REQUEST FOR RECONSIDERATION

RFC # 21005(chloroprene)

Submitted on behalf of
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I. INTRODUCTION

Pursuant to Section 8.6 of EPA's Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility and Integrity of Information Disseminated by the Environmental Protection Agency (2002) as amended (Information Quality Guidelines), Denka Performance Elastomer LLC (DPE) submits this Request for Reconsideration of the decision by the Office of Research and Development (ORD) of the Environmental Protection Agency (EPA) to deny the Request for Correction (RFC) #21005, as set forth in a letter to Mr. Patrick Walsh with DPE dated March 14, 2022. Pursuant to Section 8.6 of EPA's Information Quality Guidelines, this RFR is being submitted within 90 days of the decision. ORD's March 14, 2022, denial is attached as Exhibit 1. Pursuant to Section 8.6, the contacts for this RFR are the undersigned as counsel for DPE, and:

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In RFC #21005, DPE seeks the revisions of the Inhalation Unit Risk (IUR) for chloroprene from the 2010 Toxicological Review of Chloroprene (CAS No. 126-99-8)("the 2010 Review"). The ORD denial ("the denial") incorrectly declined to revise the IUR to account for a new peer-reviewed Physiologically-Based Pharmacokinetic (PBPK) model for chloroprene. As will be shown below, ORD failed to consider the appropriate criteria considering new scientific evidence in updating risk assessment values, such as the chloroprene IUR, and ORD incorrectly concluded that DPE had failed to identify mistakes in the 2010 Review would justify the correction today. To the contrary, the RFC identified errors in the 2010 Review, particularly in the interpretation of the epidemiological data as pointed out by the independent peer review panel in 2010 ("2010 Peer Review" or "2010 PR"), and RFC # 21005 provides the peer-reviewed PBPK model suggested by the 2010 Peer Review. In consideration of the information presented below, DPE respectfully requests the Executive Panel to vacate ORD's denial of RFC #21005, and to direct ORD to undertake the correction of the chloroprene IUR to reflect updated scientific information.

DPE requested, but EPA has declined to provide, a full administrative record on the denial. DPE has also submitted two FOIA requests in an effort to obtain, among other things, the administrative record on the RFC denial. See FOIA Tracking Nos. EPA-R6-2022-004008 & 4255. No FOIA responses have been provided to date. DPE reserves the right to supplement this RFR with new information provided by the FOIA requests.

II. BACKGROUND

DPE purchased the LaPlace, Louisiana, Neoprene facility on November 1, 2015, and almost immediately thereafter learned of the development of the 2011 National Air Toxics Assessment (NATA) (published in December 2015). The NATA was based on the IUR for chloroprene from the 2010 Review, as well as on the 2011 facility emissions and emission source

characteristics and meteorology.[1] The NATA suggested a high offsite cancer risk in the nearby community. While questioning the validity of the NATA study results, DPE promptly commenced, pursuant to a January 6, 2017, an Administrative Order on Consent with the Louisiana Department of Environmental Quality (LDEQ), and a $35 million emissions reduction project, which has successfully reduced the facility's chloroprene emissions by 85% compared with the 2014 facility emissions.

In parallel with these emission reduction efforts, in 2016, DPE began working with scientists at Ramboll to investigate the science and available evidence concerning the validity of the IUR. Commencing with a "listening session" meeting with ORD in mid-2016, DPE has been in discussions with ORD on the scientific basis for correcting the 2010 IUR.

In the 2010 Review, EPA concluded that chloroprene was a "likely human carcinogen" and set one of its highest IURs for any hazardous air pollutant based on the **default** assumption that humans are as sensitive to chloroprene exposure as the most sensitive animal species and gender in laboratory exposure experiments, the female B6C3F1 mouse.[2] As shown below,[3] the female B6C3F1 mouse was far more sensitive to chloroprene than the hamster, the Wistar rat, and the Fischer rat. By adding the lung tumor incidence values for the different exposures, the table demonstrates that for comparable numbers of exposed animals across a range of chloroprene exposures, the observed lung tumors were as follows: Hamster, **zero**; Wistar rat, **zer**o; Fischer rat, **18**; and B6C3F1 mouse, **118**. As shown below, at any given concentration, the response and estimated risk for the B6C3F1 mouse is from 6 to 160 times more than the Fischer rat. Other rodent species show virtually no response to chloroprene. PBPK models provide the best available scientific tool for adjusting chemical exposure risks from one species to another, that is, from the female B6C3F1 mouse to the human. No such adjustment was made in 2010.

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1 Toxicological Review of Chloroprene (CAS No. 126-99-8), In support of Summary Information on the Integrated Risk Information System (IRIS), EPA (2010).

2 The 2010 Review sets a chloroprene IUR of 5×10^{-4} per $\mu g/m^3$ cancer incidence risk for 70 years of exposure. As shown in DPE's RFC # 17002 this is one of the highest IUR in the IRIS database. EPA's 2011 NATA identified DPE's facility as having the highest offsite cancer risk in the United States.

3 Exhibit 3. Response to Technical Questions Regarding the Science of Chloroprene, Ramboll, June 2022 ("Ramboll RFR Response") Table 1, p. 12. *See also* Sax, *et al.*, Table XIV, p. 20.

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).

Four of the six peer reviewers of the 2010 Review concluded that basing the human risk values on the B6C3F1 female mouse would overestimate chloroprene toxicokinetics in humans.[4] The 2010 Review and the 2010 Peer Review also recognized that a Physiologically-Based Pharmacokinetic (PBPK) model would provide a better estimate of human sensitivity to chloroprene, but EPA rejected the use of the chloroprene PBPK model available at that time, concluding the model was then inadequate "for a number of" technical reasons.[5]

In response to the 2010 Peer Review, in Appendix A to the 2010 Review,[6] EPA found that in using a 72% smaller IUR, based on the male rather than the female B6C3F1 mouse, the IUR would dramatically overestimate liver and lung cancer mortalities compared to observed cancer mortalities in the epidemiological cohort studied by Marsh, et al.(2007a, 2007b). The response to the peer review comments, however, incorrectly equated the estimation with the IUR of excess cancers with the background level of cancers in the pertinent cohort – in which there were no excess cancers – and then EPA explained the discrepancy, in part based on the healthy worker effect, which the peer reviewers in 2010 concluded was minimal, if present at all.

In July 2017, DPE submitted RFC #17002, relying on a published version of a chloroprene PBPK model (Yang, et al. 2012), and on DPE's re-evaluation of the Marsh (2007a, 2007b) epidemiology data evaluated in the 2010 Review. In January 2018, EPA denied RFC #17002 ("the 2018 denial"),[7] stating repeatedly that **in the absence of new scientific evidence**, the default use

4 Drs. Hattis, Morris, Ruder, and Schlesinger. See page 14 *infra.*

5 EPA denial to RFC #17002, p. 5.

6 Appendix A, Summary of External Peer Review and Public Comments and Disposition, at A-17.

7 Letter to Robert Holden, DPE counsel, from Jennifer Orme-Zavaletta, Principal Deputy Assistant Administrator for Science, EPA, dated January 25, 2018, including "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, and "Systematic Review of Chloroprene [CASRN 126-

of the female B6C3F1 mouse sensitivity as basis for human response was appropriate.[8] DPE filed a timely Request for Reconsideration (RFR) on the 2018 denial, RFR # 17002A, in July 2018.

Immediately following the 2018 denial, DPE commenced a three-year project to develop an updated and peer-reviewed chloroprene PBPK model with a team of scientists at Ramboll US Consulting, Inc. ("Ramboll"). DPE initially provided ORD with a Work Plan for the development of the PBPK model in April 2018, and ORD committed substantial resources to provide quality assurance guidance on the PBPK model development. In the 2018 denial, ORD had identified the lack of a PBPK model as the principal deficiency in RFC #17002. After DPE filed RFR #17002A, ORD paused the review of RFR #17002A for more than two years to allow the development of the PBPK model. In meetings and emails, ORD personnel repeatedly emphasized that DPE and Ramboll should develop the PBPK model, but that ORD would perform the full human risk assessment required for a revision of the IUR. In 2019, Ramboll's PBPK model for chloroprene and risk analysis were peer reviewed and published.[9] In October 2020, a live, virtual independent peer review panel organized by Versar, Inc., and sponsored by ORD peer reviewed a further updated version of the Ramboll PBPK model. The 2020 panel provided comments, characterized as Tier 1 (Key Recommendations), Tier 2 (Suggestions), and Tier 3 (Future Work) comments. Ramboll used these comments to further improve the PBPK model.

In February 2021,[10] ORD advised DPE that it would terminate the pause in the review of RFR #17002A, and refer that RFR to an executive review panel, as required by the Information Quality Guidelines.[11] By that time, however, the PBPK model had been substantially updated and had been developed in accordance with EPA quality assurance comments at each stage of development. DPE withdrew RFR #17002A on March 1, 2021, in order to request correction of 2010 IUR with the updated PBPK model.[12]

In early 2021, Ramboll substantially revised the chloroprene PBPK model, particularly to address all Tier 1 and Tier 2 peer review comments from the 2020 peer review. On July 15, 2021, DPE submitted RFC #21005 based in large part on the revised PBPK model.

After DPE filed RFC #21005, ORD discontinued substantive communications with DPE and Ramboll about the PBPK model and RFC #21005. During the review of RFC #21005, ORD, through Versar, secretly conducted a Follow-Up independent peer review of the 2021 PBPK model

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99-8] Studies Published Since 2010 IRIS Assessment to Support Consideration of the Denka Request for Correction (RFC)," dated January 2018 (Exhibit 2).

8 2018 denial, Attachment 1, page 3. ("[I]n 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.").

9 Clewell, HJ, III, Campbell, JL, Van Landingham, C, Franzen, A, Yoon, M., Dodd, DE, Andersen, ME, Gentry, PR. 2019. Incorporation of in vitro metabolism data and physiologically based pharmacokinetic modeling in a risk assessment for chloroprene. Inhalation Toxicology 31(13-14):468-483.

10 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.).

11 Email from Vaughn Noga to Patrick Walsh, dated February 5, 2021. ("On July 17, 2019, the U.S. Environmental Protection Agency (EPA) paused the reconsideration of your Information Quality Guidelines (IQGs) request **until after the peer review results regarding your submitted PBPK model were fully assessed**. This process has now been completed. In accordance with EPA's IQGs, the EPA will now continue the Request for Reconsideration (RFR) process.")(*emphasis added*).

12 DPE Letter to Katherine Chalfant, dated March 1, 2021.

("Follow-up Peer Review").[13] Unlike the 2020 peer review, the Follow-up peer review was conducted secretly and without opportunity for Ramboll to address any questions from the peer review panel. Nonetheless, the Follow-Up peer review showed that Ramboll's 2021 model revisions and new documentation successfully addressed the Tier 1 and Tier 2 comments from the 2020 peer review.[14] The Follow-Up Peer Review raised a small number of Tier 1 comments, and Ramboll concludes that these comments can readily be addressed with minor revisions to the 2021 PBPK model.[15]

On March 14, 2022, ORD denied RFC #21005 ("the 2022 denial"). The 2022 denial was inconsistent with the decision on RFC #17002. The 2022 denial stated that the purpose of the RFC process is to correct analysis and data in the 2010 Review, **not to update** prior risk assessments based on new scientific evidence. As noted above, however, in the 2018 denial of RFC #17002, ORD said that the 2010 Review **could only be changed based on new scientific evidence**. The 2022 denial further stated that the agency did not have the resources for such updates and that updating the 2010 Review chloroprene was not a national or regional priority. The 2022 denial also provided a "courtesy technical review," in which ORD concluded, incorrectly, that even if the PBPK model were appropriate for use, in a full risk assessment with the consideration of multiple organs (the Ramboll PBPK model addresses only lung tumors), the 2010 IUR would be within a factor of two of the corrected value. Based on this analysis, ORD said that 2010 IUR was in reasonable agreement with potential adjustments using the PBPK model. In addition, the 2022 denial rejected the conclusiveness of new follow-up epidemiological studies and the Louisiana Tumor Registry data.

This RFR will show that ORD incorrectly denied RFC #21005. ORD was wrong to reject RFC # 21005 on grounds that it allegedly only provided new scientific evidence (in fact, the RFC identified errors in the 2010 Review). And, ORD's "courtesy" development of a factor of 2 difference with the inclusion of cancer risks for multiple organs **ignored the applicability of the PBPK model to both the lung and liver** – further, even using EPA's methodology, the "courtesy technical review" should have recognized that the PBPK model would produce at least a factor of 35 difference with the 2010 IUR.[16]

III. SUMMARY OF RFR ARGUMENT

EPA developed the 2010 IUR for chloroprene on the dubious proposition that in the absence of scientific information to the contrary, humans would be assumed to have the same sensitivity to chloroprene as the most sensitive species and strain in the laboratory, the female B6C3F1 mouse. The empirical evidence from the strongest epidemiology study, ORD's own 2010

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[13] Versar, 2021. Follow up – External peer review of a report on physiologically based pharmacokinetic (PBPK) modeling for chloroprene and a supplemental analysis of metabolite clearance. Washington, DC: U.S. Environmental Protection Agency. (Exhibit 4).

[14] *See* Follow-Up Report, Question 12 "*Please review the Tier 1 and Tier 2 comments from the initial review and note any which you believe have not been adequately addressed by the revised analysis. If the comment has not been adequately addressed, please provide specific suggestions as to how this can be resolved."* There were no Tier 1 or Tier 2 comments identified in response to this question.

[15] Responses to Technical Questions Regarding the Science of Chloroprene, Ramboll, June 2022 ("Ramboll RFR Report") (Exhibit 3). See Appendix A to Ramboll RFR Report for responses to Follow-up Peer Review comments.

[16] Ramboll RFR Report at 7-8.

application of the IUR to the epidemiological cohort, and the Louisiana Tumor Registry cancer data for St. John the Baptist Parish (where the DPE facility is located) are inconsistent with the high risk calculated using the IUR. EPA has only weak explanations for the absence of the real world health effects that would be seen if the calculations based on the IUR were correct.

ORD improperly and incorrectly denied RFC #21005. DPE is seeking a correction of the errors in the development of the 2010 IUR through the application of the best available science as of 2022, which now includes the peer-reviewed Ramboll 2021 PBPK model for chloroprene. The Executive Panel should grant this RFR and direct ORD to grant the RFC #21005 and develop a new chloroprene IUR.

The following are the key points that will be developed in detail in the Argument section of this RFR:

A. ORD denied RFC #17002 because it lacked new scientific evidence, and it has now denied RFC #21005 because it is based on new scientific evidence. ORD has established a "Catch 22" where no revision of an IUR is possible without new scientific evidence, but new scientific evidence will not be used to change the IUR. (See pages 7 – 11 below.)

B. ORD's denial says that the 2010 peer review "is presumptive of objectivity" and the "best available" science at the time it was developed." This view could only be persuasive if ORD had fully followed the 2010 peer review recommendations and comments. However, an examination of the 2010 peer review report shows that the 2010 peer review disagreed with ORD's conclusions on epidemiology. Four of the six 2010 peer reviewers identified the need for adjustments because the female B6C3F1 mouse would overestimate chloroprene toxicokinetics, and the 2010 peer review strongly recommended the use of a PBPK model. EPA clearly erred in its response to the 2010 peer review when its own calculations of excess risk grossly overstated cancers in the principal epidemiological cohort. (See pages 12 – 18 below.)

C. When deciding whether to correct risk assessment values based on updated scientific information, the Information Quality Guidelines require EPA to consider other statutes, impacts on public policy, and impacts on private parties. The denial of RFC #21005 failed to consider impacts on Clean Air Act decisions, public policy, including Environmental Justice, and impacts on DPE. (See pages 18 – 23 below.)

D. The Follow-up Peer Review of the PBPK model showed that it is ready for use in estimating lung and liver risks. ORD's "Courtesy Technical Review" concluded that if the PBPK model were taken at "face value," the IUR might only be adjusted by 50%. However, ORD failed to recognize that the PBPK model addressed both lung and liver pharmacokinetics, which addresses 80% of the tumors observed in the NTP mouse studies. When the PBPK model is used for the lung and liver, the 2010 IUR should be corrected by a factor of at least 35. (See pages 23 – 27 below.)

E. The epidemiological data and the Louisiana Tumor Registry data strongly support a null hypothesis on chloroprene risks to humans. The "Courtesy Technical Review"

speculates upon the possibility (without supporting data) that confounding biases, such as the healthy worker effect, may have produced the null results. If the 2010 IUR were accurate, even within a factor of 2, there would be statistically significant increase in cancer rates shown in the Louisiana Tumor Registry for St. John the Baptist Parish, and there would have been thousands of excess cancers in the Marsh epidemiological cohort. The empirical data from the Louisiana Tumor Registry and the Marsh cohort is to the contrary. (See pages 27 – 30 below.)

In summary, based on EPA's errors in handling the peer reviewer comments in 2010, ORD should re-open the IUR for further review in response to RFC # 21005. Instead, ORD says now that the 2010 peer review establishes an insuperable burden for correcting the 2010 IUR. The Executive Panel needs to step in and correct this misguided decision by ORD.

Argument – The Executive Panel Should Direct ORD to Grant RFC #21005

Each of the arguments below addresses specific procedural or scientific errors in ORD's denial of RFC #21005, each of which provides a basis to reverse the denial. Collectively, the arguments should compel the reversal of the denial.

A. ORD's Denial Of The RFC On Grounds That DPE Had Not Identified Errors In The 2010 Review Is Incorrect And Constituted An Arbitrary And Capricious Re-Interpretation Of The Information Quality Guidelines.

1. RFC #21005 Identified Errors in the 2010 Review.

In its denial, ORD states that it denied the RFC because DPE's submission does not identify errors in the 2010 Review. That interpretation is simply wrong. For example, the RFC (at 9 – 10) quoted in full from Dr. Gibb, a 2010 peer reviewer, about his conclusion that ORD had "grossly misrepresented" the epidemiology data and failed to adjust the 2010 Review accordingly. (See pages 12 – 14 below.)

Throughout this process, DPE has documented significant errors in the 2010 Review. The errors include, without limitation (1) EPA set the human IUR for chloroprene without compensating for the differences in chloroprene sensitivity between the female mouse and humans; (2) EPA completed the 2010 Review without using a PBPK model, as strongly recommended by peer reviewers of the 2010 Review; and, (3) in responding to the 2010 peer review in 2010, EPA incorrectly calculated excess risk in the principal epidemiological cohort, which ORD should have recognized produced a nonsensical result. (EPA's incorrect evaluation of the male mouse IUR for the Louisville epidemiology cohort is discussed in pages 17 – 18 and 27 - 29 below.)

2. ORD arbitrarily and capriciously "moved the goal posts" in rejecting the consideration of new scientific evidence.

When ORD denied DPE's RFC # 17002, ORD stated with respect to multiple technical errors raised by DPE that the RFC was being denied for the failure to present new scientific evidence. For example:

- With respect to epidemiological evidence, ORD said, "**no new scientific evidence was provided in the DPE RFC that would alter this [epidemiological] conclusion**."[17]

- With respect to IRIS' reliance on the data from the female B6C3F1 mouse, ORD said, "**no new scientific evidence was provided in the DPE RFC that would alter the interpretation and application of data from female mouse lung tumors in IUR derivation**."[18]

- With respect to whether tumor types in laboratory studies were statistically independent, ORD said, "**no new scientific evidence, including any statistical analyses, was provided in the DPE RFC that would alter the multitumor modeling used in the derivation of the IUR**."[19]

- With respect to whether chloroprene has a mutagenic mode of action, ORD said, "**no new scientific evidence was provided in the DPE RFC that would alter this conclusion**."[20]

- With respect to whether the IUR for chloroprene is implausibly higher than IURs for similar chemicals, ORD said, "**no new scientific evidence was provided in the DPE RFC that would alter the derivation of the IUR**."[21]

- With respect to whether IRIS had improperly classified chloroprene as "likely to be carcinogenic to humans," ORD said, "**no new scientific evidence was provided in the DPE RFC that would alter the conclusion of the IRIS assessment that chloroprene is appropriately classified as likely to be carcinogenic to humans**."[22]

- With respect to a possible revision of the Reference Concentration (RfC) for Chronic Inhalation Exposure, ORD said, "**no new scientific evidence was provided in the DPE RFC that would alter the development and derivation of the RFC for chloroprene**."[23]

In light of these comments, DPE has worked cooperatively with ORD for approximately three years to provide the new scientific evidence – the PBPK model developed by Ramboll – which is the new scientific evidence requested by ORD and peer reviewers of the 2010 Review. In addition, DPE has evaluated and submitted new epidemiological studies by Marsh, et al. (2021), reflecting epidemiological follow-up through 2017 on cohorts examined by Marsh, et al. (2007a, 2007b), and DPE submitted new health data developed by the Louisiana Tumor Registry on cancer rates in Louisiana and St. John the Baptist Parish. But ORD stated that it had no obligation to review

[17] 2018 Denial attachment 1 at 2 *(emphasis added).*
[18] 2018 Denial attachment 1 at 3 *(emphasis added).*
[19] 2018 Denial attachment 1 at 4 *(emphasis added).*
[20] 2018 Denial attachment 1 at 5 *(emphasis added).*
[21] 2018 Denial attachment 1 at 8 *(emphasis added).*
[22] 2018 Denial attachment 1 at 8 *(emphasis added).*
[23] 2018 Denial attachment 1 at 9 *(emphasis added).*

new scientific evidence, and only provided a limited "courtesy technical review" of the new scientific evidence.

ORD's denial of the RFC was not based on the inadequacy of this new scientific evidence. Rather, the denial was based on ORD's incorrect conclusion that DPE failed to identify errors in the 2010 Review. In fact, in its denial ORD's stated reasons for the refusal to fully consider the new scientific evidence were as follows:

> The RFC process is intended to provide a mechanism to correct errors where the disseminated product does not meet information quality standards. The 2010 IRIS Chloroprene Toxicological Review was subject to rigorous independent peer review and public comment in 2010. Consistent with EPA Information Quality Guidelines, this peer review is **presumptive of objectivity and "best available" science at the time it was developed**. The Information Quality Guidelines commits EPA to ensure, "to the extent practicable" that:
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> "The substance of the information is accurate, 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"…." In applying these principles, **"best available" usually refers to the availability at the time an assessment is made**."
>
> EPA Information Quality Guidelines recognize that scientific information about chemical hazards and risk changes and may need to be updated over time. However, **the RFC process is not a mechanism to commit EPA to undertake scientific updates of its risk assessment products, such as IRIS Toxicological Reviews**. EPA Information Quality Guidelines recognize explicitly that a decision to launch an updated assessment depends on important programmatic factors….

Denial letter at 1 *(bold emphasis added).*

Simply put, ORD has unlawfully "moved its regulatory goalposts."[24] It first denied RFC #17002 based on DPE's failure to present new scientific evidence, notwithstanding DPE's identification of multiple errors in the 2010 Review. Now, after more than three years of work and associated costs in cooperation with ORD, ORD has denied the RFC based on its unfounded position that DPE did not identify errors in the 2010 Review, notwithstanding DPE's presentation of significant new scientific evidence. Such action is arbitrary and capricious and otherwise unlawful under the Administrative Procedures Act (APA).

As explained by the U.S. Supreme Court in *Dept. of Homeland Security v. Regents of the Univ. of California:*[25]

[24] *See* Wages & White Lion Investments, L.L.C. v. FDA, 16 F.4th 1130, 1134 (5th Cir. 2021).
[25] 140 S.Ct. 1891 (2020).

- An agency is required to engage in "reasoned decision making"[26] and its action must be "adequately explained;"[27]
- The agency must consider and assess "important aspects of the problem" before it;[28]
- When an agency rescinds a prior policy its reasoned analysis must consider the alternatives that are within the ambit of the existing policy;[29] and
- When an agency changes course, it must be cognizant that longstanding policies may have engendered serious reliance interests that must be taken into account, and it would be arbitrary and capricious for the agency to ignore such matters.[30]

In *Regents*, the Supreme Court vacated DHS's rescission of its immigration program known as Deferred Action on Childhood Arrivals (DACA) on several grounds. The overriding reason was DHS's failure to comply with the procedural requirement that it provide a reasoned explanation for its action.[31] More specifically, DHS's failure to consider continuing DACA's policy of forbearance on removal of aliens as an alternative even if the aliens' benefits were terminated rendered DHS's rescission of DACA arbitrary and capricious.[32] In addition, DHS's failure to assess whether there were reliance interests, determine whether such interests were significant, and weigh such interests against competing policy concerns, was a second and independent reason that it's rescission of DACA was arbitrary and capricious.[33]

Here, ORD's denial of the RFC is arbitrary and capricious for similar reasons. First, ORD failed to provide a reasoned explanation for its decision to deny the RFC based on the incorrect assertion that DPE failed to identify errors in the 2010 Review action, rather than in consideration of the new scientific information provided by DPE. Further, ORD's change of course to not consider the new scientific information presented by DPE was arbitrary and capricious because it was not based on reasoned decision-making nor was it adequately explained; ORD did not consider important aspects of the issue, including alternatives such as fully evaluating the scientific information presented by DPE; and importantly ORD did not adequately consider and assess DPE's significant reliance on its prior policy and requests for the new scientific information and the significant time and money spent by DPE in cooperation with EPA in providing that information.

In addition, the Fifth Circuit's recent decision in *Wages & White Lion Investments, L.L.C. v. FDA,*[34] which cites *Regents*, is analogous and instructive. In *Wages*, the FDA had issued in 2016 its "Deeming Rule" which deemed "e-cigarettes" to be a "new tobacco product" under the 2009 Family Smoking Prevention and Tobacco Control Act (TCA). The problem was that by that time, manufacturers were widely marketing e-cigarettes throughout the U.S. To avoid an overnight shutdown of the entire industry, FDA delayed enforcement of the Deeming Rule but forced e-

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26 *Id*. at 1905.
27 *Id*. at 1907.
28 *Id.* at 1910.
29 *Id*. at 1913.
30 *Id.*
31 *Id*. at 1916.
32 *Id.* at 1913.
33 *Id.* at 1913-15.
34 16 F.4th 1130 (5th Cir. 2021).

cigarette manufacturers to meet a series of requirements and staggered deadlines to keep their products on the market, including submittal of onerous premarket tobacco applications (PMTAs) to FDA. Initially, FDA's guidance stated that in general FDA did not expect that applicants will need to conduct long-term studies of e-cigarettes to support a PMTA. However, FDA later, in 2021, changed its mind and required the very thing it said it would not—namely, long-term studies of e-cigarettes. Less than a week after FDA changed its regulatory requirements, the plaintiff e-cigarette manufacturer, Triton, submitted a letter to FDA stating that it would conduct long-term studies of its products. About two weeks later, however, FDA issued a marketing denial order to Triton stating that the key basis for the denial was that the plaintiff's PMTA lacked "robust and reliable evidence" from long-term studies. Triton then filed suit for review and a stay of FDA's order pending that review.

The Fifth Circuit stayed FDA's disposition of Triton's PMTA finding, among other things, that Triton had shown a strong likelihood of success on the merits. The court found that FDA had "moved its regulatory goalposts" when it changed the regulatory requirements for PMTAs.[35] It explained that FDA had pulled a "surprise switcheroo" on the regulated entities by announcing that it required the very studies that it originally expected it didn't need.[36] The court held that FDA failed to reasonably consider the relevant issues and reasonably explain its order denying Triton's PMTA, failed to consider alternatives "when changing from its no-long-term-studies-necessary policy to its apparent long-term-studies-required policy," and failed to consider and adequately assess Triton's legitimate reliance interests.[37] For all of these reasons, the court found that FDA's order was likely arbitrary, capricious, or otherwise unlawful and granted the stay of that order.

Similarly, in the present case, ORD has changed from its "you identified errors but failed to provide new scientific evidence" position (in the denial of RFC #17002) to its current "you provided new scientific evidence but failed to identify errors" position (in the denial of RFG #21005). And ORD did so without explaining this flip-flop in its position, without considering alternatives including full evaluation of the new scientific evidence, and without considering and assessing DPE's significant and legitimate reliance interests in reliance on ORD's stated need for new scientific evidence (including three years of work and expense in developing the PBPK model). ORD clearly "moved its regulatory goalposts" and pulled a "surprise switcheroo" on DPE, without providing any reasoned explanation for such action. ORD's decision is arbitrary, capricious, and otherwise unlawful in violation of the APA. The Executive Panel should correct ORD's decision.

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35 *Id*. at 1134-35.
36 *Id*. at 1138, citing Azar b. Allina Health Services, 139 S.Ct. 1804, 1810 (2019).
37 *Id.* at 1134-39.

B. ORD Is Mistaken – The 2010 Peer Review And ORD's Response To The 2010 Peer Review Support The Granting Of The RFC.

ORD states that the 2010 "peer review is presumptive of objectivity and 'best available' science at the time it was developed";[38] however, the 2010 peer review highlighted weaknesses in the 2010 Review that need to be fixed, and DPE's RFC provides the appropriate mechanism.

EPA published the peer reviewer comments on the 2009 Draft Review in the "Final Peer Review Comments," dated January 25, 2010 (hereinafter referred to as "2010 PR Comments").[39] The 2010 Review only provides a simplified "Summary of External Peer Review and Public Comments and Disposition," included as Appendix A to the final 2010 Review.[40] The two documents must be read together to understand the errors in ORD's denial of the RFC.

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); and
6. Richard B. Schlesinger, Ph.D. (toxicologist).[41]

The expertise of each reviewer is important in assessing the comments.

1. The 2010 Peer Review shows that ORD "grossly misrepresented" the epidemiological data.

In his peer review comments, Dr. Herman J. Gibb, one of only two epidemiologists on the peer review panel, strongly criticized EPA's epidemiological interpretations.[42] He 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). He strongly criticized EPA's cancer risk conclusions, stating: "The statement … 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."[43] In the same vein, he noted, "The statement … that there was 'some evidence' of liver/biliary passage cancer risk being

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38 2022 Denial at 1.

39 Attached as Exhibit 5. Relevant comments have been highlighted by DPE's counsel for convenience.

40 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.

41 Areas of expertise developed by Ramboll's internet research.

42 2010 PR Comments at 25-27.

43 2010 PR Comments at 25 (*emphasis added*).

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."[44]

As ORD had done in 2010, it repeated in the courtesy technical review in the 2022 denial, discounting the null results of the epidemiology based on the "healthy worker effect." The 2022 denial's Exhibit A stated, "the healthy worker effect tends to reduce the association between an exposure and the outcome because workers, as a group, are healthier than the general population comparison groups." Dr. Gibb stated the following regarding "the healthy worker effect":

> 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 such a short life expectancy following diagnosis, **I would expect the healthy worker effect for liver cancer to be minimal if it even exists**. [Emphasis added.]

The 2010 peer review comments are, in ORD's words, "presumptive of objectivity" and "best available science."[45] Therefore, "presumptive of objectivity and best available science," the denial was wrong to rely on the healthy worker effect.

Further, the 2010 peer review refutes ORD's conclusion that the epidemiology is suggestive of an association between workplace exposure to chloroprene and cancer. 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 [i.e., the draft 2010 Review] has not been transparent in its reasoning that there is a risk of liver cancer.**[46]

ORD changed only two words from the 2009 Draft Review to the 2010 Review to respond to Dr. Gibb's comments. 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).[47]

In the 2010 Review, ORD changed only two words in this paragraph as follows:

> 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

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44 *Id.*
45 2022 denial, Exhibit A at 8.
46 2010 PR Comments at 27 (*emphasis added*).
47 2009 Draft Review at 4-18.

> workers exposed to chloroprene in different cohorts on different continents (i.e., U.S., China, Russia, and Armenia). . . ."[48]

"Reasonably" was changed to "fairly," and the word "suggestive" was added. ORD clearly ignored the 2010 peer review comments, which were "presumptive of objectivity" and "best available." Therefore, the 2010 Review has errors that are critical and need be corrected. The epidemiological studies and the Louisiana Tumor Registry data are discussed further below, but clearly, the 2010 peer review supports the granting of the RFC.

2. ORD failed to adjust for the overestimate of risk from the female B6C3F1 mouse Highlighted by the 2010 Peer Review.

ORD's charge question to the 2010 peer review panel most relevant to its selection of the female B6C3F1 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.[49]

("Question C2"). All six peer reviewers agreed with the use of the B6C3F1 NTP study, but **four of the six peer reviewers** expressed concerns related to the overestimate human response (2010 PR Report at 30 – 31):

- Dr. Hattis – "metabolic concentration **could have been informed** by application of the preliminary PBPK model."

- Dr. Morris – "**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**."

- Dr. Ruder – "The text in section 5.4.4 explains the derivation of the inhalation risk but does not explain why inhalation in mice was chosen over inhalation in rats from the same study. **I assume there are physiological differences which make mice a more suitable choice, but none were provided here**."[50]

- Dr. Schlesinger – 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**."

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[48] 2010 Review at 42.

[49] 2010 PR Comments at 30.

[50] 2010 PR Comments at 31 *(emphasis added)*. DPE has not been able to identify any explanation in the 2010 Review of physiological differences which make mice a more suitable choice than rats.

None of the peer reviewers said that they agreed with the default use of the female B6C3F1 mouse IUR for the human IUR without adjusting for differences in species sensitivity.

Additional comments focused on the important differences between human response and the response of the B6C3F1 mouse:

- "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.**"[51]

- "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?"[52]

- "**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."[53]

- "**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. . . ."[54]

- "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."[55]

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[51] 2010 PR Comments at 40 *(emphasis added).*
[52] 2010 PR Comments at 57.
[53] 2010 PR Comments at 57 *(emphasis* added).
[54] 2010 PR Comments at 59-60 *(emphasis added).*
[55] 2010 PR Comments at 62 *(emphasis added*).

In response to comments by the 2010 peer reviewers—and by the public—regarding the significant differences in the metabolism of chloroprene across species, ORD stated three times in the 2010 Review's 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."[56] In summary, the 2010 Peer Review clearly shows that the female B6C3F1 mouse IUR overestimates human response to chloroprene.

3. The 2010 Peer Review Report identifies the need for the PBPK Model.

Only one of the six 2010 peer reviewers, Dale Hattis, Ph.D., was an expert in PBPK modeling. His comments show that if a PBPK model is ready for use with chloroprene, it should be used to update the IUR.

- Dr. Hattis urged the application of a PBPK model, noting that "the dosimetry, in terms of active metabolite concentration" which "could have been informed by application of a preliminary PBPK model."[57]

- Dr. Hattis also noted a "significant omission" by Dr. DeWoskin of EPA, in that there was a lack of an analysis "of the potential to use a PBPK model for estimation of human vs. mouse and rat delivered doses in modeling cancer dose response relationships for chloroprene."[58]

John B. Morris, Ph.D. also, in his general impression on toxicological review, stated:

- "[T]he toxicokinetic data is not adequately synthesized in the overall mode of action relative to potential species differences and extrapolation to man. PBPK modeling would be **a highly appropriate way** to incorporate kinetic data into the risk assessment."[59]

As the denial stated, the 2010 "peer review is presumptive of objectivity and 'best available' science at the time it was developed." It is extraordinary that ORD would rely on the 2010 peer review now to suggest that a peer-reviewed PBPK model should not be used to adjust the chloroprene IUR today.

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[56] 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. \misleading [discuss further with RE].

[57] 2010 PR Comments at 30.

[58] 2010 PR Comments at 10.

[59] 2010 PR Comments at 6.

4. EPA's 2010 Response to the External Peer Review and Public Comments showed a gross disparity between estimated and observed lung and liver cancers.

In the 2010 Review's response to peer review and public comments (2010 Review, Appendix A, page A-17), ORD evaluated the risk calculation of a smaller IUR against the principal epidemiological cohort. As explained below, ORD's clear error in this evaluation shows that the RFR should be granted.

ORD used the male mouse IUR to calculate the number of expected **excess** lung and liver cancer cases for the Louisville plant cohort developed in the Marsh et al. (2007a, 2007b) study. ORD used the median occupational exposure concentration estimated by Marsh, correcting for lifetime exposure. The occupational exposure concentrations documented in Marsh et al. (2007b) had declined over time, from 20 ppm (~ 1035 ug/m3) before 1960 to less than 0.5 ppm (~ 26 ug/m3) in 1990. ORD used the male mouse IUR of 1.4 x 10^{-4} per $\mu g/m^3$, 72% lower than the final IUR in the 2010 Review of 5 x 10^{-4} per $\mu g/m^3$. The male mouse IUR was tested against the occupational cohort of known causes of death (n=2,282), not against the cohort of all exposed workers **(**n=5,486) (which ORD should have used to estimate lung and liver cancer incidence). Nonetheless, using the male mouse IUR and the wrong cohort, ORD estimated in 2010 that it expected 293 **excess** lung and liver cancers for the chloroprene exposed workers cohort at the Louisville plant, compared with the observed 283 lung and liver cancer mortalities in the cohort.

However, what ORD failed to recognize is **that the IUR calculates excess cancers as compared with the expected background rate of cancers in an unexposed population**. In fact, Marsh et al. (2007b) determined the standardized mortality ratios (SMR) for chloroprene exposed workers both lung and liver cancers were <1.0, indicating that the exposed workers had lung and liver cancers at rates below the background rate of lung and liver cancers for unexposed populations. In the exposed worker cohort in Louisville, 283 lung and liver mortalities had been documented in the Marsh 2007 study, which is a value less than would be expected in an unexposed population. As noted above, the occupational exposure concentrations documented in Marsh et al. (2007b) had declined over time, from ~ 1035 ug/m3 before 1960 to less than ~ 26 ug/m3 in 1990. Despite these exposure levels, the cohort had no demonstrable excess lung and liver cancers.

In 2010, ORD used the male mouse IUR of 1.4 x 10^{-4} per $\mu g/m^3$, 72% below the final IUR of 5 x 10^{-4} per $\mu g/m^3$, to estimate expected excess lung and liver cancers in the Louisville exposed worker cohort. ORD estimated that this cohort would have 293 excess cancers, that is, ORD estimated 293 more lung and liver cancers than would be expected in an unexposed population. ORD then compared the estimated excess cancers, 293, with the observed lung and liver cancers, 283, and concluded that there was no problem with the male mouse IUR.

ORD made basic mistakes in 2010. It should have recognized that its calculation would have more than doubled the number of observed lung and liver cancer mortalities (for example, if the SMR had been 1.0, the expected background cancer rate would have been 283, and to this number ORD should have added the estimated 293 lung and liver excess cancers, to yield a value of 576 to compare with the observed 283). It should have recognized that the final IUR of 5 x 10^{-4} per $\mu g/m^3$ was 72% larger than the male mouse IUR. And ORD should have used the **total**

exposed cohort (n=5,486) to estimate lung and liver cancers. ORD should have predicted **3,891** excess lung and liver cancers.[60] This is a gross disparity between observed lung and liver cancer (283) versus calculated excess cancers using EPA's final IUR (3,891).

In the 2010 Review, Appendix A, EPA noted that there were possible confounding issues with these calculations, including the Marsh exposure assessment, latency periods, and incomplete assessments of cause of death. Nonetheless, the fact remains that the cohort had no excess cancers greater than expected background cancer rates, and these limitations are common to epidemiology studies. (Notably, the latency issues are largely resolved with Marsh et al. (2021), which updated the cohort through 2017, increasing the minimum latent interval to 45 years. This update added 47,299 person-years of observation and 1,399 deaths, and again confirming the null result associated with chloroprene exposure.) EPA should have recognized in 2010 that the IUR generated an enormously flawed cancer estimate of 3,891 when no excess cancers were observed. Had ORD recognized the errors in its response to the peer review, it would have recognized the inaccuracy in both the male mouse and the female mouse IUR.

The 2010 Review, Appendix, A concluded the discussion with a shrug of the shoulders, saying "EPA has not developed an Agency-wide policy to apply uncertainty factors." (Page A-19). EPA's 2010 errors in not recognizing that the IUR calculates excess cancers, not using the final IUR, not using the correct cohort size, and not trying to reconcile the 2010 Review's toxicological risk estimates with the epidemiological data show that the RFR should be granted.

C. ORD Failed to Evaluate Required Factors Under the Information Quality Guidelines.

ORD failed to consider relevant factors in deciding whether to update the IUR with new scientific evidence, and in failing to evaluate the extent to which inaccurate and inflated risk estimates will have a detrimental impact on DPE and the public, including environmental justice communities.

1. The Information Quality Guidelines and the Case Law Specify the Factors to be Evaluated with Scientific Updates.

EPA developed the Information Quality Guidelines pursuant to the Information Quality Act,[61] which requires Federal agencies to develop guidelines for "ensuring and maximizing the quality, objectivity, utility, and integrity of information (including statistical information) disseminated by Federal agencies." In implementing the "best available science" requirement, the Information Quality Guidelines require EPA to take into consideration other statutory requirements, the availability of peer-reviewed science, and the impacts of the incorrect information on the agencies and the public. As recognized in the denial, Section 6.4 of the Information Quality Guidelines specifies with respect to updates on scientific information:

> **In applying these principles, "best available" usually refers to the availability at the time an assessment is made. However, EPA also recognizes that scientific**

[60] For more detail, see the attached Ramboll RFR Report at 13 – 14.
[61] Section 515 of Pub. L.aw 106-554(2000), codified as 44 U.S.C. § 3504(d)(1) and § 3516.

> **knowledge about risk is rapidly changing and that risk information may need to be updated over time. When deciding which influential risk assessment should be updated and when to update it, the Agency will take into account its statutes and the extent to which the updated risk assessment will have a clear and substantial impact on important public policies or private sector decisions.** In some situations, **the Agency may need to weigh the resources needed** and the potential delay associated with incorporating additional information in comparison to the value of the new information in terms of its potential to improve the substance and presentation of the assessment. [Bold *emphasis* added.]

ORD failed to consider the three balancing factors it committed to in the Information Quality Guidelines when making decisions about updating prior risk values. Specifically, ORD failed to consider:

1. The other statutes involved, particularly the Clean Air Act and the importance of best available science to Clean Air Act requirements;
2. The extent of a substantial impact of the updated information on public policies, including but not limited to Environmental Justice;
3. The extent of a substantial impact of the updated information on private sector decisions, including DPE's decisions about future investments in the Louisiana Neoprene plant; and,
4. That the DPE Neoprene plant is the only Neoprene production facility in the United States.

The denial completely ignored these factors, other than to downplay the extent of the risk adjustment required by the PBPK model as perhaps only 50% (that is, a factor of 2) when the effects on multiple organs are considered. (This adjustment factor will be discussed in more detail below (see pages 26 - 27), but even using ORD's flawed methodology, it must be recognized that the Ramboll PBPK model was developed to consider both lung and liver pharmacokinetics, and at the very least the IUR should be adjusted downwards by a factor of 35.

ORD also concluded that it would not accept the RFC due to IRIS resource constraints, which might sound reasonable, but it ignores and fails to consider that the IUR is a limited portion of the 2010 Review. The update of the IUR can be compartmentalized. At the very least, ORD should have considered, or the extent agency resources were considered, the modest nature of the re-opening to review the IUR.

The Information Quality Guidelines expressly incorporate the Safe Drinking Water Act (SDWA) approach to the use of best available science. In *Chlorine Chemistry Council v. EPA*,[62] the D.C. Circuit Court of Appeals vacated an EPA Order for being "arbitrary and capricious and in excess of statutory authority."[63] EPA ignored the best available evidence at the time found by an advisory group organized by the agency.[64]

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62 *Chlorine Chemistry Council v. Env't Prot. Agency*, 206 F.3d 1286 (D.C. Cir. 2000).

63 *Id.* at 1291.

64 *Id.* at 1288.

In July 1994, EPA issued a proposed rule that would set the maximum contaminant level goal (MCLG) for chloroform at zero under the SDWA.[65] EPA's proposal to set the MCLG at zero was based on its "finding of an *absence* of data to suggest a threshold level below which there would be no potential carcinogenic effects."[66] In 1998, EPA published a Notice of Data Availability (NODA) on chloroform, where it was concluded that "although it was 'a likely carcinogen to humans above a certain dose range, [it was] unlikely to be carcinogenic below a certain dose range.'"[67] EPA agreed with the NODA and proposed an MCLG for chloroform at 300 parts per billion.[68] Despite this, when it was time to promulgate a final rule in December 1998, EPA set its MCLG for chloroform back to zero.[69]

"[EPA] justified the action on the basis that 'additional deliberations with the Agency's [Science Advisory board] on the analytical approach used' and on the underlying scientific evidence were needed 'prior to departing from a long-held EPA policy.'"[70] The Court found that the SDWA "states unequivocally that 'to the degree that an Agency action is based on science, the Administrator shall use … the best available, peer-reviewed science and supporting studies conducted in accordance with sound and objective scientific practices,'" and that "[i]n promulgating a zero MCLG for chloroform EPA openly overrode the 'best available' scientific evidence, which suggested that chloroform is a threshold carcinogen."[71] As a result, the Court vacated the rule as it was "arbitrary and capricious and in excess of statutory authority."[72]

Similarly, the Clean Air Act requires EPA to base air quality standards on the latest scientific information. Specifically, the statute states: "Air quality criteria for an air pollutant shall accurately reflect **the latest scientific knowledge** useful in indicating the kind and extent of all identifiable effects on public health or welfare which may be expected from the presence of such pollutant in the ambient air, in varying quantities."[73] ORD's failure to consider and appropriately act upon the new scientific information violates this Clean Air Act requirement.

ORD's inaction also violates federal policy announced by President Biden. On the day of his inauguration, President Biden issued an Executive Order stating, among other things, that in carrying out its charge to promote and protect public health and the environment, "the Federal Government must be guided by the best science and be protected by processes that ensure the integrity of Federal decision-making."[74] One week later, the President issued an Executive Order stating that "it is the policy of [his] Administration to make evidence-based decisions guided by the best available science and data," and ordering that "[o]fficials and employees across [his] Administration shall seek from scientists, engineers, and other experts the best available scientific and technological information and advice."[75] That same day, President Biden issued a memorandum to the heads of the executive departments and agencies, stating:

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65 *Id.*
66 *Id.* at 1287.
67 *Id.* at 1288.
68 *Id.*
69 *Id.*
70 *Id.*
71 *Id.* at 1290.
72 *Id.*
73 42 U.S.C. § 7408(a)(2).
74 Executive Order on Protecting Public Health and the Environment and Restoring Science to Tackle the Climate Crisis, dated January 20, 2021.
75 Executive Order on the President's Council of Advisors on Science and Technology, dated January 27, 2021.

> It is the policy of my Administration to make evidence-based decisions guided by the best available science and data. Scientific and technological information, data, and evidence are central to the development and iterative improvement of sound policies, and to the delivery of equitable programs, across every area of government. Scientific findings should never be distorted or influenced by political considerations. When scientific or technological information is considered in policy decisions, it should be subjected to well-established scientific processes, including peer review where feasible and appropriate, with appropriate protections for privacy.[76]

The memorandum generally directed the executive departments and agencies to act in accordance with this policy.

DPE provided ORD with the three times peer-reviewed PBPK model, which had been developed by Ramboll in coordination with ORD on quality assurance. By failing to consider and take appropriate action based on the model, ORD violated federal law and policy when it declined to apply the best available science.

2. ORD should have considered how the failure to update the chloroprene IUR affects the Clean Air Act Requirements.

As shown above, the Information Quality Guidelines required ORD to take into account "its statutes," such as the Clean Air Act, particularly Section 112 for the control of hazardous air pollutants,[77] as well as the public policy implications with respect to other statutes, such as the analogous Louisiana Air Control Law within the Louisiana Environmental Quality Act.[78] To give but a few examples, within the last two years, EPA has (i) sent DPE multiple Clean Air Act Section 114 information requests, (ii) conducted a Clean Air Act inspection, (iii) required DPE to install Method 325 fenceline monitors for chloroprene, and (iv) maintained an SPod community monitoring network around the facility. In addition, EPA has propounded Resource Conservation and Recovery Act (RCRA) Section 3007[79] information requests, concerning in part, chloroprene emissions, and it has conducted a facility inspection for the same reasons. These inquiries and monitoring are based on the assumption that IUR is correctly derived under 2010 Review. In this sense, the statutes are being administered based on IUR and DPE has been impacted. In addition, EPA itself is expending substantial resources considering the impacts of chloroprene emissions, assuming that the 2010 IUR is accurate.

Even if, as the Courtesy Technical Review states, the use of the PBPK model, "taken at face value," would only result in a 50% downward adjustment of the IUR, this is a huge factor supporting the re-opening of the value of the IUR in the 2010 Review. If it is higher by at least a

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[76] Memorandum on Restoring Trust in Government Through Scientific Integrity and Evidence-Based Policymaking, dated January 27, 2021.
[77] 42 U.S.C. § 7412.
[78] La. R.S. 30:2051 *et seq.*
[79] 42 U.S.C. § 6927.

factor of 35 (see pages 26 - 27), DPE, EPA LDEQ, and the public are devoting substantial resources to a non-problem.

3. Revising the IUR will have a substantial impact on the updated information on public policies, including but not limited to Environmental Justice.

To identify but one public policy concern, the Biden administration and the Regan-led EPA have repeatedly stressed the importance of Environmental Justice.[80] Administrator Regan's November 2021 Journey to Justice, in which he visited St. John the Baptist Parish where DPE is located and is one of the largest employers, strongly emphasized the importance of Environmental Justice. RFC #21005 should have been granted because Environmental Justice communities deserve scientifically updated and accurate risk assessment information.

4. Revising the IUR will have a substantial impact on private sector decisions, such as DPE's investments in the Louisiana Neoprene plant.

As noted above, shortly after DPE acquired the Louisiana Neoprene facility on November 1, 2015, it learned of the development of the 2011 NATA (published in December 2015). The NATA relied on the IUR for chloroprene, combined with estimated emissions of chloroprene from the DPE facility, emission parameters such as stack height and exit gas flows, and meteorology. Largely as a result of the NATA, DPE entered into an Administrative Order on Consent with LDEQ and spent $35 million to reduce chloroprene emissions by 85%, compared to 2014 facility emissions. However, even with these emission reductions, based on the IUR, there have been suggestions, which DPE strongly disagrees with as not representing the "best available science," that DPE should further reduce its chloroprene emissions to achieve a 1-in-10,000 risk value of lifetime exposure level of 0.2 $\mu g/m^3$ over 70 years.

Private sector decisions, such as DPE's, to invest additional millions of dollars in pollution control measures, as well as on facility maintenance and operations, will be impacted greatly by ORD's failure to update the IUR for the currently best available scientific information. ORD's denial ignored this factor. Further, this is the only Neoprene production facility in the United States and without the DPE facility, all of DPE's customers would have to import Neoprene or find alternative products. Even a factor of 2 (as ORD suggests) or 35 (see pages 26 - 27 below) adjustment would have a huge impact on DPE's investment decisions.

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[80] *See* https://www.epa.gov/environmentaljustice, "Environmental justice is the fair treatment and meaningful involvement of all people regardless of race, color, national origin, or income, with respect to the development, implementation, and enforcement of environmental laws, regulations, and policies. This goal will be achieved when everyone enjoys:

- The same degree of protection from environmental and health hazards, and
- Equal access to the decision-making process to have a healthy environment in which to live, learn, and work."

5. In denying the RFC, ORD ignored DPE's proposal for a compartmentalized update of only the IUR within the 2010 Review.

In the denial, ORD based its decision on resource constraints for the review of prior toxicity assessments:

> Given the finite resources of the IRIS Program, IRIS assessment activities are based on the priority needs of EPA National Program and Regional Offices identified through a structured internal nomination process. Any new scientific information submitted though the RFC process would be considered if an update was initiated based on (1) the topic is identified as a National Program or regional Office priority need, and (2) acceptance of the nomination by the IRIS Program given available resources. (Denial at 1 - 2.)

In evaluating its resource constraints, ORD ignored DPE's suggestion that the update could be accomplished with a focused, compartmentalized modification of the 2010 Review. Had ORD considered compartmentalized changes to the 2010 Review, it would have dramatically reduced the concerns about resource constraints. Further, ORD ignored the resource demands on that EPA's other offices created by an erroneously high IUR for chloroprene, including but not limited to Region 6, OECA, and OAR.

D. ORD's "Courtesy Technical Review" Incorrectly Interpreted the PBPK Model and Health Data as Consistent with the IUR.

In the denial, after concluding that ORD had no duty to update the 2010 IUR with new scientific information, ORD said (page 2):

> However, EPA is providing a courtesy technical review in its response to this RFC(Appendix A). This courtesy review substantially exceeds EPA's commitment toward addressing an RFC and should not be interpreting as setting a precedent for any future RFC request. Within the scope of this review, open science issues were identified concerning the PBPK model predictions proposed by Denka. EPA engaged external expert peer reviewers for aspects of this courtesy review (Versar, 2021). It should be noted that even if the PBPK model predictions were accepted at face value, the findings of EPA's courtesy review do not support Denka's assertion that applying the submitted PBPK model would lead to a large decrease in estimated risk compared with the existing IRIS assessment.

The courtesy technical review, Appendix A in the denial, contained flawed analyses of the PBPK model and of the new epidemiological land health data submitted in support of the RFC. Had ORD properly performed the courtesy technical review, it would have recognized the importance of granting the RFC. This RFR should be granted to require ORD to correct the courtesy technical review.

1. The 2021 PBPK Model is Peer Reviewed and Ready for Use, and shows that the 2010 IUR should be corrected, at eh very least, by a factor of 35.

The Ramboll PBPK model has now been peer reviewed three times, and oy od ready for use. First, Ramboll published the PBPK model and its results in *Inhalation Toxicology.*[81] Then, as noted in Appendix A, "EPA hosted an extensive independent panel peer review the revised model and supporting *in vivo* metabolic model, with resulting parameters, model predictions, and uncertainty analyses…." The 2020 panel addressed multiple charge questions, and provided a number of Tier 1 (Key Recommendations), Tier 2 (Suggestions), and Tier 3 (Future Work) recommendations. As noted in Ramboll Appendix A (Exhibit 3), "the [2020] external peer reviewers identified a substantial number of key ("tier 1") recommendations necessary for strengthening the scientific basis for the PBPK model, reducing model uncertainties, and accurately evaluating such uncertainties before the model is applied for risk assessment." After DPE submitted RFC # 21005,[82] EPA hosted an extensive Follow-up External Peer Review, which documents the resolution of the majority of Tier 1 and Tier 2 comments from October 2020.

The Follow-up peer reviews included:

- Nan-Hung Hsieh, Ph.D.
- Kenneth M. Portier, Ph.D.
- Kan Shao, Ph.D.
- Jordan Ned Smith, Ph.D.
- Raymond S.H. Yang, Ph.D
- Yihang Zhu, Ph.D.

Charge Question 11 to the Follow-up PR Panel may be the most important question, and eh peer reviewers strongly endorsed the PBPK model:

> Question 11 - *Please comment on the capacity of the PBPK model to provide sound estimates of chloroprene inhalation dosimetry in mice, rats, and humans. Please comment on the reliability of model predictions of the rate of chloroprene metabolism in liver and lung for use in animal-to-human extrapolation.*

In response, four of the six peer reviewers concluded that the model was appropriate for use in risk assessment. The peer reviewers stated:

- Dr. Hsieh: "The limitation of the in vivo data is a crucial factor that can reduce the reliability of the model predictions and also be applied in animal-to-human extrapolation."[83]
- Dr. Portier: "Under the WHO/IPCS (2020) guidance on the acceptability of predictions, Ramboll has shown that the PBPK model has the capacity to provide sound estimates of chloroprene inhalation dosimetry in mice, rats, and humans across a wide range of

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[82] Follow-up – External Peer Review of a Report on Physiologically Based Pharmacokinetic (PBPK) Modeling for Chloroprene and a Supplemental Analysis of Metabolic Clearance, prepared for EPA by Versar, Inc., December 6, 2021.

[83] Follow-up PR Report at 9.

values for input and state parameters. Also, this PBPK model has been shown capable of reliably predicting rates of chloroprene metabolism in the liver and lung of animals and humans to within 2 orders of magnitude or less. Within the limitations of available data and with this accuracy acceptability target, the model should be considered a reliable tool for predicting chloroprene metabolism and for providing sound estimates of chloroprene inhalation dosimetry."[84]

- Dr. Shao: "I believe that the reliability of the PBPK model has been improved."[85]
- Dr. Smith: "[T]his model offers an improved risk assessment tool compared to traditional standardized uncertainty factors."[86]
- Dr. Yang, (by cross-reference to Question 8): "[w]hen we use such technologies [as PBPK models] to justify the relaxation of risk assessment on a very reactive chemical such as [chloroprene] which might have very significant negative impact on people, particularly those without money, lawyers, we must be very, very careful. I would urge Ramboll colleagues to study the Transtrum et al. (2015) paper, if you haven't already done so, and examining carefully such shortcomings mentioned in the paper, existed in your PBPK modeling and analyses. "Tier 1 recommendation).[87]
- Dr. Zhu: "No comments."[88]

Similarly supportive responses were provided to charge Question 12:

Question 12 - *Please review the Tier 1 and Tier 2 comments from the initial review and note any which you believe have not been adequately addressed by the revised analysis. If the comment has not been adequately addressed, please provide specific suggestions as to how this can be resolved.*

The peer reviewer responses were:

- Dr. Hsieh: "[S]ome in vivo information (e.g., PK data) from mice and human are necessary."[89]
- Dr. Portier: "I noted no Tier 1 and Tier 2 comments that had not been addressed by Ramboll… I did note concern about a number of Tier 2 recommendations suggested the need for additional chloroprene metabolism studies…. In each case, Ramboll's reply was that *the laboratory at which the chloroprene metabolism studies were performed is no longer active and we were unable to find any commercial or academic laboratories that*

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84 Follow-up PR Report at 21.

85 Follow-up Peer Review Report at 32.

86 Follow-up PR Report at 44.

87 Follow-up PR Report at 56. Dr. Yang states that the discussion of Markov Chain Monte Carlo modeling "worried me a lot: and cites to Transtrum MK, Machta BB, Brown KS, Daniels BC, Myers CR, and Sethna JP, (2015) Perspectives: Sloppiness and emergent theories in physics, biology, and beyond, J. Chem. Phys. 143:1-13. The Ramboll Report at 28 responds further to Dr. Yang's comments. Moreover, Dr. Yang' comments confuse risk assessment quantification with policy judgments for managing risk. *See, e.g.,* Memorandum to Heads of Executive Departments and Agencies, from Susan E. Dudley, Administrator, Office of Information and Regulatory Affairs, Office of Management and Budget, , "Updated Principles for Risk Analysis,: Sept. 19, 2007 at 4 ("In undertaking risk analysis, agencies should establish and maintain a clear distinction between the identification, quantification, and characterization of risks, and the selection of methods or mechanisms for managing risks.")

88 Follow-up PR Report at 68.

89 Follow-up PR Report at 10.

could perform such studies with chloroprene. … I have no idea how this issue can be a addressed other than through future funding."[90]

- Dr. Shao: "Ramboll did an excellent job providing comprehensive responses to address reviewers; comments, especially providing detailed calculation process for clarification."[91]
- Dr. Smith (by cross-reference to responses to Questions 5 and 10): "Tier 1 Key Recommendation: I suggest Ramboll include metabolism data with inhibitors from Himmelstein et al. (2001 and 2004) in their report as direct experimental evidence for the prole of CYP2E1 in metabolism of chloroprene."[92] "Previously I suggested that male and female physiological parameters should be implemented independently to ensure that physiologies of both sexes are considered (Tier 1)."[93]
- Dr. Yang: "I wish Ramboll were a little more receptive to utilization of the U.K. scientists."[94]
- Dr. Zhu: "No comments."[95]

As shown above, the majority of the follow-up peer review panel support the immediate use of the PBPK model in risk assessments. Moreover, as shown in the attached Ramboll Response to Follow-up External Peer Review, any remaining Tier 1 and Tier 2 comments and recommendations can be addressed, allowing for application of the PBPK model in the estimation of an IUR.

2. The Courtesy Technical Review Incorrectly Concludes that an IUR Revision Based on the PBPK Model Would only Increase the IUR by a Factor of 2.

The courtesy technical review states that even if the PBPK model were taken at "face value," that if cancer risks to multiple organs are considered, the final IUR would only be adjusted by a factor of two because lung tumors only accounts for about 40% of the total cancer incidence in mice in the NTP studies. ORD concluded that PBPK model would only be appropriate for an adjustment of lung risk assessment, and that the total estimated cancer risk would be reduced by no more than 50% or a factor of 2.

ORD appears to have simply compared the composite IUR estimated by ORD in the 2010 review based on the incidence for all tumors with the IUR based on the incidence of tumors in all tissues except the lung. However, the PBPK model already has the ability to estimate dose metrics for the lung **and liver**.[96] Therefore, the PBPK model can be applied to estimate dose metrics for all tumors observed in both the lung and the liver, which would account for the vast majority of the observed tumors in the NTP (1998) bioassay.

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90 Follow-up PR Report at 21.
91 Follow-up PR Report at 33.
92 Follow-up PR Report at 40.
93 Follow-up PR Report at 43.
94 Follow-up PR Report at 58.
95 Follow-up PR Report at 68.
96 Ramboll Report at 7.

In addition, the courtesy technical review appears to have developed composite IURs based on the incidence of tumors in organs other than the lung, using external air concentration as the dose metric. However, DPE is not aware of, and the courtesy technical review does not cite, any basis for a mixed mode-of-action with one mode-of-action for the lung used in the PBPK model (dose metrics based on reactive products in the tissue due to local metabolism of chloroprene), and another mode-of-action for all other organs (assuming direct chloroprene reactivity based on air concentrations). The PBPK model documentation sets out a compelling case for doe metrics based on total metabolism that provides, in the words of follow-up peer reviewer Dr. Portier, "the capacity to provide sound estimates of chloroprene inhalation dosimetry in mice, rats, and humans across a wide range of values for input and state parameters."[97]

Ramboll has applied the PBPK model in calculations similar to those in the courtesy technical review, and the resulting IUR, using the default approach for the remaining tumors, would actually be an order of magnitude lower than the IUR from the 2010 IRIS assessment. Moreover, the use of a different dose metric for tumors in tissues other than lung and liver is scientifically inappropriate, because the mode of action is the same. Ramboll concludes that if the PBPK model is applied to the lung and the liver, and the potential risk of tumors for other organs are not considered (consistent with the vinyl chloride risk assessment methodology) the IUR would be reduced by a factor of 35.

For more details, see the attached Ramboll RFR Report, pages 4 – 14.

E. New Health Data Confirm That The IUR Should be Revised.

Updated epidemiological information and the Louisiana Tumor Registry (LTR) cancer incidence data provide zero support for a linkage between chloroprene exposure and cancer incidence or mortality, yet the courtesy technical review speculates that each null finding could be the result of confounding biases to produce the null result. The RFC identifies (1) a major new follow-up epidemiological studies by Dr. Gary Marsh, *et al.*, released in 2021, that shows no increased cancer mortality among U.S. chloroprene workers, and (2) new cancer incidence data from the LTR that shows the incidence of cancers near the DPE Facility are at or below state-wide averages for cancers of potential concern. ORD explains away this information, relying on the presumption that the 2010 peer review guarantees the soundness of the conclusion that there is a suggestive link between chloroprene exposure and cancer incidence.

1. The Marsh Epidemiology Studies and EPA's Misinterpretation of the Marsh Studies in 2010, show that the RFC Should be Granted.

EPA has concluded that "the most recent and comprehensive"[98] epidemiological study, the historical cohort study of industrial workers exposed to chloroprene conducted by Dr. Gary Marsh and colleagues (the "2007 Marsh Study," which is referred to by Dr. Marsh, below, as the "University of Pittsburgh study").[99] (Other epidemiology studies Russia, China, and Armenia are of poor quality.) The 2010 Review rejected the 2007 Marsh Study's conclusions, gave substantial weight to the lower quality older studies, and incorrectly concluded that chloroprene exposure

[97] Follow-up PR Report at 21.
[98] 2010 Review at A-12.
[99] For a description of the Marsh Study, see page 2 of the Marsh Report.

resulted in excess liver cancer risk. As shown above, Dr. Gibb on the 2010 peer review panel, called EPA's interpretation of the 2007 Marsh study, as "grossly misrepresenting" the data.

In a 2018 Marsh report (prepared in connection with RFR #1799A),[100] Dr. Marsh explains what EPA got wrong in 2010 as follows (page 1):

- [N]o statistically significant evidence of a positive trend between the duration or level of chloroprene exposure and liver cancer was observed among workers in this rigorous study.

- EPA incorrectly concluded in the 2010 Review that the University of Pittsburgh study revealed evidence of a dose-response relationship between cumulative chloroprene exposure and liver cancer mortality risk. This conclusion was based on EPA's misinterpretation of certain risk values that were inflated by inordinately low liver cancer mortality rates in the baseline category used to calculate relative risks.

- EPA's assertion of a dose-response for chloroprene and liver cancer starkly contrasts with the University of Pittsburgh study authors' conclusion that the study provided no evidence of such an exposure –response relationship.

- Overall, the available epidemiological evidence provides no consistent or credible evidence of chloroprene carcinogenicity in humans.

RFC #21005 also called ORD's attention to 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").[101] 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."[102] 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).[103] The follow-up period was from 2001-2017, and added 47,299 and 19,942 person-years of observation and 1,399 and 214 new deaths to the Louisville and Pontchartrain Works cohorts, respectively.[104] This resulted in improved statistical precision.

In their follow-up study, Marsh (2021) again performed both external and internal mortality comparisons.[105] The external comparisons revealed statistically significant deficits in deaths at both plants, and internal comparisons revealed **no consistent evidence of exposure-response**

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[100] Exhibit 6 to this RFR, Gary Marsh, PhD, FACE, and Natalie Sudor Egnot, DfPH, "Critical Review of 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)," Cardno ChemRisk (April 24, 2018)(originally submitted in support of RFR # 17002A).

[101] 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.

[102] Marsh 2021 at 126.

[103] Marsh 2021 at 126.

[104] Marsh 2021 at 127.

[105] Marsh 2021 at 126.

relationships.[106] 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."[107]

The courtesy technical review cannot explain away these results.

2. The Ramboll RFR Report identifies what the Courtesy Technical Review Got Wrong.

The Ramboll RFR Report (Exhibit 3 at pages 9 to 14) clearly identifies what ORD misunderstood in reviewing RFC #21005, including the following:

- ORD says the RFC did not demonstrate errors in the 2010 Review, but as shown, ORD clearly misunderstood the relative risk data from the 2007 and 2021 Marsh studies, both in 2010 and in the denial, and failed to give any weight in the denial to the objective evidence provided by the LTR that demonstrates that St. John the Baptist Parish has below average cancer incidence compared to statewide statistics.

- ORD speculated that the Marsh 2021 study results might be due to the healthy worker effect. As shown above, Dr. Gibb on the 2010 peer review panel disagreed that the healthy worker effect was significant for chloroprene, and as the Ramboll report shows, the healthy worker effect is minimal with long, follow-up periods provided in the Marsh 2021 report. The healthy worker effect would not have produced the apparently protective relationship between occupational chloroprene exposure and cancer deaths shown by standardized mortality rate values far below the null value of 1.0.

- ORD speculated that the results of the Marsh studies might be explained by uncontrolled confounding, such as smoking and alcohol use, but ORD failed to consider the likely magnitude of the systematic differences between exposure groups or between the worker and the general populations that would have been necessary to produce the observed relationships.

- ORD criticized the Marsh exposure estimation method, but the worker categorization method used by Marsh was more sophisticated than methods used in prior studies. Prior studies characterized possible exposure based on job titles alone, whereas Marsh *et al*. considered time in job, time in task, and industrial processes specific to the period of employment in the specific job and plant.

- ORD faults Marsh 2021 for not including updated health information from two European plants. However, because the focus of EPA's risk assessment is the vicinity of the Louisiana Neoprene plant, this would make the focus on U.S. plants in the Marsh 2021 results more, rather than less, applicable to the U.S. situation.

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[106] Marsh 2021 at 133 (*emphasis assed*).
[107] Marsh 2021 at 135 (*emphasis added*).

- As to the LTR data, it is true that the data only reflect cancer incidence among Louisiana residents, and do not provide epidemiological information relating to exposure and duration. However, if the NATA cancer risk estimations were correct, St. John the Baptist Parish would not have cancer incidence rates below statewide averages (St. John the Baptist Parish is shown to be in the bottom quartile for liver and lung cancers and for all cancers, combined in the most recent data available, reflecting average incidence for the period 2014-2018).

IV. CONCLUSION

In 2010, EPA developed the IUR for humans for chloroprene exposure based on the default assumption that humans were as susceptible to chloroprene as the female B6C3F1 mouse. The available scientific evidence supports that the female B6C3F1 mouse is far more sensitive to chloroprene than the male B6C3F1 mouse, the Fischer rat, the Wistar rat, and the hamster. These differences in sensitivity are explained by species-specific differences in pharmacokinetics. Because of these differences, four of the six 2010 peer reviewers expressed concern that the use of the female B6C3F1 mouse would produce an overly conservative IUR. In 2010 EPA failed to adjust the IUR for differences between humans and the female B6C3F1 mouse. This RFR should be granted so that the PBPK model can correct the 2010 IUR for pharmacokinetic differences between humans and the female B6C3F1 mouse.

Further, although the 2010 Review was peer reviewed, ORD failed to correct the "gross misrepresentation: of the epidemiological data." Further, in a "reality check" of the male mouse IUR (1.4×10^{-4} $\mu g/m^3$), in the response to the peer review comments, ORD failed to recognize that the Marsh et al. studies demonstrated no excess lung or liver cancer risk for the Louisville cohort. Had this 2010 calculation relied upon the entire exposed cohort (n=5,486) rather than the cohort with known causes of death (cohort size, n=2,282) and the final recommended composite IUR based on the female mouse data of 5×10^{-4} $\mu g/m^3$ rather than the male mouse IUR of 1.4×10^{-4} $\mu g/m^3$, the results would have demonstrated a large over prediction of excess lung and liver cancers (3,891 versus 283). This was a clear error in the 2010 Review, and this RFR should be granted to correct this error.

In 2017, DPE filed RFC #17002, which EPA denied because it identified errors in the 2010 Review, but failed to introduce "new scientific evidence" to correct the 2010 IUR. DPE worked for more than three years with ORD on quality assurance issues in the development of a new peer reviewed PBPK model for chloroprene. Based on the progress with the PBPK model, in 2020 DPE withdrew RFR #17002A in order to better move forward with the PBPK model. The PBPK model was the subject of an External Independent Peer Review in October 2020, and based on those peer review comments, Ramboll extensively revised and improved the PBPK model.

DPE submitted RFC #21005 in July 2021 based on the revised PBPK model. EPA sponsored a Follow-up External Independent Peer Review of the revised PBPK model, and the majority of the peer reviewers approved the use of the PBPK model for risk assessment. On March 14, 2022, however, ORD denied RFC #21005 because it was based on new scientific evidence, the PBPK model, new epidemiological data (Marsh (2021)), and new LTR data. As shown above, ORD's flip-flop on the need for and use of new evidence in the RFC was arbitrary and violates administrative procedure requirements. Further, the denial incorrectly stated that RFC #21005 did

not identify errors in the 2010 Review. This RFR needs to be granted to correct ORD's flawed procedures and errors.

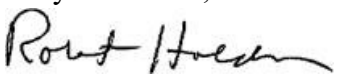
Finally, although ORD does not suggest it was a basis for the denial, the denial provides a courtesy technical review, in which ORD concluded that that the PBPK model would only affect the 2010 IUR by a factor of 2, which was a small enough difference to be within the bounds of accuracy of the 2010 IUR. In fact, using ORD's assumptions, Ramboll concludes that the application of the PBPK model would lower the chloroprene IUR by a factor of 35. Further, the courtesy technical review incorrectly attributes the lack of association of increase cancer risk from chloroprene in Marsh (2021) and the LTR data to causes such as the healthy worker effect, which Dr. Gibb as a 2010 peer reviewer had shown was not a significant epidemiological factor for chloroprene related cancer incidence. The RFR should be granted to correct these errors.

In summary, there is no empirical evidence to support the very large 2010 chloroprene IUR – one of the highest IURs of any hazardous air pollutant regulated by EPA. ORD has stubbornly resisted the application of the best available science to the chloroprene IUR in its responses to RFC #17002 and RFC #21005. ORD has a crucial role in accurately quantifying risks. ORD has abandoned its proper role in tenaciously sticking with the default assumption that humans are as sensitive to chloroprene as the female B6C3F1 mouse. The RFR should be granted to correct this error.

With all due respect, DPE requests that this Executive Panel reverse ORD's decision denying RFC # 21005, and direct ORD to accept the RFC and to re-evaluate the 2010 chloroprene IUR to reflect the currently available best available science, including the 2021 Ramboll PBPK model for chloroprene, and to consider DPE's comments and data in response to the Courtesy Technical Review and the Follow-up Peer Review Report.

Submitted on this 10th day of June 2022.

Respectfully submitted,

By: 

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LIST OF EXHIBITS

Exhibit 1: EPA March 2022 Denial Letter of RFC 21005

Exhibit 2: EPA January 2018 Denial to DPE's RFC

Exhibit 3: Ramboll Report – *Response to Technical Questions Regarding the Science of Chloroprene*

Exhibit 4: December 6, 2021 - Comment Report – Follow-up – *External Peer Review of a Report on Physiologically Based Pharmacokinectic (PBPK) Modeling for Chloroprene and a Supplemental Analysis of Metabolite Clearance*

Exhibit 5: January 26, 2010 – Final Reviewer Comments – *External Peer Review Meeting on the Toxicological Review of Chloroprene*

Exhibit 6: 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 (RFR #17002)

Exhibit 7: DPE's RFC dated July 15, 2021 with Attachments