EPA

Attachment 1

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

January, 2018

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

The Request

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(IUR) of 5 x 10^{-4} per ug/m^3 be replaced with a value derived by Ramboll Environ of 3.2 x 10^{-6} per ug/m^3, or withdrawn; 2) the EPA cancer classification of chloroprene as a "likely" human carcinogen be classified instead as a "suggestive" human carcinogen; and 3) the EPA derived Reference Concentration (RfC) be withdrawn pending further IRIS review.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

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

Response

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

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

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

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

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

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

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

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

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

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

The following 5 subtopics are addressed in turn.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Conclusion

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

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