Denka Performance Elastomer LLC
560 Highway 44
LaPlace, LA 70068

July 15, 2021

Via Electronic Mail (quality@epa.gov)

Re: Request for Correction - Toxicological Review of Chloroprene (CAS No. 126-99-8) In Support of Summary Information on the Integrated Risk Information System (IRIS)

Dear Sir or Madam:

On behalf of Denka Performance Elastomer LLC (DPE), I submit this Request for Correction (RFC) under the Information Quality Act and the U.S. Environmental Protection Agency's (EPA or "the Agency") Information Quality Guidelines (IQG or "the Guidelines").[1] Through the submission of this RFC, DPE asks EPA to re-evaluate certain conclusions set forth in the "Toxicological Review of Chloroprene (CAS No. 126-99-8) In Support of Summary Information on the Integrated Risk Information System" in consideration of new scientific information concerning the cancer effects of chloroprene on humans, as discussed in this RFC and accompanying materials.

I. INTRODUCTION

In September 2010, the EPA released the "Toxicological Review of Chloroprene (CAS No. 126-99-8) In Support of Summary Information on the Integrated Risk Information System (IRIS)"[2] ("2010 Review") for the Integrated Risk Information System (IRIS). In the 2010 Review, EPA calculated a human cancer Inhalation Unit Risk (IUR) of 5 x 10^{-4} per µg/m^3 cancer risk for 70 years of exposure based on data from the female B6C3F1 mouse. In 2010, in the absence of a sufficiently rigorous Physiologically-Based Pharmacokinetic (PBPK) model to estimate human toxicological response based on the mouse data,[3] EPA defaulted to the assumption that it would use the female B6C3F1 mouse IUR as a proxy to estimate human risk from chloroprene inhalation. Without the use of a PBPK model to account for significant metabolic differences between humans and the female B6C3F1 mouse, the IUR developed by EPA overstated the risks associated with

[1] Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity, of Information Disseminated by the Environmental Protection Agency, EPA/260R-02-008 October 2002. Available at https://www.epa.gov/sites/production/files/2020-02/documents/epa-info-quality-guidelines_pdf_version.pdf.

[2] EPA/635/R-09/010F (September 2010).

[3] See 2010 Review, pp. 21 and 132.

human exposure to chloroprene. These risk estimates have caused unwarranted concern among members of the community surrounding DPE's facility, despite substantial epidemiological evidence indicating that EPA's risk estimate is unrealistically conservative.

Despite DPE's belief that the facility's chloroprene emissions do not pose a risk to the community, at a cost of $35 million, and in just over a year of work, DPE reduced its chloroprene emissions by 85 percent under a voluntary agreement with Louisiana Department of Environmental Quality (LDEQ) and because of DPE's commitment to excellence in environmental stewardship. Even so, we recognize that there continue to be concerns about the cancer risk posed by chloroprene, and DPE is committed to addressing those concerns based on the best available scientific information.

This RFC presents what DPE and its scientific consultants believe is the best and most up-to-date science for re-evaluating the 2010 IUR, including important new scientific information developed since 2010. Specifically, in support of this RFC, DPE is submitting the following:

1. A new PBPK model for chloroprene which underwent review by an EPA external peer review panel in 2020 and has been updated in response to comments from the peer review panel in 2021 (Exhibit A[4]); and
2. Updated epidemiological data and studies published since 2010 (summarized in Exhibit B[5]).

The above information supports the conclusion that chloroprene is less carcinogenic to humans than to the female B6C3F1 mouse. Based on discussions with EPA's Office of Research and Development, this RFC does not address all risk factors required for the determination of the IUR; however, considering the PBPK model results alone, it appears that the 2010 IUR may overstate human risk by more than 2 orders of magnitude.

DPE believes that the 2010 Review can be appropriately revised with a narrowly focused update to Section 6.2.4 ("Cancer/Inhalation," consisting of one paragraph of text on the IUR estimation on pages 147 and 148) and supplements to sections 3.5 ("Physiologically Based Toxicokinetic Models"), 4.1 ("Studies in Humans – Epidemiology, Case Reports, Clinical Controls"), and Section 5.4 ("Cancer Assessment"). We appreciate the opportunity to present this information to EPA, and we look forward to answering any questions you may have about this information.

A. How This RFC Differs from DPE's 2017 RFC

This is DPE's second RFC requesting the correction of the chloroprene IUR. On June 26, 2017, DPE filed RFC # 17002. EPA denied RFC # 17002 on January 25, 2018, primarily on the basis that DPE had not presented sufficient new information developed since 2010 to justify the

[4] Report by Ramboll entitled "Incorporation of in Vitro Metabolism Data in a Physiologically Based Pharmacokinetic (PBPK) Model for Chloroprene- Revised Documentation in Response to USEPA Peer Review," and dated July 15, 2021.

[5] Report by Ramboll entitled "Epidemiological Basis for Supporting a Correction of the Chloroprene Inhalation Unit Risk (IUR): Update," dated July 15, 2021.

request. In particular, EPA concluded that the Yang, *et al.* (2012) PBPK model used to support the 2017 RFC[6] lacked quality assurance and quality control review and that EPA did not have sufficient documentation to verify the PBPK model. DPE filed a timely Request for Reconsideration (RFR # 17002A) on that decision but withdrew the RFR on March 1, 2021, in order to submit a new RFC supported with new information, including the new Ramboll 2021 PBPK model.

DPE believes that this new RFC provides the new information EPA suggested would be necessary in the denial of RFC # 17002. The new information is set forth in two separate reports prepared by scientists at Ramboll: Exhibit A, entitled "Incorporation of In Vitro Metabolism Data in a Physiologically Based Pharmacokinetic (PBPK) Model for Chloroprene" and Exhibit B, entitled "Epidemiological Basis Supporting a Correction of the Chloroprene Inhalation Unit Risk (IUR)".

Exhibit A documents the new PBPK model's results and methodology, and also includes Ramboll's additional documentation and analyses undertaken to respond to comments from the peer review of the 2020 PBPK model report that was overseen by EPA. It also contains a thorough response to each of the peer reviewers' Tier 1 and Tier 2 comments, as requested by EPA on December 15, 2020.

Exhibit B provides follow-up epidemiological data on U.S. workers in Neoprene production facilities, including DPE's Louisiana facility through 2017, as published in 2021 by Dr. Gary Marsh, *et al.*, which shows no increased cancer mortality among any worker cohort exposed to chloroprene. Exhibit B also summarizes robust cancer incidence data available from the Louisiana Tumor Registry which shows only average and below average cancer incidence near the DPE facility for lung and liver cancers, the cancers of concern for chloroprene from the epidemiological studies as set out in the 2010 Review.[7]

B. This RFC Satisfies EPA's Information Quality Guidelines

Section 8.23 of EPA's Information Quality Guidelines, provide the criteria for EPA to grant an RFC. We believe that this RFC satisfies these criteria for the following reasons:

8.2 What should be Included in a Request for Correction of Information?

Persons requesting a correction of information should include the following information in their Request for Correction (RFC):

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

[7] A scientific review of the IRIS study by Ramboll scientists identified serious flaws in the 2010 Review. This review has been published in the peer-reviewed scientific journal *Risk Analysis.* Sax SN, Gentry PR, Van Landingham C, Clewell HJ, Mundt KA. 2020. Extended Analysis and Evidence Integration of Chloroprene as a Human Carcinogen. *Risk Analysis*. 40(2):294-318 , available at https://onlinelibrary.wiley.com/doi/epdf/10.1111/risa.13397

- Name and contact information for the individual or organization submitting a complaint; identification of an individual to serve as a contact.
- A description of the information the person believes does not comply with EPA or OMB guidelines, including specific citations to the information and to the EPA or OMB guidelines, if applicable.
- An explanation of how the information does not comply with EPA or OMB guidelines and a recommendation of corrective action. EPA considers that the complainant has the burden of demonstrating that the information does not comply with EPA or OMB guidelines and that a particular corrective action would be appropriate.
- An explanation of how the alleged error affects or how a correction would benefit the requestor.

This RFC will go into more detail below, but this RFC meets the above criteria as follows:

First, this RFC is submitted on behalf of Denka Performance Elastomer LLC (DPE), located at 560 Highway 44, LaPlace, Louisiana 70068. The undersigned may be contacted by U.S. mail, by email at Patrick-walsh@denka-pe.com, and by telephone at 504-536-7573.

Second, the following sections of the 2010 Review contain information that does not comply with EPA and OMB Guidelines and that need to be revised or supplemented to reflect the best available scientific information:

- 6.2.4 ("Cancer/Inhalation," consisting of one paragraph of text on the IUR estimation on pages 147 and 148);
- 3.5 ("Physiologically Based Toxicokinetic Models");
- 4.1 ("Studies in Humans – Epidemiology, Case Reports, Clinical Controls"); and
- 5.4 ("Cancer Assessment").

Third, Section 4.8 of the Guidelines commits EPA "to work to ensure that our many policies and procedures are appropriately implemented, synthesized, and revised as needed"; Section 5.1 commit EPA to using "quality" scientific information; and Section 4.2 commits EPA to using peer reviewed information, where possible, and preferably externally peer reviewed information of special importance. For influential scientific risk assessment information like the 2010 Review, the EPA Guidelines (at page 22) require EPA to ensure that:

(A) The substance of the information is *accurate, reliable and unbiased*. This involves the use of:

(i) *the best available science and supporting studies conducted in accordance with sound and objective scientific practices*, including, when available, peer reviewed science and supporting studies; and

(ii) data collected by *accepted methods* or *best available methods* (if the reliability of the method and the nature of the decision justifies the use of the data).

These criteria and others support this RFC, which requests that EPA update the 2010 IUR, which was based on a default assumption in the absence of a peer reviewed PBPK model, with the new Ramboll PBPK model, which was externally peer reviewed in October 2020 and which now contains supporting documentation to address the peer review panel's suggestions.

Fourth, granting this RFC and applying the best available science to the estimation of the chloroprene IUR will benefit DPE, the only maker of Neoprene in the United States and the only major permitted emission source of chloroprene in the United States, because it will correct that misimpression that DPE's facility poses a cancer risk to people in the nearby community. It will also benefit federal and state agencies that administer air pollution laws because it will allow them to make decisions based on the best available science. This is explained in more detail in the Background section below.

II. Background

DPE's Neoprene production facility is located in the Pontchartrain Works facility near LaPlace, Louisiana, in St. John the Baptist Parish. The plant was originally built and operated by E. I. du Pont de Nemours and Company (DuPont) in the 1960s. Since then, a portion of the facility has produced Neoprene by synthesizing and polymerizing chloroprene. Neoprene is a synthetic rubber used to make medical and military equipment, clothing, and consumer products like cell phone cases.

On November 1, 2015, DPE acquired the Neoprene production facility from DuPont and established its headquarters in St. John the Baptist Parish. DPE directly employs about 230 people and is the second-largest private employer in the Parish.

In December 2015, just weeks after DPE acquired the facility, EPA released the 2011 National Air Toxics Assessment (NATA). Among other things, 2011 NATA involved a nationwide review of chemical plant emissions and a screening for potential air pollution-related health risks nationwide. The NATA used air dispersion models, 2011 emissions,stack parameters, and meteorology, along with available IRIS health risk values. Using the 2010 IUR for chloroprene, the 2011 NATA estimated on a screening level basis that the DPE plant produced the greatest offsite cancer risk of any chemical plant in the United States.

Because of the concerns arising from the 2011 NATA, DPE invested more than $35 million to substantially reduce emissions from the facility within 2 years after acquiring it from DuPont, even though DPE believed that these concerns were (and are) unwarranted. On January 6, 2017, DPE and LDEQ, in cooperation with EPA, entered into a voluntary Administrative Order on Consent (AOC), under which DPE committed to reduce chloroprene emissions by 85 percent compared to the faculty's 2014 emissions. The AOC involved:

- Interim measures (additional condensers) to reduce emissions in 2017;
- The construction and installation of a Regenerative Thermal Oxidizer (RTO) to control emissions from the Neoprene process area (started up in December 2017);
- The construction of and installation of the Monomer Emission Reduction Project (MERP) to route emissions from the Monomer process area to the facility's Halogen Acid Production Furnace (started up in December, 2017); and

- Wastewater and other controls in the Poly Building to reduce wall fan emissions.

The total cost of these projects was more than $35 million, and LDEQ acknowledged that DPE successfully met the 85 percent emission reduction target.[8] Since that time, DPE has continued to take measures to further reduce emissions to the extent feasible.

At the same time, DPE is concerned that members of the community around the facility continue to be unduly alarmed by the 2011 NATA, its 2014 update, and the IUR included in the 2010 Review. As a result, DPE has spent more than 3 years working with independent scientific experts and with EPA to assist in the development of a PBPK model in order to provide a better scientific basis for assessing the cancer risk posed by chloroprene. As discussed in Section III below, the PBPK model shows that the current IUR substantially overstates the risk of chloroprene. Further, as summarized in Section IV and Exhibit B of this RFC, recent epidemiology studies of Neoprene workers and community cancer data from the state-run Louisiana Tumor Registry (LTR) suggest that chloroprene emissions from the DPE facility do not pose increased cancer risk.

III. The Development, Methodology, and Results of the 2021 Ramboll PBPK Model

EPA's own assessment of the uncertainties of its 2010 cancer risk assessment is informative on the determination of the best available science today. Because EPA noted the need for a PBPK model in 2010 and recognized the uncertainties in its cancer risk assessment, those recognized limitations in the 2010 Review strongly suggest that the 2021 PBPK model effectively closes the self-identified gap in EPA's risk assessment in the 2010 Review.

A. In 2010, EPA Recognized the Need for a PBPK Model

PBPK models provide the best scientific approach for the quantitative adjustment for differences in pharmacokinetics among rodents and humans, which can potentially inform differences in response across species.[9] By basing the IUR on toxicological response in 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."**[10] The 2010 Review explained this 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

[8] See letter from Lourdes Iturralde, LDEQ Assistant Secretary, to Patrick Walsh, DPE SHE Manager, dated May 20, 2020: https://edms.deq.louisiana.gov/app/doc/view?doc=12184387

[9] The U.S. EPA has long considered application of adequately validated PBPK models to be "accepted as a scientifically sound approach to estimating the internal dose of a chemical at a target site and as a means to evaluate and describe the uncertainty in risk assessments." U.S. EPA. Approaches for the Application of Physiologically Based Pharmacokinetic (PBPK) Models and Supporting Data In Risk Assessment (Final Report). U.S. Environmental Protection Agency, Washington, D.C., EPA/600/R-05/043F, 2006, available at https://cfpub.epa.gov/si/si_public_record_Report.cfm?Lab=NCEA&dirEntryID=157668.

[10] 2010 Review, p. 139 (emphasis added).

> 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**.[11]

In the 2010 Review, EPA assessed the uncertainties in in the cancer risk assessment in Section 65.4.7, and noted that a PBPK model would reduce this uncertainty:

> Another source of uncertainty comes from the interspecies extrapolation of risk from mouse to human. The two rodent species for which bioassay data were available— mouse and rat—vary in their carcinogenic responses to chloroprene, in terms of both site specificity and magnitude of response (Section 4). **Ideally, a PBPK model for the internal dose(s) of the reactive metabolite(s) would decrease some of the quantitative uncertainty in interspecies extrapolation;** however, current PBPK models are inadequate for this purpose (Section 3)…

The 2021 Ramboll PBPK model has been developed with a carefully performed analysis of pharmacokinetic differences between mice and humans, and the calculation methodologies have been carefully evaluated with sensitivity and uncertainty analyses, and when appropriate, parameter selection based on the most conservative choice. The multiple uncertainties of unknown significance identified in the 2010 Review compared with the 2021 PBPK model clearly show that the "best available science" standard under the EPA Guidelines supports the replacement of the 2010 default assumption with the application of the 2021 PBPK model into the dose-response assessment.

B. The Development of the Ramboll PBPK Model

In the 2010 Review, EPA declined to use the Himmelstein (2004) PBPK model, concluding that that model was "inadequate for application for calculation of internal dose metrics or interspecies dosimetry extrapolations."[12] Instead, and in the absence of a PBPK model it could use in 2010, EPA adopted the default assumption that humans were as sensitive and had comparable pharmacokinetics of chloroprene as the female B6C3F1 mouse strain, the most sensitive species and sex in the 1998 National Toxicity Program (NTP) studies of chloroprene. When DPE submitted its original RFC in 2017 (RFC 17002), it suggested that EPA use the Yang, *et al.* (2012) PBPK model, but in Attachments 1 and 2 to EPA's January 25, 2018 denial of the RFC, the Agency raised a number of concerns about the Yang, *et al.* model.

In April 2018, Ramboll submitted a work plan to EPA for the development of a new PBPK model to address the concerns that EPA noted in the denial of RFC17002. Since that time, EPA has conducted an extensive quality assurance review of the PBPK model development and of the final model. At EPA's request, Ramboll conducted an experiment to provide data to inform a

[11] 2010 Review, p. 141 (emphasis added).

[12] 2010 Review, p. 21.

chloroprene mass-transport parameter (Kgl), a parameter also included in the model based on comments from EPA. The 2019 version of the PBPK model and its documentation was peer reviewed and published in *Inhalation Toxicology*.[13]

EPA continued the QA/QC work with Ramboll and retained Versar, a third-party contractor, to oversee an external peer review of the 2020 Ramboll PBPK model. The peer review panel, which met on October 5-6, 2020, included nine experts on toxicology, PBPK models, and statistics. The peer review panel comments were set out in its Post Meeting Peer Review Report dated December 17, 2020.[14]

The Post Meeting Peer Review Report identifies approximately[15] 50 Tier 1 comments (issues necessary to address) and Tier 2 comments (issues suggested to be addressed). As part of this RFC, we are including "Ramboll's Response to External Peer Review Tier 1 and Tier 2 Comments/Suggestions, " which addresses all of these comments (see Exhibit A, Supplemental Materials G) and provides a summary of important new calculations, sensitivity analyses, and parameter analyses that have been conducted as part of the revisions to the model. Exhibit A, Supplemental Materials F,[16] provides the detail on the development of the sub model for the PBPK model to estimate epoxide and other metabolite concentrations. This was completed in response to a Tier 1 comment from a peer reviewer and is also summarized in Supplemental Materials G. We believe that all the Tier 1 and Tier 2 peer review comments have been resolved in the 2021 model and associated documentation.

In response to the peer review comments, Ramboll performed additional sensitivity/uncertainty analyses and literature searches. Also, at the request of the peer reviewers, Ramboll developed an extended version of the model to describe the downstream metabolism of chloroprene in order to compare model predictions using alternative dose metrics. The results of this extension of the model demonstrate that the use of a dose metric based on total metabolism is consistent with the cross-species relationship of the toxicity and carcinogenicity of chloroprene, but one based on epoxide area under the curve (AUC) is not. These results support the use of total metabolism as the most appropriate dose metric for the carcinogenicity of chloroprene.

C. The IUR Should Be Corrected to Reflect the 2021 Ramboll PBPK Model

Overall, the application of the 2021 PBPK model is expected to result in the estimation of an IUR that is approximately two orders of magnitude below that of the 2010 IUR. ORD has

[13] Clewell HJ 3rd, Campbell JL, Van Landingham C, Franzen A, Yoon M, Dodd DE, Andersen ME, Gentry PR. 2020. Incorporation of in vitro metabolism data and physiologically based pharmacokinetic modelling in a risk assessment for chloroprene. *Inhalation Toxicology*. 31(13-14):468-483.

[14] Post-Meeting Peer Review Summary Report, External Peer Review of a Report on Physiologically–based Pharmacokinetic (PBPK) Model for Chloroprene (Ramboll, 2020) and Supplemental Analysis of Metabolic Clearance (U.S. EPA, 2020, December 17, 2020, U.S. EPA and Versar, Inc).

[15] Some comments have multiple parts, and some comments are redundant of others.

[16] Exhibit A, Supplemental Materials F, is entitled "Reactive Metabolite Modeling."

requested that DPE limit its request for review to the adoption of the PBPK model, and that DPE not address all risk assessment factors that IRIS may consider in re-evaluating the IUR. However, the PBPK results strongly support the revision of the IUR to include the application of the PBPK model rather than the default assumption that humans and mice metabolize chloroprene in the same manner, and therefore, would respond similarly.

IV. New Epidemiological and Cancer Incidence Data Support the Findings of the PBPK Model and this RFC

A. The 2010 Review

As explained in Ramboll's report entitled "Epidemiological Basis for Supporting a Correction of the Chloroprene Inhalation Unit Risk (IUR): Update" (Exhibit B), the epidemiological evidence does not support a causal relationship between chloroprene and cancer in humans. Dr. Herman J. Gibb, one of the two epidemiologists on the peer review panel that reviewed the 2009 draft version of the 2010 Review, agreed with this conclusion and found that the epidemiology data reviewed by IRIS provided "little if any evidence" that chloroprene exposure increases the risk of either respiratory or liver cancer, the two cancers EPA indicated were associated with chloroprene exposure. At that time, Dr. Gibb wrote:

> As the document acknowledges on page 4-17, there is little if any evidence that chloroprene increases the risk of respiratory cancer. The limitations of the earlier studies (Li et al. 1989, Bulbulyan 1998, 1999) are significant with regard to whether or not they indicate an increased risk of liver cancer from chloroprene exposure. The largest and what appears from the document to be the best conducted study (Marsh et al., Louisville cohort) provides little if any evidence that a liver cancer risk exists. Furthermore, the document has not been transparent in its reasoning that there is a risk of liver cancer.
>
> In summary, the descriptor of "likely to be carcinogenic to humans" is supported by the animal and genotoxicity data, **but not by the human data. While the descriptor is appropriate, the document should not try to make more of the epidemiologic studies than is warranted.**[17]

In its review of the epidemiological evidence on chloroprene exposure, the 2010 Review analyzed a study by Dr. Gary Marsh, *et al.*, the results of which were reported in 2007 in a series of publications[18] (referred to collectively as "Marsh 2007") in the peer-reviewed journal, *Chemico-*

[17] Final Reviewer Comments, External Peer Review Meeting on the Toxicological Review of Chloroprene (CAS No. 126-99-8), January 26, 2010, p. 27 (emphasis added).

[18] Marsh GM, Youk AO, Buchanich JM, Cunningham M, Esmen NA, Hall TA, Phillips ML. 2007a. Mortality patterns among industrial workers exposed to chloroprene and other substances. I. General mortality patterns. Chemico-Biological Interactions.;166(1-3):285-300; Marsh GM, Youk AO, Buchanich JM, Cunningham M, Esmen

Biological Interactions. Marsh 2007 was the most comprehensive and methodologically robust [study available] based on the size of the cohort, amount of follow-up time, and completeness of exposure assessment, among other strengths. [19] The study involved 12,430 workers exposed to chloroprene at various industrial sites, including two US sites: the DuPont Louisville, KY, site (5,507 individuals) and the DuPont (now DPE) Pontchartrain, LA, site (1,357 individuals). Despite finding no evidence of elevated mortality risks from lung, liver, or other cancers between workers in either cohort and the corresponding regional populations, EPA considered Marsh 2007 as supportive of a causal association between chloroprene exposures and elevated mortality from liver cancer. This conclusion was based entirely on comparisons between exposure groups within the Louisville cohort, despite the very low liver cancer mortality rates among the Louisville employees and the fact that no instances of liver cancer mortality were observed in the Pontchartrain cohort. Again, when compared to liver cancer mortality rates in corresponding regional populations, there were no excess liver mortalities among workers in the Louisville or the Pontchartrain cohort.[20]

B. A Major New Follow-Up Epidemiological Study by Dr. Gary Marsh, *et al.*, Released in 2020, Shows No Increased Cancer Mortality among U.S. Chloroprene Workers

The conclusions of Dr. Gibb and Dr. Marsh were further confirmed by a new follow-up epidemiological study by Dr. Gary Marsh, *et al.*, published in February 2021 in the *Journal of Occupational and Environmental Medicine* and entitled "Mortality Patterns Among Industrial Workers Exposed to Chloroprene and Other Substances: Extended Follow-Up" ("Marsh 2021").[21] The express purpose of the new study was "[t]o update the U.S. portion of a historical cohort mortality study of workers with potential exposure to chloroprene (CD) and vinyl chloride (VC) with focus on lung and liver cancer."[22] The subjects of the study were workers from the former DuPont Neoprene facility in Louisville, Kentucky (Plant L), and the Pontchartrain Works Neoprene facility in Laplace, Louisiana (Plant P) (the former DuPont, now the DPE Neoprene facility). The follow up period was from 2001-2017, and added 47,299 and 19,942 person-years of observation and 1399 and 214 new deaths to the Louisville and Pontchartrain Works cohorts, respectively.[23] This resulted in improved statistical precision.

NA, Hall TA, Phillips ML. 2007b. Mortality patterns among industrial workers exposed to chloroprene and other substances. II. Mortality in relation to exposure. *Chemico-Biological Interactions.* 166(1-3):301-16.

[19] Bukowski JA. 2009. Epidemiologic evidence for chloroprene carcinogenicity: Review of study quality and its application to risk assessment. *Risk Analysis*, 29(9):1203–1216.

[20] Exhibit B, p. 4.

[21] Marsh GM, Kruchten A, Buchanich JM. Mortality Patterns Among Industrial Workers Exposed to Chloroprene and Other Substances: Extended Follow-Up. J Occup Environ Med. 2021 Feb 1;63(2):126-138.

[23] Exhibit B, p. 5.

[23] Exhibit B, p. 5.

In their follow up study, Marsh, *et al.,* again performed both external and internal mortality comparisons. The external comparisons revealed statistically significant *deficits* in deaths at both plants, and internal comparisons revealed **no consistent evidence of exposure-response relationships**. Marsh 2021 concluded that "the risk of death from all cancers or from the sites of a priori interest (lung and liver cancer) **is unrelated to exposure to [chloroprene]** at levels experienced by workers in the two U.S. sites."[24]

EPA should reevaluate the 2010 IUR to consider the significant findings of Marsh 2021. As Dr. Gibb commented in 2009:

> 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.[25]

This comment is even more relevant today with the additional information from the 2021 Marsh study.

C. New Cancer Incidence Data from the Louisiana Tumor Registry Shows the Incidence of Cancers near the DPE Faculty Are at or Below State-wide Averages for Cancers of Potential Concern

The PBPK model's findings are corroborated by the health data compiled and published by the Louisiana Tumor Registry (LTR), an independent and rigorous source of cancer incidence data which has been recognized consistently as one of the leading cancer registries in the nation.[26] The LTR has compiled annual reports on cancer incidence for decades. Data that were compiled after the 2010 Review were recently published and have been compiled and released in various reports. These data show that St. John Parish, the Parish in which the DPE facility is located,

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[24] Marsh 2021, p. 135 (emphasis added).

[25] Final Reviewer Comments, External Peer Review Meeting on the Toxicological Review of Chloroprene (CAS No. 126-99-8), January 26, 2010, p. 34. See also Sax SN, Gentry PR, Van Landingham C, Clewell HJ, Mundt KA. 2020. Extended Analysis and Evidence Integration of Chloroprene as a Human Carcinogen. *Risk Analysis*. 40(2):294-318.

[26] See FN 10. The National Cancer Institute, the Centers for Disease Control and Prevention, and the North American Association of Central Cancer Regis-tries have consistently recognized and validated the Louisiana Tumor Registry's high-quality da-ta. The LTR was one of nine NCI-SEER registries awarded 1st Place for data quality in 2020, the 11th consecutive year that the Louisiana Tumor Registry was recognized for the high quality, completeness and timeliness of its data. The LTR also earned Gold Certification again in 2020 by the North American Association of Central Cancer Registries (NAACCR). This designation recognizes registries that have achieved the highest NAACCR standard for complete, accurate, and timely data to calculate standard incidence statistics. LTR has earned this designation every year since 1997. The LTR was also given the Registry of Distinction Award from the Centers for Disease Control and Prevention's National Program of Cancer Registries this year. See "Cancer Reporting in St. John Parish Findings Vali-date Louisiana Tumor Registry Data," March 1, 2021. https://www.lsuhsc.edu/newsroom/Cancer%20Reporting%20in%20St.%20John%20Parish%20Findings%20Validate%20Louisiana%20Tumor%20Registry%20Data.html.

experiences average, or even below-average rates of cancer incidence.[27] As Ramboll summarized in Exhibit B, "LTR data at neither the Parish nor the census tract level indicate elevated rates of the cancers potentially associated with chloroprene exposure in St. John the Baptist Parish compared to Louisiana."[28]

V. CONCLUSION

DPE believes that the Ramboll 2021PBPK model and the PBPK report responding to peer review comments provide a strong basis for updating the IUR included in the 2010 Review, which should make it better aligned with the epidemiological evidence.

Because of the large toxicokinetic differences between mice[29] 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 PBPK model does not address all risk factors that affect the determination of the IUR, but it provides the foundation for a full IRIS revision of the 2010 IUR. DPE respectfully requests that EPA grant this RFC and initiate a formal revision of the 2010 chloroprene IUR.

Respectfully submitted,

Patrick A. Walsh, CIH
Safety, Health, and Environmental Manager
Denka Performance Elastomer LLC

[27] Exhibit B, pp. 7-12.

[28] Exhibit B, p. 7.

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

LIST OF EXHIBITS

Exhibit A: Report by Ramboll entitled "Incorporation of In Vitro Metabolism Data in a Physiologically Based Pharmacokinetic (PBPK) Model for Chloroprene- Revised Documentation in Response to USEPA Peer Review," and dated July 15, 2021.

Attachments to Exhibit A:

- Supplemental Materials A: Supplemental Tables
- Supplemental Materials B: Re-estimation of Metabolism Parameters
- Supplemental Materials C: IVIVE Literature Review
- Supplemental Materials D: Metabolism Parameter Calculations
- Supplemental Materials E: Model Files
- Supplemental Materials F: Reactive Metabolite Modeling
- Supplemental Materials G: Responses to Peer Reviewer Comments

Exhibit B: Report by Ramboll entitled "Epidemiological Basis for Supporting a Correction of the Chloroprene Inhalation Unit Risk (IUR): Update," dated July 15, 2021.