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Via Federal Express and Electronic Mail (quality@epa.gov)
Information Quality Guidelines Staff
U.S. Environmental Protection Agency
William Jefferson Clinton North
1200 Pennsylvania Avenue, NW
OEI Quality Staff, Suite 5315
Washington, DC 20004

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

Dear Sir or Madam:

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

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

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

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

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

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

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

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

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

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

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5 EPA Guidelines at p. 22.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

[9] EPA Guidelines at p. 15.

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

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

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

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

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

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

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10 EPA Guidelines at p. 15.

11 EPA Guidelines at p. 15.

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

13 2010 IRIS Review at p. 123.

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

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

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

17 EPA Guidelines at pp. 20-23.

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

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

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

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

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18 EPA Guidelines at p. 19.

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

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

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

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

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

EPA Guidelines at p. 22 (emphases added).

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

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

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24 EPA Guidelines at p. 23.

25 EPA Guidelines at p. 23.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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32 Ramboll Environ Report at p. 15.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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37 Ramboll Environ Report at p. 27.

38 2010 IRIS Review at p. 123.

39 Ramboll Environ Report at p. 28.

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

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

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

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

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

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

[41] 2010 IRIS Review at p. 141.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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44 Ramboll Environ Report at p. 24.

45 2010 IRIS Review at p. 123.

46 2010 IRIS Review at p. 113.

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

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

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

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

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

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

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

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

[47] Ramboll Environ Report at p. 53.

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

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

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

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

V. Other Required Information

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

For this Request, the contact information is as follows:

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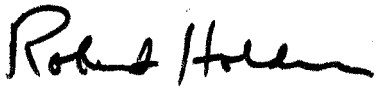
[49] *See* https://www.epa.gov/la/laplace-louisiana-background-information.

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

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

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

Very truly yours,



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REH:ddt
Enclosure

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