") released two reports noting significant deficiencies in the IRIS process and

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[17] *See* OMB Staff Working Comments on EPA's Toxicological Review of Chloroprene and draft IRIS Summary (dated July 2010) of August 30, 2010 ("OMB Comments"), included in Exhibit D. OMB criticized EPA's failure to follow "generally-accepted [financial] disclosure practices for peer reviewers, particularly for reviews with significant public policy implications" and the lack of clarity in Appendix A in "lump[ing]" comments and responses together OMB Comments at 1. OMB also recommended that EPA perform "a quick letter review approach to ensure that the expert reviewers were comfortable with the way their comments were addressed," given the substantive changes EPA made to the draft chloroprene review after the peer review process was completed. OMB Comments at 1.

[18] *See* EPA (Environmental Protection Agency). (2009). National Center for Environmental Assessment Policy and Procedures for Conducting IRIS Peer Reviews. Washington, DC: U.S. Environmental Protection Agency. Available at https://www.epa.gov/sites/production/files/2014-05/documents/policy_iris_peer_reviews.pdf.

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recommending critical changes to the weight-of-evidence analysis and public transparency standards.[19]

- ***EPA Failed to Respond Appropriately to Peer Review Comments on the 2009 Draft Review:*** EPA made significant revisions and additions to the 2009 Draft Review in response to sharp criticisms by peer reviewers, but failed to correct its scientific findings on epidemiology and toxicology. The revised draft of the 2010 Review was not submitted to the peer review panel for approval.

- ***EPA Rejects DPE's RFC on the Basis that the 2010 Review Had Been Reviewed Prior to Publication:*** In the Denial, EPA declined to address the merits raised in the RFC on the basis that the 2010 Review's conclusions were supported by the "numerous" review groups and the peer review panel.

To correct the unfortunate sequence of events set out above, EPA should grant the RFR and apply the best available science to its toxicological review of chloroprene. DPE is willing to work with EPA to derive a correct, transparent, and fully documented IUR for its consideration. DPE would welcome the opportunity to ensure that its findings undergo the highest quality peer-review process and that the final result reflects the scientific quality standards that EPA has committed to uphold.

For these reasons, DPE now submits this RFR, along with additional supporting documents produced by experts with Ramboll[20] (the "Ramboll RFR Report") and with Cardno ChemRisk,[21] including Dr. Gary Marsh,[22] (the "Marsh Report"), seeking the reversal of EPA's Denial and the withdrawal and reevaluation of the 2010 Review.[23]

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[19] National Research Council. 2011. *Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde*. Washington, DC: The National Academies Press and National Research Council, and, National Research Council. 2014. *Review of EPA's Integrated Risk Information System (IRIS) Process*. Washington, DC: The National Academies Press.

[20] Ramboll was previously known as Ramboll Environ until January 1, 2018.

[21] The new report by Ramboll titled "Response to EPA Denial of Chloroprene RFC #17002" and dated July 2018 is attached hereto as Exhibit E. The report by Cardno ChemRisk titled "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)," dated April 24, 2018. is attached hereto as Exhibit F.

[22] Dr. Marsh was the principal investigator of the University of Pittsburg chloroprene historical cohort study, discussed below as the "Marsh studies."

[23] Dr. Marsh's report does not include any new findings that may require peer review—he is simply providing an opinion on EPA's interpretation of data that was available to EPA at the time 2010 Review was formulated.

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SUMMARY OF ARGUMENT

1. The epidemiological evidence does not support a causal relationship between chloroprene and cancer. The peer review record refutes EPA's epidemiological findings in the 2010 Review. EPA's refusal to reconsider those findings because they were supported by the peer review panel is thus wholly unfounded. In fact, EPA disregarded the harsh criticism from Dr. Gibb, one of the two epidemiologists on its peer review panel. In his comments, Dr. Gibb stated that EPA had "grossly misrepresented" the epidemiological data when it concluded that there is evidence of an exposure-response relationship among workers exposed to chloroprene with respect to liver cancer mortality. The RFC reiterated this concern. EPA did not correct this major error in the final 2010 Review.[24]

2. EPA ignored both its own Guidelines for Carcinogen Risk Assessment[25] and the Peer Review Panel when it selected the mouse as predictive of human response. The Denial states, "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."[26] Because every available line of scientific evidence indicates that female mice are more sensitive to chloroprene than humans as a result of pharmacokinetic differences between the species, EPA's selection of the female mouse is contrary to its own guidelines. Even the 2010 Review itself recognizes that "[c]hloroprene oxidation in lung microsomes was much greater (approximately 50-fold) for mice compared with the other species,"[27] and that "[t]he observation that mice generally metabolized chloroprene into its epoxide metabolite at equal or faster rates than other species and hydrolyzed the epoxide more slowly."[28] Despite these profound differences between humans and mice, EPA failed to apply any pharmacokinetic correction when calculating the IUR. The result is an IUR that is highly inflated and not predictive of human response to chloroprene. Further, the peer review record shows that the appropriateness of the mouse for the derivation of the IUR was sharply questioned by Dr. Morris, a toxicologist on the peer review panel. EPA ignored Dr. Morris's concerns both in the 2010 Review and in the Denial.

3. The epidemiological data does not support a finding that Chloroprene is a "likely" human carcinogen. EPA's determination that chloroprene is a "likely" human carcinogen must be reconsidered because it was based in part on EPA's erroneous interpretation of the epidemiological evidence. Further, EPA's characterization of chloroprene as a "likely" human

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[24] Although this RFR focuses on EPA's mishandling of the peer review process, EPA was also unresponsive to comments submitted by the public that were highly critical of the Draft 2010 Review. Please see the Ramboll RFR Report for additional analysis related to EPA's handling of public comments.

[25] EPA (Environmental Protection Agency). (2005). Guidelines for Carcinogen Risk Assessment. Washington, DC: U.S. Environmental Protection Agency. US EPA/630/P-03/001F, available at https://www.epa.gov/sites/production/files/2013-09/documents/cancer_guidelines_final_3-25-05.pdf.

[26] Denial Attachment 1 at 3 (emphasis added).

[27] 2010 Review at 13.

[28] 2010 Review at 80.

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carcinogen is highly misleading to the public, since the term "likely" implies a high level of probability.

4. Attachment 2 requires peer review under EPA's own polices. Attachment 2 of the Denial, which is an update of peer-reviewed scientific literature related to the IRIS review of chloroprene, reaches scientific conclusions that, per EPA guidelines, require external peer review.

ARGUMENT AND ANALYSIS

I. The 2010 Review Grossly Misrepresents the Epidemiological Data on Chloroprene carcinogenicity.

A. Summary of RFC Arguments

In the RFC, DPE presented evidence that the 2010 Review should be corrected because it is based on erroneous epidemiological conclusions. The RFC showed that (a) EPA should have given considerable evidentiary weight to what EPA itself calls "the most recent and comprehensive"[29] epidemiological study, the historical cohort study of industrial workers exposed to chloroprene conducted by Dr. Gary Marsh and colleagues (the "Marsh Study"),[30] and (b) EPA should have given little to no evidentiary weight to the older, methodologically questionable epidemiological studies on chloroprene from Russia, China, and Armenia, which EPA itself admits have considerable limitations. The Marsh Study concluded that there are no higher rates of cancer following chloroprene exposure in workers compared with the unexposed general population. The 2010 Review rejected the Marsh Study's conclusions, gave substantial weight to the lower quality older studies, and incorrectly concluded that there is a positive association between liver cancer and chloroprene exposure.

The 2010 Review also misinterpreted the Marsh Study. Although the Standard Mortality Ratios (SMRs) from the Marsh Study showed lower rates of cancers among chloroprene-exposed workers than in the general population, the 2010 Review relied on the *appearance* of higher (but not statistically significant) Relative Risks (RRs), which compare the rate of cancers among more highly chloroprene-exposed groups to the risk in the least exposed group of workers (workers with less than 10 years of experience). As the Marsh Study demonstrates, the chloroprene exposure-related RRs were inflated because they were compared to a subgroup of workers within the cohort with the lowest exposure levels *who had a considerably lower than expected incidence of cancer mortalities*. EPA misinterpreted these results in the 2010 Review and improperly concluded that data from the Marsh Study indicate a positive association between chloroprene exposure and cancer mortality.

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[29] 2010 Review at A-12.

[30] For a description of the Marsh Study, see page 2 of the Marsh Report.

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B. Summary of EPA's Response

EPA's Denial did not consider the RFC arguments on the epidemiological data. EPA rejected DPE's request to correct its epidemiological findings for the sole reason that the 2010 Review had "fully considered" the issues raised in the RFC and that drafts of the 2010 Review had been subjected to a review procedure, which included internal review, an external peer review panel, White House review, and interagency review. In Attachment 1 of its Denial, EPA said:

- "The EPA fully addressed the … epidemiological evidence during the development and publication of the IRIS chloroprene assessment;[31]
- "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;"[32] and
- **"[T]wo reviewers further suggested** that the strength of the epidemiological evidence was sufficient to change the descriptor to 'carcinogenic to humans.'"[33]

As explained below, EPA erred in its reliance on the peer review panel's support for its epidemiological determinations and in fact misrepresented the extent of that support.

C. The Denial misrepresents the peer review panel's position on the epidemiological findings of the 2010 Review.

The RFC presents a thorough analysis of EPA's flawed review of the epidemiological data and, backed by sound statistical analysis, challenges EPA's cancer risk findings. But rather than address the merits of DPE's analysis, the Denial incorrectly states that the peer review panel supported 2010 Review's epidemiological findings.

EPA published the complete peer reviewer comments on the 2009 Draft Review in a document titled "Final Peer Review Comments," dated January 25, 2010 (hereinafter referred to as "PR Comments").[34] Instead of referring directly to the PR Comments, Attachment 1 of the Denial refers to the peer review comments as paraphrased in the "Summary of External Peer

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[31] Denial Attachment 1 at 2.

[32] Denial Attachment 1 at 2 (emphasis added).

[33] Denial Attachment 1 at 2 (emphasis added).

[34] A copy of the PR Comments is attached hereto as Exhibit G. Relevant comments have been highlighted by DPE's counsel for convenience.

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Review and Public Comments and Disposition," included as Appendix A to the final 2010 Review.[35]

The Denial's reliance on Appendix A rather that the PR Comments is improper, as Appendix A lacks critical information included in the PR Comments: Appendix A does not name the peer reviewers or describe their affiliations, it does not include the complete peer reviewer comments, and it does not specify which peer reviewer submitted which comments (which is important considering the reviewers' differing areas of expertise). Most important, Appendix A obscures particularly harsh peer review criticism of EPA's findings and methods and distorts certain peer reviewer comments—all of which may have led EPA to misstate the peer review panel's support for the 2010 Review's findings.

As shown in the PR Comments (but not in Appendix A), EPA's 2010 external peer review panel consisted of the following experts:

1. Herman J. Gibb, Ph.D., M.P.H. (epidemiologist)
2. Dale Hattis, Ph.D. (statistician with expertise in PBPK models).
3. Ronald L. Melnick, Ph.D. (toxicologist)
4. John B. Morris, Ph.D. (toxicologist)
5. Avima M. Ruder, Ph.D. (NIOSH epidemiologist).
6. Richard B. Schlesinger, Ph.D. (toxicologist)

(For clarity, the PR Comments did not reveal the area of expertise of each reviewer; this information was gathered by Ramboll and is included in the Ramboll RFR Report.)

1. Dr. Herman Gibb, an expert in epidemiology, strongly disagreed with the 2009 Draft Review's interpretation of the epidemiological data.

In his comments on the 2009 Draft Review, Dr. Herman J. Gibb, one of only two experts in epidemiology on the peer review panel, strongly criticized EPA's interpretation of epidemiological data.[36] Specifically, Dr. Gibb questioned the validity of EPA's liver cancer risk findings given the multiple confounding factors, such as the prevalence of Hepatitis B in China and alcohol consumption in Russia (known risk factors for liver cancer mortality), and other limitations that likely influenced the results of the studies on which EPA relied. Dr. Gibb also criticized EPA's conclusions on the significance of the epidemiological data with respect to cancer risk. On page 4-18 of the 2009 Draft Review, EPA had stated:

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[35] Every citation to the peer review comments in Attachment A of the Denial are to Appendix A of the 2010 Review, rather than to the PR Comments document.

[36] PR Comments at 25-27.

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> The observation of an increased risk of liver cancer mortality is reasonably consistent and there is some evidence of an exposure-response relationship among workers exposed to chloroprene in different cohorts in different continents (i.e. U.S., China, Russia, and Armenia).[37]

In response, however, Dr. Gibb said, "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."[38] Dr. Gibb's rejection of EPA's interpretation of the epidemiological evidence was unequivocal.

Dr. Gibb provided EPA and the peer review panel with the following comments on the 2009 Draft Review's analysis of liver cancer risk,

- 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 … that there was "some evidence" of liver/biliary passage cancer risk being associated with chloroprene exposure is followed by the statement … 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 … is not evident in the summary of the overall weight of evidence …. Furthermore, a healthy worker effect for liver cancer? With

[37] 2009 Draft Review at 4-18.

[38] PR Comments at 25 (emphasis added).

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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.[39]

Dr. Gibb concluded his critique of EPA's findings as follows:

> 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.**[40]

As shown above, Dr. Gibb strongly disagreed with EPA's epidemiological findings.[41] EPA's statement in the Denial that "[t]he evaluation of the epidemiological evidence . . . was **unanimously supported** by the external peer review panel" is therefore erroneous.[42] This glaring misstatement alone requires a reversal of the Denial.

2. Despite Dr. Gibb's harsh criticism, EPA did not adjust its findings, and the final 2010 Review still grossly misrepresents the epidemiological data.

EPA did not adequately address Dr. Gibb's criticisms in the final 2010 Review. As Ramboll states in its RFR Report, "Although EPA asserted that discussion of the epidemiological

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[39] PR Comments at 26-27 (emphasis added).

[40] PR Comments at 27 (emphasis added).

[41] Dr. Avima Ruder, the other epidemiologist on the peer review panel, did not comment on EPA's review of the epidemiological evidence in response to the charge question to which Dr. Gibb supplied the above comments.

[42] Attachment 1 at 2 (emphasis added). As discussed above, the Denial's citations to the peer review comments are not to the original PR Comments, but to Appendix A, the abbreviated summary of peer review and public comments that downplay the peer reviewers' criticisms. (As a side note, please recall that EPA justifies the Denial in part based on "White House" review, apparently referring to OMB Comments, which criticized Appendix A for lumping comments together and for lacking clarity.)

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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."[43] Moreover, EPA did not change its conclusions with respect to liver cancer risk, despite Dr. Gibb's clear disagreement that evidence of liver cancer risk exists.

As discussed above, Dr. Gibb's peer review comments said, "[t]he 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" (emphasis added). Again, page 4-18 of the 2009 Draft Review reads:

> The observation of an increased risk of liver cancer mortality is reasonably consistent and there is some evidence of an exposure-response relationship among workers exposed to chloroprene in different cohorts in different continents (i.e. U.S., China, Russia, and Armenia).[44]

EPA's only response to Dr. Gibbs' disagreement was a purely cosmetic change. It included this same sentence in the final 2010 Review, except that EPA changed "**reasonably** consistent" to "**fairly** consistent" and added the word "suggestive" before the word "evidence." The changes made to the revised sentence, below, are emphasized in bold for convenience:

> The observation of an increased risk of liver cancer mortality is **fairly** consistent and there is some **suggestive** evidence of an exposure-response relationship among workers exposed to chloroprene in different cohorts on different continents (i.e., U.S., China, Russia, and Armenia). . . ."[45]

Given Dr. Gibbs' complete disagreement with EPA's interpretation of the epidemiological data, it is untenable for EPA to defend the 2010 Review's epidemiology findings on the basis that they were supported "unanimously" by the peer review panel.

As explained in detail in the Ramboll RFC and RFR Reports and in the Marsh Report, the analysis of the epidemiological data included in the final 2010 Review was severely flawed, and the findings that followed that analysis were scientifically unfounded. Dr. Marsh identifies the following major errors in the 2010 Review:

A. "[T]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 [Marsh Study] (Leet et al. 1982; Pell 1978). The results of these studies were inappropriately considered as independent of the [Marsh Study] within the 2010 Review even though the [Marsh Study] included members of the

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[43] Ramboll RFR Report at 5.

[44] 2009 Draft Review at 4-18.

[45] 2010 Review at 42.

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prior cohorts and was specifically designed to address limitations of these studies."[46]

B. "[T]he epidemiological studies published before the [Marsh 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 [Marsh Study] to support their conclusion that chloroprene is "*likely to be carcinogenic*" in humans."[47]

C. "The authors of the 2010 Review gave many of the poorer quality studies the same weight as the more robust [Marsh Study]."[48]

Additionally, Dr. Marsh found that "the 2010 Review also **grossly misrepresented** the results of the [Marsh Study] . . . . Specifically, the 2010 Review focused on a limited series of results from the [Marsh Study] based on internal comparisons among workers at the Louisville plant, and others based on comparisons among DuPont workers nationally."[49] As the Ramboll RFR Report explains, EPA "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 . . . . This ultimately **created the appearance of an increased risk in the higher exposure groups where none existed."**[50] EPA ignored this explanation of the data, even though it was "clearly noted by [the Marsh Study] and reiterated in public comments provided by Dr. Marsh,"[51] As a result, Dr. Marsh concludes, the 2010 Report "inappropriately and inaccurately suggests that the results of the exposure-response analysis of the Louisville cohort . . . indicate a '*dose-response trend*' between chloroprene exposure and liver cancer mortality."[52] The Marsh Study in fact failed to "identify any elevated risks of cancer, including liver and lung cancers, among the cohort of chloroprene-exposed workers."[53] Dr. Marsh and his colleagues actually "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."[54]

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[46] Marsh Report at 3.

[47] Marsh Report at 3.

[48] Marsh Report at 3.

[49] Marsh Report at 4 (emphasis added).

[50] Ramboll RFR Report at 6.

[51] Ramboll RFR Report at 6.

[52] Marsh Report at 5.

[53] Marsh Report at 2.

[54] Marsh Report at 2 (emphasis added).

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In short, the changes EPA made to its analysis in response to the peer reviewer comments were cosmetic; they disregarded Dr. Gibbs' most important criticism, which is that EPA's liver cancer risk findings are not supported by the epidemiological evidence.

3. EPA further misrepresented the peer reviewers' comments regarding the strength of the epidemiological evidence.

The Denial incorrectly states that "two reviewers . . . suggested that the strength of the epidemiological evidence was sufficient to change the descriptor to 'carcinogenic to humans.'"[55] To be sure, Dr. Ronald L. Melnick and Dr. Dale Hattis, neither of whom are epidemiologists, suggested that EPA consider changing the descriptor for chloroprene to "carcinogenic to humans." That suggestion was based not on the "strength of the epidemiological evidence," as the Denial states,[56] but on the entire body of evidence reviewed by EPA and, more importantly, only on that evidence in relation to EPA's overly broad and misleading definition of what is a "likely" human carcinogen, as stated in the 2005 Guidelines for Carcinogen Risk Assessment (the "2005 Cancer Guidelines"). Neither Dr. Melnick nor Dr. Hattis either stated or implied in any of their comments that the epidemiological evidence is sufficient to change the descriptor to "carcinogenic to humans."

Clearly, EPA erred when it said, "Two reviewers suggested that the strength of the epidemiological data was sufficient to change the descriptor to 'carcinogenic to humans.'" Based on this misstatement, the Denial should be reversed.

D. EPA's treatment of the epidemiological data in the 2010 Review and in Appendix A is internally inconsistent.

Despite EPA's contrary analysis and interpretation of the Marsh Study in the 2010 Review, Appendix A, states that the publications reporting the results of the Marsh Study are "[t]he most recent and comprehensive studies," and that they "**failed to observe statistically significant relationships between exposure and outcome.**"[57] EPA also recognized in Appendix A that the four non-Marsh studies had important methodological limitations. In fact, EPA stated that these limitations "**made it difficult to draw firm conclusions regarding the findings of these studies**."[58]

Having found that the Marsh Study did not find statistically significant relationships between exposure and cancer and that the four non-Marsh studies were inconclusive, EPA then drew the diametrically opposed conclusion that the epidemiological data provides "fairly

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[55] Denial Attachment 1 at 2.

[56] As mentioned above, it appears that the drafters of the Denial did not review the original peer review commentary, but rather looked to Appendix A of the IRIS Report for information on the peer review comments. Page 11 of Appendix A states: "Two reviewers suggested that the strength of the epidemiological data was sufficient to change the descriptor to 'carcinogenic to humans.'" This language mirrors the language in the Denial.

[57] 2010 Review at A-12 (emphasis added).

[58] 2010 Review at A-12 (emphasis added).

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consistent evidence of liver cancer." Despite EPA's conclusion that it is "difficult to draw firm conclusions regarding the findings of these [four] studies," it did draw the firm conclusion that there is enough of an association in the epidemiological data to call chloroprene a "likely" human carcinogen. EPA's conclusions in the 2010 Report, which Dr. Gibb said "grossly misrepresents" the epidemiological evidence, and in Appendix A are therefore internally inconsistent.

These internal inconsistencies require a reversal of the Denial.

II. The 2010 Review applied a series of conservative assumptions, beginning with the improper selection of the female mouse (the most sensitive species) as predictive of human response to chloroprene, which, together, led to a highly inflated IUR for chloroprene.

A. Summary of RFC Argument

EPA selected the female of mouse strain B6C3F1, rather than the Fischer rat, as the primary basis of the IUR because, according to the data presented in the studies conducted by the National Toxicology Program (NTP) on these two species (NTP 1998), the female mouse is the species[59] and gender "most sensitive" to chloroprene. In the RFC, DPE argued that:

A. There are substantial cross-species differences in chloroprene toxicity,

B. The female mouse is uniquely sensitive to chloroprene exposure, with lung tumors being the most sensitive endpoint,

C. EPA failed to account for these species differences with the IUR and simply assumed, contrary to the evidence, that humans and female mice metabolize and eliminate chloroprene in the same manner as humans, and

D. Significant differences between the way humans and mice metabolize chloroprene cannot be disregarded in the human carcinogenicity evaluation.

Thus, DPE argued, the IUR grossly exaggerates cancer risks to humans.

B. Summary of EPA's Response

The Denial justifies the selection of the female mouse as the basis for the chloroprene IUR as follows:

> In accordance with the EPA Guidelines on Carcinogen Risk Assessment (2005), in the absence of data to the contrary, EPA utilizes the most sensitive species and sex in estimating cancer risk

[59] The incidence of lung tumors is statistically elevated at all exposure levels in both female and male mice.

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> to humans, which in the case of chloroprene, is the female mouse.[60]

EPA also states that "[t]he 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."[61]

C. EPA's choice of the female mouse violates its own guidelines.

In developing the IUR, EPA relied on data from the NTP on mice and rats. Based on the number of tumors and tumor sites, EPA determined that the female mouse is the species and sex most sensitive to chloroprene exposure, with the lung tumors as the most sensitive endpoint. As a result, EPA selected the female mouse, as opposed to the rat or any other animal species tested, as the most appropriate animal from which to derive the human IUR. In selecting the female mouse, EPA applied a default assumption that, according to EPA guidelines, should be applied only *in the absence of data to the contrary*. The discussion in the 2010 Review explaining EPA's decision to use this default assumption is as follows:

> The calculated composite unit risk is based on the most sensitive endpoint (risk of any tumor type) in the most sensitive species and sex (female mouse). **There is no information on chloroprene to indicate that the observed rodent tumors are not relevant to humans. Further, no data exist to guide quantitative adjustment for differences in sensitivity among rodents and humans**.[62]

By basing the IUR on the female mouse, EPA "assumed that humans are as sensitive as the most sensitive rodent sex/species tested," the female B6C3F1 mouse, "even though 'true correspondence is unknown.'"[63]

In the Denial, EPA defends its selection of the mouse as the basis for the IUR, stating that, "[i]n 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."[64] In fact, the 2005 Guidelines for Carcinogenic Risk Assessment do not contain the language EPA refers to in the Denial. A different EPA document, however, cited in the 2005 Cancer Guidelines (Methods for

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[60] Denial Attachment 1 at 3.

[61] Denial Attachment 1 at 3.

[62] 2010 Review at 141 (emphasis added).

[63] 2010 Review at 141.

[64] Denial Attachment 1 at 3 (emphasis added).

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Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (1994)[65]), states the following:

> 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.[66]

Thus, according to EPA guidelines, and the peer review comments, as discussed below, EPA should have considered the available toxic kinetic evidence to determine which species is most "relevant" to humans before deciding to base the IUR on the most sensitive species. EPA did not perform this critical threshold analysis.

Contrary to EPA's findings that "no information on chloroprene to indicate that the observed [female mouse] tumors are not relevant to humans,"[67] the data available at the time of the IRIS review of chloroprene "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."[68] The 2010 Review itself recognizes that "[c]hloroprene oxidation in lung microsomes was much greater (approximately 50-fold) for mice compared with the other species,"[69] and that "[t]he observation that mice generally metabolized chloroprene into its epoxide metabolite at equal or faster rates than other species and hydrolyzed the epoxide more slowly."[70]

In fact, every available line of scientific evidence indicates that the female mouse is uniquely sensitive to chloroprene, in that the tumor response is much greater in mice than in other species, including humans, as a result of pharmacokinetic differences. Table 1 in the Ramboll RFR Report, inserted below, demonstrates the huge differences in responsiveness to chloroprene among rodents.

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[65] EPA (Environmental Protection Agency). (1994). Methods for Derivation of Inhalation Reference Concentrations (RfCs) and Application of Inhalation Dosimetry. Washington, DC: U.S. Environmental Protection Agency. US EPA/600/8-90/066f.

[66] Methods of Derivation at 1-5 (emphasis added).

[67] 2010 Review at 141.

[68] Ramboll RFR Report at 9.

[69] 2010 Review at 13.

[70] 2010 Review at 80.

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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).

As the above table shows, at any given concentration, the response and estimated risk in the B6C3F1 mouse is from 6 to 160 times more than the Fischer rat. Other rodent species show virtually no response to chloroprene.

EPA therefore disregarded its own guidelines when it selected, by default, the most sensitive species as the basis for the IUR rather than a more relevant species, ignoring evidence that the toxicokinetics of chloroprene in the mouse is different than in the human and that the mouse metabolizes chloroprene very differently compared to other rodents and humans as a result of pharmacokinetic differences. EPA's selection of the female mouse as the basis for the human IUR, without the application of a PBPK model to account for the significant biological and metabolic differences between the mouse and the human, has resulted in a highly inflated IUR that is not representative of human response

EPA's Denial does not address the RFC's argument that the IUR does not accurately predict human response to chloroprene because the female mouse is uniquely sensitive to the chemical. Instead, the Denial refutes the RFC's assertion that the female mouse is *uniquely* sensitive to chloroprene—even though EPA determined in the 2010 Review, and states in the Denial, that the female mouse is the species *and sex* most sensitive to chloroprene—based on a comparison of data on female and male mouse metabolism of chloroprene. The issue raised in the RFC, however, is not whether the male mouse response to chloroprene differs from that of the female mouse; rather, it is whether an IUR derived from female mouse data overestimates

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risk to humans given how much more sensitive mice are to chloroprene than humans. As Ramboll notes in its RFR Report, "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."[71] If EPA chooses to derive the chloroprene IUR from female mouse date, EPA must address these differences in sensitivity to chloroprene between mice and humans, and a toxicologically rigorous way of doing so is through the use of a PBPK model.

The Denial should be reversed for further consideration of this issue pursuant to EPA's guidelines.

D. The 2010 Review ignored the peer reviewer's comments questioning the relevance of the female mouse data.

For reasons unknown to DPE, none of the charge questions to the peer reviewers concerned the toxicokinetics of chloroprene, even though this is a critical aspect for predicting the effects of the chemical on humans. Dr. John B. Morris, an expert in toxicology, in fact commented 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."[72]

EPA's charge question to the peer review panel most relevant to its selection of the female mouse as the basis of the IUR was:

> 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.[73]

("Question C2"). Given its particularly high metabolic activation rate, two of the three toxicologists on the expert panel questioned the choice of the B6C3F1 mouse in their responses to Question C2:

- Dr. Morris questioned the selection of the mouse lung tumor data as the basis of the IUR, commenting that "the mouse lung data may overestimate the risk to humans" and that the rat may be a more appropriate predictor of human response:

> Inclusion of the mouse lung tumor data for dose-response evaluation may be scientifically problematic. **As is commonly**

[71] Ramboll RFR Report at 8.

[72] PR Comments at 6.

[73] PR Comments at 30.

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> **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.[74]

- Dr. Schlesinger, also a toxicologist, likewise noted 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.**"[75]

- Dr. Ruder noted, "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.**"[76]

- Dale Hattis urged the application of a PBPK model to the data, noting that "the dosimetry, in terms of active metabolite concentration AUC, could have been informed by application of a preliminary PBPK model."[77]

- Only Dr. Melnick, the third toxicologist on the panel, agreed with the selection of the mouse, as the most sensitive species, to be scientifically justified, though, as discussed below, he later commented on EPA's deficient discussion of the metabolic differences among species.[78]

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[74] PR Comments at 30-31 (emphasis added).

[75] PR Comments at 31 (emphasis added).

[76] PR Comments at 31 (emphasis added).

[77] PR Comments at 30.

[78] Similarly, Dr. Melnick made the following comments related to EPA's discussion on toxicokinetics:

- "**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." PR Comments at 56 (emphasis added).

- "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." PR Comments at 56.

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Throughout the PR Comments, Dr. Morris repeatedly challenged EPA's selection of the mouse as the basis for the calculation of the IUR as well as EPA's explanation of the way different species metabolize chloroprene, as illustrated by the following comments:

- "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.**"[79]

- "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). . . . **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.**"[80]

- "More detail should be provided on the metabolism kinetics for chloroprene. . . . 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?"[81]

- "**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** . . . . 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**." . . . [T]his type of species difference (mouse to human pulmonary metabolism) is hardly unique to chloroprene. For example, consider styrene."[82]

- "The discussion of species differences . . . 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 [sic] 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. . . . This would also serve to emphasize the potential role of metabolism relative to

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[79] PR Comments at 6 (emphasis added).

[80] PR Comments at 40 (emphasis added).

[81] PR Comments at 57.

[82] PR Comments at 57 (emphasis added).

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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."[83]

- 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 . . . . 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."[84]

The peer reviewer comments, in addition to the related discussions in the Ramboll RFC Report and Ramboll RFR Report, demonstrate that EPA made a serious error when, contrary to its own guidelines, it failed to consider which animal is closest to the human metabolically before defaulting to the most sensitive species, sex, and endpoint. Moreover, as Dr. Morris repeatedly pointed out, the metabolic activity in the female mouse lung is different, given its "extraordinarily high pulmonary metabolism rates," and therefore is not relevant to the development of a human IUR.

EPA ignored these concerns both in the final 2010 Review and in the Denial. The Denial simply states that these issues were "fully addressed" and its derivation of the IUR is supported by the "numerous review groups and the majority of the external peer review panel."[85] Given the numerous peer review comments questioning EPA's selection of the mouse, the Denial's defense of the IUR based on support from the peer review panel is evasive and misleading.

E. EPA's response to the peer reviewers' concerns regarding the relevance of the female mouse lung data was deficient.

In response to comments by the peer reviews—and by the public—regarding the significant differences in the metabolism of chloroprene across species, EPA stated three times in Appendix A that "discussion added to Section 3.3 indicate that differences in epoxide production in the lungs of mice and humans are not as great as 50-fold . . . but may be as little as 2- to 10-fold."[86] This statement in Appendix A contradicts EPA's finding in the 2010 Review that

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[83] PR Comments at 59-60 (emphasis added).

[84] PR Comments at (emphasis added).

[85] Denial Attachment 1 at 3.

[86] 2010 Review at A-14, A-20, and A-38. EPA further states, "These additional data also indicated that in some cases (i.e., glutathione transferase activity) detoxification of the epoxide A-14 metabolite may be faster in mice than humans. Additionally, the evidence for further oxidation of (1-chloroethenyl)oxirane in mice, but not in humans, rats, or hamsters was characterized." 2010 Review at A-14, A-20, and A-38. This explanation, however, appears to be purely speculative and may in fact be misleading [discuss further with RE].

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"[c]hloroprene oxidation in lung microsomes was much greater (approximately 50-fold) for mice compared with the other species,"[87] and that "[t]he observation that mice generally metabolized chloroprene into its epoxide metabolite at equal or faster rates than other species and hydrolyzed the epoxide more slowly."[88] According to Ramboll, this finding "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."[89]

EPA does not explain how it arrived at the new 2- to 10-fold figure, which was never put before a peer review panel. In any event, EPA's discussion of whether the toxicokinetic difference between the mouse and humans is a 50-fold difference or a 2 to 10-fold difference is telling. In either case, the toxicokinetics indicate the mouse–based IUR is inappropriately high. Moreover, EPA's discussion completely ignores the question of whether the mouse is representative of human metabolic activation and detoxification of chloroprene.

Clearly, EPA's response to the peer review questions did not address Dr. Morris' well-founded concern that using mouse data to calculate the IUR would result in an over-estimated IUR. As Ramboll summarizes in its RFR Report, "by using default methodology to calculate an IUR, EPA [in the 2010 Review] 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 calculated a highly inflated IUR that is inconsistent with a full integration of the evidence."[90]

Further, any additions or changes EPA made to the 2010 Review in attempt to clarify the discussion on toxicokinetics were never peer reviewed. EPA should therefore withdraw the IUR and either reevaluate its selection of the mouse data for the derivation of the IUR, in adherence with relevant EPA guidelines, or apply a PBPK model to adjust the IUR to take into account the significant metabolic differences between mice and humans.

Based on EPA's failure to address the multiple lines of evidence showing great differences between the pharmacokinetics of the mouse and the human, EPA's erroneous reliance on a "default assumption" to use mouse data to calculate the human IUR requires a reversal of the Denial

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[87] 2010 Review at 13.

[88] 2010 Review at 80.

[89] Ramboll RFR Report at 9.

[90] Ramboll RFR Report at 7 (internal citations omitted).

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F. If EPA chooses to derive the IUR from female mouse data, EPA should apply a PBPK model to account for the vast differences in toxicokinetics between mice and humans.

As part of the RFC, DPE proposed the application of a PBPK model to adjust for toxicokinetic differences between mice and humans. Considering EPA's selection of female mice as the basis of the IUR, the most significant error in the 2010 Review was EPA's failure to follow its own (and the National Research Council'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 should be accounted for with PBPK modeling to apply the best available science to the IUR.

The RFC suggested that EPA apply the most recent peer reviewed PBPK model for chloroprene (the "Yang Model"), which was published in 2012—after the publication of the 2010 IRIS Review.[91] In response, EPA provided a substantive assessment of the Yang Model in Attachment 2 of its Denial in which EPA expressed some concerns with the model.

In Attachment 2 of the Denial, EPA states that it attempted to acquire the Yang Model code from Dr. Harvey Clewell, one of the authors of the Yang Model, so that EPA could run the Model. However, EPA reported certain issues with the code packages that Dr. Clewell provided. In light of EPA's comments in Attachments 1 and 2 regarding the Yang Model, DPE engaged Dr. Clewell with Ramboll to develop a new PBPK model that addresses EPA's concerns. As discussed above, DPE is in communication with EPA regarding the newly developed PBPK model and hopes to continue to work with EPA to achieve the best scientific outcome by applying the new model to the IUR.[92]

G. Peer Reviewers Suggested the IUR Should be Constrained by the Epidemiological Data

EPA should also withdraw the IUR in light of the null results of the epidemiological data. According to the epidemiological data, there is no proven link between chloroprene exposure and liver and lung cancer mortality at the occupational exposure levels reflected in the epidemiological literature. The 2005 Cancer Guidelines offer the following recommendation:

> **[N]ull results from a well-designed and well-conducted epidemiological study that contains usable exposure data can help to define upper limits for the estimated dose of concern for human exposure in cases where the overall weight of the evidence indicates that the agent is potentially carcinogenic in**

[91] *See* Yang Y, Himmelstein MW, and Clewell HJ. (2012). Kinetic modeling of b-chloroprene metabolism: Probabilistic in vitro–in vivo extrapolation of metabolism in the lung, liver and kidneys of mice, rats and humans. Toxicology in Vitro 26:1047–1055.

[92] *See* Exhibit B.

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> **humans**. Furthermore, data from a well-designed and well conducted epidemiologic study that does not show positive results, in conjunction with compelling mechanistic information, can lend support to a conclusion that animal responses may not be predictive of a human cancer hazard.[93]

Dr. Morris, in his peer review comments, agreed with the 2005 Cancer Guidelines recommendation, asking:

> **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.**[94]

Similarly, Dr. Gibb commented:

> **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**.[95]

EPA attempted to calculate the projected cancer risk based on its IUR number, and to compare that number to the cancer mortality rate in the Marsh studies. According to Ramboll, however, EPA made the following significant errors in its calculations:

- "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 $\mu g/m^3$)."[96]

- "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."[97]

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[93] 2005 Cancer Guidelines 2-3 (emphasis added.

[94] PR Comments at 44-45 (emphasis added).

[95] PR Comments at 34.

[96] Ramboll RFR Report at 11.

[97] Ramboll RFR Report at 11.

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As Ramboll explains in its RFR Report, "EPA's calculation underestimated the upper bound of cancer cases at approximately 300, which EPA claimed was consistent with the observed number of cancer mortality cases reported in the [Marsh Study] (*i.e.*, 283 deaths due to either respiratory or liver cancer)."[98] Because of the above calculation errors, EPA's results are false and misleading.

Ramboll performed the comparison calculation correctly using EPA's final IUR value of 5 x 10-4 per $\mu g/m^3$ and found that "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 Studies], and is even much higher the total number of all cancer mortality cases observed in the full cohort (652 cases)."[99] This comparison, or "reality check," as Dr. Gibb calls it, demonstrates that the 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."[100] Analyses included in the Ramboll RFC Report similarly show that the recommended IUR is highly inflated.

Based on the analyses provided in the Ramboll RFC and RFR Report there is a "large discordance" between the IUR number and the epidemiological evidence. EPA should therefore follow the advice of Drs. Morris and Gibb, the recommendations of the Ramboll RFC Report, and EPA's own guidelines, and adjust the IUR to better reflect the null results of the epidemiological data.[101]

H. EPA applied multiple conservative assumptions and arbitrarily rounded the IUR up twice when calculating the IUR.

Although the overly conservative selection of the female mouse lung is the most significant source of bias affecting the accuracy of the chloroprene IUR, EPA applied a number of additional assumptions in calculating the IUR that increased the conservative bias and led to unsupported uncertainty in the IUR.

In all, the chloroprene IUR derived in the 2010 Review was based on the following assumptions:

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[98] Ramboll RFR Report at 11 (internal citations omitted).

[99] Ramboll RFR Report at 11 (emphasis added).

[100] Ramboll RFR Report at 12.

[101] See also Ramboll RFC Report, Section 11, "Cancer Risk Assessment: Validation of the Chloroprene IUR."

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1. Despite evidence indicating that the female B6C3F1 mouse metabolizes chloroprene differently than the human, and therefore may not be relevant to humans, EPA selected the female mouse as the basis of the IUR by default;
2. EPA assumed lung tumors in mice to be a systemic lesion and not a portal-of-entry effect, resulting in a dosimetric adjustment for extrapolating from animals to humans that essentially makes the mice equivalent to the human with regards to systemic delivered dose and therefore, cancer risk (i.e., application of a DAF =1);
3. EPA calculated a composite risk estimate based on multiple tumor sites, although multi-tumor data were inconsistent and relatively weak for most tumor sites;[102]
4. EPA rounded the IUR from 2.7×10^{-4} to 3×10^{-4} prior to applying an age-dependent adjustment factor, increasing the IUR further;
5. EPA applied an age-dependent adjustment factor based on the assumption of a mutagenic mode of action; and
6. EPA rounded a second time from 4.5×10^{-4} to 5×10^{-4} to arrive at its final adjusted IUR number.[103]

The Ramboll RFC Report concludes that the above additional assumptions alone (those other than the selection of the most sensitive species assumption) "contribute to a risk estimate that is over-estimated by about a factor of 5."[104] The double rounding alone led to an arbitrary 20% increase in the calculated IUR. EPA should withdraw the IUR number to consider whether these additional conservative assumptions (and overly conservative calculations) led to unrealistically high estimates of risk.

III. EPA should have given the peer review panel an opportunity to review the changes and additions EPA made to the 2009 Draft Review in response to the panel's comments.

The 2010 Review disregarded critical peer review comments related to the epidemiologic data and the derivation of the IUR for chloroprene based on the mice data.[105] The most significant of these deficiencies is that, despite the multiple critical comments submitted by the peer reviewers and extensive revisions made to the 2009 Draft Review in response to review comments, EPA reserved to itself the decision about whether it had adequately responded to the peer review comments.

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[102] "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." Ramboll RFR Report at 13. Please refer to Section 3.2.3 of the Ramboll RFC Report for Ramboll's critique of EPA's use of a multi-tumor approach in calculating the IUR

[103] *See* Ramboll RFC Report at 29. Table 7.1 of the Ramboll RFC Report shows how EPA applied multiple conservative assumptions and rounded up **twice** to arrive at its final IUR number.

[104] Ramboll RFC Report at 30. Please refer to the Ramboll RFC Report for a more extensive discussion of EPA's multiple errors in calculating the chloroprene IUR.

[105] *See* Ramboll RFR Report at 2-3.

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Given the treatment of comments by Drs. Gibb and Morris, the question arises as to whether the IRIS peer review process of 2010, which has drawn repeated scientific, NAS, and Congressional criticisms was complete and objective. The revised 2009 Draft Review was submitted for interagency and White House review, but that review generated less than five pages altogether of (mostly critical) commentary from just two White House offices and one federal agency. Moreover, OMB noted that significant changes to the Reference Concentration (RfC) calculation should have been re-peer reviewed:

> 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).**[106]

DPE agrees with the OMB Comments that the final 2010 Review should be subject to an additional stage of peer review, one objective of which should be verification that the original peer review was faithfully and substantively completed.

EPA should not be both judge and jury of its scientific findings, which, in this case, it appears it was. However, it is not too late for EPA to provide for a follow-up peer review of the published 2010 Review should EPA correctly choose to do so.

IV. EPA's determination that chloroprene is a "likely human carcinogen" is based on flawed epidemiological determinations and therefore must be reversed.

The 2010 Review bases the classification of chloroprene as a likely human carcinogen on five criteria:

(1) Animal studies;
(2) Epidemiological evidence for liver cancer;
(3) Suggestive epidemiological evidence of lung cancer risk;
(4) A proposed mutagenic mode of action (MOA); and
(5) Structural similarities between chloroprene and known human carcinogens, 1,3-butadiene and vinyl chloride.[107]

With respect to item 2, the 2010 Review in fact found only "**suggestive evidence** of an exposure-response relationship [with respect to liver cancer] among workers exposed to chloroprene."[108] Further, as shown in the Ramboll RFC and RFR Report, and the Marsh Report,

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[106] OMB Comments at 1 (emphasis added).

[107] 2010 Review at 96.

[108] 2010 Review at 42 (emphasis added).

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the epidemiological evidence does not support any finding of an association between exposure to chloroprene and liver cancer, suggestive or otherwise. Item 2, above, is therefore erroneous.

With respect to EPA's lung cancer findings (Item 3), EPA itself made it clear in the 2010 Review that "there was not consistent evidence of an exposure-response relationship across various chloroprene exposure categories."[109] Item 3, therefore, is also erroneous. Because the determination that chloroprene is a "likely human carcinogen" is based in part on EPA's erroneous conclusions with respect to the Epidemiological data, EPA should withdraw and reevaluate its classification of chloroprene.

Further, the determination that chloroprene is a "likely" human carcinogen is highly misleading to the public, since the term "likely" implies a certain level of probability, that is, more probable than not. EPA's 2005 Guidelines for Carcinogen Risk Assessment, however, state that "the use of the term 'likely' as a weight of evidence descriptor does not correspond to a quantifiable probability" and allows an overly broad range of data to support the descriptor. To avoid confusion to the public, EPA should apply the "likely" designation to be consistent with the plain language meaning of "likely."

V. Attachment 2 of the Denial contains scientific determinations by EPA that must be peer reviewed.

Attachment 1 of EPA's Denial generally did not address the merits of DPE's arguments that concerned EPA's interpretation of the scientific evidence available at the time in the 2010 IRIS Review. As explained above, rather than address the merits of these arguments, EPA chose to stand by the correctness of the 2010 Review primarily because it had undergone a review process. EPA did, however, address the merits of DPE's arguments related to scientific literature published since the 2010 Review in Attachment 2, entitled "Systematic Review of Chloroprene [CASRN 126-99-8] Studies Published Since 2010 IRIS Assessment to Support Consideration of the Denka Request for Correction (RFC),".

According to Attachment 2, "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."[110] EPA listed the following as its objectives in compiling Attachment 2:

- 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.

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[109] 2010 Review at 40.

[110] Denial Attachment 2 at 2.

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- 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. . .[111]

In other words, Attachment 2, is essentially an update to the 2010 Review,[112] which, because it rejects yet another peer reviewed and published PBPK model (the Yang model, published in 2012) and draws conclusions related to the toxicity of chloroprene based on new studies, has a tremendous impact on DPE. Yet, EPA's analysis and findings expressed in Attachment 2 have not undergone the IRIS review process, which mandates external peer review.[113]

DPE therefore requests that EPA withdraw both the 2010 Review, as well as Attachment 2, in order to properly review and reevaluate the entire body of evidence in light of new studies and to subject its updated review to external peer review.

CONCLUSION AND REQUEST FOR RELIEF

DPE is seeking the application of the best available science to the Toxicological Review of Chloroprene. The EPA refused to consider the merits of the scientific arguments presented in the RFC; the Denial largely rests on the assumption that the 2010 Review is correct because it underwent peer, interagency, and White House review. EPA may not simply presume, however, that the 2010 Review cannot be reconsidered for correctness simply because drafts versions of the Review had been reviewed before its publication. The 2010 Review is not a rule or regulation, but only guidance, and therefore EPA should not consider the 2010 Review as a final and controlling document. Further, because the 2010 Review was finalized prior to the National Academy of Sciences reform recommendations for IRIS improvement, the need for quality assurance of EPA's response to the peer review comments on the 2010 Review is heightened.

DPE's RFC presented EPA with compelling evidence that the 2010 Review both grossly misinterpreted the epidemiological evidence and overestimated the IUR by basing it on data

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[111] Denial Attachment 2 at 2.

[112] *See, e.g.,* U.S. EPA. IRIS Toxicological Review of 1,4-Dioxane (with Inhalation Update) (Final Report). U.S. Environmental Protection Agency, Washington, DC, EPA/635/R-11/003F, 2013, in which new studies regarding the toxicity of 1,4-dioxane via the inhalation route of exposure became available after the initial draft of the review had already undergone external peer review. EPA updated it's the information in its draft IRIS Review of 1,4-dioxane to incorporate the findings of the new studies and submitted the review for a limited second round of peer review.

[113] *See* EPA (Environmental Protection Agency). (2009). National Center for Environmental Assessment Policy and Procedures for Conducting IRIS Peer Reviews. Washington, DC: U.S. Environmental Protection Agency. Available at https://www.epa.gov/sites/production/files/2014-05/documents/policy_iris_peer_reviews.pdf.

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from the female mouse, the laboratory species most sensitive to chloroprene. Rather than address the merits of the RFC, Attachment 1 to the Denial repeats nine times that EPA "fully addressed" the issues raised in the RFC in 2010 and that the 2010 Review had gone through "numerous agency review groups," White House review, and peer review.

This RFR shows, however, that EPA did not change its conclusions despite harsh peer review comments questioning EPA's erroneous finding that the epidemiological evidence demonstrates a link between chloroprene exposure and liver cancer and challenging the appropriateness of the female mouse as the basis of the IUR in light of the large pharmacokinetic differences between mice and other animal species, including humans. Further, this RFR shows that the interagency and White House review consisted of a total of only five pages of comments from one federal agency and two White House Offices, and that some of those comments were in fact critical of the EPA peer review response document (Appendix A of the 2010 Review).

As to the epidemiological data, peer reviewer Dr. Gibb, one of two epidemiologists on the panel, concluded that the 2009 Draft Review "grossly misrepresented" the epidemiological data and that the epidemiological data does not show an association between chloroprene exposure and cancer. DPE's RFC clearly explained EPA's mistakes in its 2010 interpretation of the epidemiological data. This RFR has provided additional information on the epidemiological data, including a report from Dr. Gary Marsh that explains EPA's mistakes in interpreting the data from his study and why the four additional epidemiological studies of poor quality should be given less weight than the Marsh Study. Dr. Marsh states that not only did his study not identify a positive association between cancer and chloroprene exposer in workers, but that the workers exposed to chloroprene actually had a deficit in the number of expected cancers as compared with the general population.

As to the toxicological data, peer reviewer Dr. Morris, a toxicologist, strongly questioned the relevance of the mouse as a surrogate for the human response to chloroprene. EPA's response to the 50-fold difference in mouse pulmonary activity as identified by Dr. Morris is to say that based on epoxide metabolic activity, perhaps mice are only 2 to 10 times more sensitive than humans. Regardless of whether EPA's response is correct, mice clearly metabolize chloroprene differently from humans, and EPA should use a PBPK model to adjust for those differences if it chooses to calculate the IUR based on mouse data.

DPE has incurred more than $30 million in costs for pollution control equipment. Notwithstanding these investments in pollution control technology, DPE's Neoprene facility may face closure if the IUR is not corrected and the ambient air target of 0.2 $\mu g/m^3$ for chloroprene is not adjusted accordingly. DPE is submitting this RFR because it believes that the application of the best available science will result in pollution control goals that are technologically feasible and attainable, and that do not create unfounded fears with the public.

EPA's Information Quality Act review panel has the authority to correct the improper Denial of DPE's RFC. DPE requests that EPA take the following corrective action:

- Immediately issue notice to the public that the 2010 Review has been suspended (or withdrawn), pending further review; and

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- 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 RFC:

    - Correct its erroneous interpretation of the epidemiological evidence to reflect the evidence as a whole shows no association between chloroprene exposure and increased liver or lung (or any other) cancer risk;

    - Reconsider the selection of the mouse as the primary basis of the IUR and review the evidence to consider whether a different species, such as the rat, may be more relevant to projected human response.

    - If EPA uses the mouse, apply a PBPK model to adjust for known metabolic differences between mice and humans.

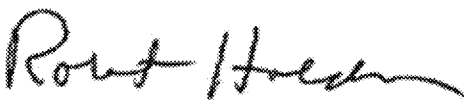
    - Replace the 2010 IRIS IUR of 5×10^{-4} excess cancers per $\mu g/m^3$ of chloroprene exposure with an IUR of 3.2×10^{-6} per $\mu g/m^3$, which incorporates the best available science and adjusts for differences between mice and humans; and

    - Withdraw EPA's determination that chloroprene is a "likely to be carcinogenic to humans" given EPA's misinterpretation of the epidemiological evidence and the misleading nature of the term "likely."

Alternatively, DPE requests that EPA *immediately withdraw the incorrect IUR and the classification of chloroprene as a "likely" human carcinogen pending further review*, and then correct those values to reflect the best available science and sound and objective scientific practices.

Thank you for your consideration of this matter.

Respectfully Submitted,



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Submitted on this 23rd day of July, 2018

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LIST OF EXHIBITS

1. Exhibit A:
    a. Letter from Jennifer Orme-Zavaleta to Robert E. Holden, dated January 25, 2018, denying the Request for Correction submitted by DPE on June 26, 2017
    b. 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)*, dated January, 2018
    c. 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), dated January 2018

2. Exhibit B:
    a. Letter from Robert E. Holden to Jennifer Orme-Zavaleta, dated April 6, 2018
    b. Workplan to Provide a Physiologically-Based Pharmacokinetic (PBPK) Model to Support the Inhalation Unit Risk (IUR) for Chloroprene, dated March 23, 2018
    c. Letter from Robert E. Holden to Jennifer Orme-Zavaleta, dated May 17, 2018
    d. EPA comments on DPE Workplan to provide a physiologically-based pharmacokinetic (PBPK) model to support the inhalation unit risk for chloroprene, dated June 13, 2018

3. Exhibit C: Request for Correction - Toxicological Review of Chloroprene (CAS No. 126-99-8) and Exhibits 1-6, dated June 26, 2018 and submitted on behalf of Denka Performance Elastomer LLC

4. Exhibit D:
    a. OMB Staff Working Comments on EPA's Toxicological Review of Chloroprene and draft IRIS Summary (dated July 2010), dated August 30, 2010
    b. CEQ Comments on Interagency Science Discussion draft of the IRIS Toxicological Review - Chloroprene, dated August 24, 2010
    c. NIEHS/NTP Comments on Toxicological Review of Chloroprene, undated

5. Exhibit E: Response to EPA Denial of Chloroprene RFC #17002, dated June 2018 and prepared by Ramboll

6. Exhibit F: 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) dated April 2018 and prepared by Cardno ChemRisk

7. Exhibit G: Final Reviewer Comments, External Peer Review Meeting on the *Toxicological Review of Chloroprene* (CAS No. 126-99-8), dated January 26, 2010

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