UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OFFICE OF
RESEARCH AND DEVELOPMENT

Patrick Walsh
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Dear Mr. Walsh,

This letter is in response to the Request for Correction (RFC) received by the U.S. Environmental Protection Agency (EPA) from Denka Performance Elastomer LLC (Denka) on July 15, 2021. The RFC request was assigned RFC 21005 for tracking purposes. In the RFC letter, Denka asked EPA to re-evaluate certain conclusions presented in the 2010 IRIS Chloroprene Toxicological Review in consideration of new scientific information concerning the cancer effects of chloroprene on humans. The materials submitted by Denka present new analyses and express views on how these products should be used in the risk assessment of chloroprene, but the Denka submission does not identify errors in the 2010 IRIS assessment. After careful consideration, EPA has concluded that the underlying information and conclusions presented in the 2010 IRIS Toxicological Review of Chloroprene and its supporting materials are consistent with EPA's Information Quality Guidelines (U.S. 2002). Hence the RFC is denied.

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 the 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:

> "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"…." 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 knowledge 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 and resource availability. 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

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through 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. Importantly, the availability of new scientific information does not necessarily mean that existing IRIS toxicity values are outdated or not based upon the best available science. For example, EPA's 2018 denial of a prior RFC submitted by Denka indicated that the new scientific information described in that RFC would not alter the conclusions of the 2010 IRIS Assessment (see January 24, 2018, EPA Response to RFC 17002 Attachment 2 "Systematic Review of Chloroprene [CASRN 126-99-8] Studies Published Since 2010 IRIS Assessment to Support Consideration of the Denka Request for Correction (RFC)").

The RFC process does not require that EPA evaluate the potential impact of new scientific information on an existing IRIS toxicity value.

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 interpreted as setting a precedent for any future RFC request. Within the scope of the courtesy 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 provided by the Denka 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.

Your Right to Appeal

If you are dissatisfied with the response, you may submit a Request for Reconsideration (RFR) as described in EPA's Information Quality Guidelines. The EPA requests that any such RFR be submitted within 90 days of the date of the EPA's response. If you choose to submit an RFR, please send a written request to the EPA Information Quality Guidelines Processing Staff via mail (Information Quality Guidelines Processing Staff, Mail Code 2821T, USEPA, 1200 Pennsylvania Avenue, NW, Washington, DC 20460); or electronic mail (quality@epa.gov). If you submit an RFR, please reference the case number assigned to this original Request for Correction (RFC #21005). Additional information about how to submit an RFR is listed on the EPA Information Quality Guidelines website at https://www.epa.gov/sites/default/files/2020-02/documents/epa-info-quality-guidelines_pdf_version.pdf.

Sincerely,

Maureen R. Gwinn, Ph.D.
Principal Deputy Assistant Administrator

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Cc: Vaughn Noga, Chief Information Officer and Deputy Assistant Administrator for Environmental Information, Office of Mission Support

Katherine Chalfant, Director of Enterprise Quality Management Division, Office of Mission Support

Appendix A: EPA Courtesy Technical Review of New Scientific Information Presented in RFC 21005
Appendix B: References

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Appendix A: EPA Courtesy Technical Review of New Scientific Information Presented in RFC 21005

A. Background on the Denka RFC Submission

In 2010, EPA disseminated the IRIS Program's peer-reviewed Chloroprene Toxicological Review. EPA's consideration of pharmacokinetic (PK) modeling in the chloroprene assessment dates to this 2010 IRIS assessment and peer review, where a model by Himmelstein et al. (2004) proposed dosimetry estimates. The 2010 IRIS assessment explained why the Himmelstein 2004 results were not sufficient for incorporation into the IRIS assessment. In 2017, Denka filed an RFC (RFC 17002) submitting results of modeling by Yang et al. (2012) which extended the Himmelstein study with some additional *in vitro* data and expanded statistical modeling. On January 24, 2018, EPA rejected the 2017 RFC submitted by Denka. EPA evaluated the Yang results as part of its RFC response, noting limitations in the work (see Attachment 2 of EPA's denial). For example, the specific computer code used in the Yang et al. (2012) model could not be obtained. EPA needed the code to be able to adequately evaluate the model quality. Since the rejection of the 2017 RFC, EPA has engaged extensively with Denka and Ramboll[2] on the scientific issues related to Denka's proposals for applications of PBPK modeling which they view as supporting lower risk estimates for chloroprene. Notably, much of the core set of *in* vitro metabolism data underpinning the original Himmelstein et al. (2004) model remains at issue with Denka.

Denka responded to EPA's rejection of the 2017 RFC by filing a RFR (RFR 17002A) on July 24, 2018, which contained an updated and, at that time, unpublished model that had not been peer-reviewed developed by Ramboll addressing the same *in vitro* data set. EPA engaged substantially with Denka in the 2018-2020 period, contributing to quality assurance of the Ramboll model and providing suggestions on how to address model deficiencies (e.g., modeling of uptake of chloroprene by the *in vitro* reaction mix) and extend the model to attempt to address the fate of reactive metabolites. Importantly, while EPA provided feedback on quality assurance, EPA does not consider these discussions to constitute a formal quality assurance review, as the discussions alone did not satisfy the QA requirements outlined in the Quality Assurance Project Plan (QAPP) for Dosimetry and Mechanism-Based Models developed by the U.S. EPA's Office of Research and Development (U.S. 2020b).

With Denka and Ramboll's cooperation, EPA hosted an extensive independent panel peer review in October 2020 to evaluate the revised model and supporting *in vitro* metabolic model, with resulting parameters, model predictions, and uncertainty analyses described by Ramboll (2020), and the alternate uncertainty analysis described by U.S. EPA (2020). The 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 (see Final 2020 Chloroprene PBPK and Uncertainty Analysis Peer Review Report). The tier 1 issues identified by peer reviewers are technical matters that would require resolution before application of the model would be recommended.

After further technical interactions with EPA, Denka withdrew its RFR (RFR 17002A) on March 1, 2021. Subsequently, Denka submitted the current RFC in July 2021 (RFC 21005). This RFC contains new unpublished modeling analyses of the same *in vitro* database, more extensive statistical analyses, comparison with one *in vivo* study, and introduces modeling for reactive metabolites that has not been previously reviewed. To assist in preparing a response to RFC 21005, EPA conducted a follow-on independent letter peer review of the revised 2021 PBPK model, the results of which have been made available (see Versar, 2021). However, EPA is not obligated to review unpublished works submitted under the RFC/RFR process.

B. Technical Consideration of the 2021 Denka RFC 21005

Under EPA's Information Quality Guidelines, the RFC process does not require that EPA evaluate the potential impact of new scientific information on an existing IRIS toxicity value. However, because of significant investment by both Denka and EPA in considering the new PBPK approaches (discussed above), EPA is providing a technical analysis as part of its consideration of the July 2021 RFC. In this response, the EPA is addressing the following assertions raised in Sections III and IV in the Denka RFC 21005:

Assertion 1	IUR Should Be Corrected to Reflect the 2021 Ramboll PBPK Model (Exhibit A4 in the RFC). Denka states that: "The IUR Should Be Corrected to Reflect the 2021 Ramboll PBPK Model. Overall, the application of the 2021 PBPK model is expected to result in the estimation of an IUR that is approximately two orders of magnitude below that of the 2010 IUR."
Assertion 2	Major New Follow-Up Epidemiological Study by Dr. Gary Marsh et al., Released in 2020, Shows No Increased Cancer Mortality among U.S. Chloroprene Workers (summarized in Exhibit B5 in the RFC).
Assertion 3	New Cancer Incidence Data from the Louisiana Tumor Registry Shows the Incidence of Cancers near the Denka Faculty are At or Below State-wide Averages for Cancers of Potential Concern (summarized in Exhibit B5 in the RFC).

EPA Response to Assertion 1: IUR Should be Corrected to Reflect the 2021 Ramboll PBPK Model

EPA approached this submission by asking available peer reviewers from the Fall 2020 peer review to examine the new modeling work and advise on the extent to which it resolved tier 1 identified issues and was suitable for application (see Versar, 2021). The peer reviewers noted significant improvements in the model analysis, but multiple reviewers' comments and recommendations indicate that key uncertainties remain. These uncertainties include fundamental model assumptions, e.g., that chloroprene itself is treated as inactive but may be reactive and that data from studies on a different compound can be used to infer key metabolic rates. Some reviewers raised questions regarding whether the model was sufficiently reliable for use in risk assessment or, minimally, that additional experimental data should be obtained, and further analyses conducted to more fully quantify uncertainties. For example, two reviewer comments identify ongoing uncertainty about whether 7-ethoxycoumarin activity is an

appropriate predictor of chloroprene's oxidative metabolism and the extent to which cytochrome P450s (CYPs) enzymes other than CYP2E1 might contribute to this activity. In addressing the discrepancy between model predictions and the mouse *in vivo* pharmacokinetic (PK) data, one reviewer noted that chloroprene has constitutive chemical reactivity that may result in loss of the parent compound throughout the body. The model over-predicts blood concentrations observed after inhalation exposure to mice and the reviewer commented that this over-prediction may occur because it does not account for this constitutive reactivity. This constitutive reactivity may also explain the cancer incidence in mouse and rat tissues which do not have significant CYP enzyme metabolic activity. A separate example is noted by another reviewer regarding the statistical analysis of uncertainty in the metabolic parameters, where it appears that the joint uncertainty in Kgl may not have been incorporated. Kgl is a parameter that determines the rate of chloroprene transport between the air and liquid phases in the *in vitro* metabolic system that was used to determine the metabolic parameters for the rate of chloroprene oxidation in the lung and liver of mice, rats, and humans. Because the estimated values of those parameters depend on the value of Kgl, uncertainty in Kgl has an impact on the uncertainty of the metabolic parameters and hence overall quantitative uncertainty of the PBPK model in which they are used. Some of the uncertainties may require additional experimental data to resolve (e.g., CYP 2E1-specificity and evaluation of Kgl at the mixing speed used in the *in vitro* metabolic studies).

In addition, the Ramboll PBPK model seeks to quantify the impact on cancer risk due to differences between mice or rats and humans. These metabolic data are foundational to the PBPK modeling, and if all significant uncertainties in the PBPK model were addressed, the model predictions would incorporate these metabolic differences. In this regard, as pointed out by one of the reviewers, the Ramboll analysis does not address cancer risk outside of the lung. The limits of applicability of the Ramboll model is important because the National Toxicology Program (NTP) chronic mouse and rat inhalation bioassays, upon which the inhalation unit risk (IUR) for chloropropene was based, demonstrated the occurrence of multiple tumors beyond the lung (National Toxicology, 1998). The NTP chronic bioassays reported significantly increased incidence of neoplasms in liver, lung, forestomach, Harderian gland, mammary gland, Zymbal's gland, kidney, and the circulatory system in mice and in the lung, mammary gland, thyroid, kidney, and the oral cavity in rats. These tumor incidence results are summarized in "Background Description for Chloroprene PBPK Modeling", provided for the 2020 external peer review of the PBPK model. The 2010 IRIS assessment also cited human evidence of an association between liver cancer risk and occupational exposure to chloroprene and found suggestive evidence of an association between lung cancer risk and occupational exposure in support of reaching a hazard conclusion of "likely to be carcinogenic to humans."

Ramboll's analyses assert that the risk of human lung cancer is minimal compared to mice, making the current IRIS IUR an overestimate of risk. EPA has not undertaken the technical analysis to reach a conclusion on concurrence with this assertion. But, if accepted at face value, the lung only accounts for about 40% of the total cancer incidence in mice (National Toxicology, 1998). Since the existing Ramboll model cannot be used to address risk in other tissues, the same standard inter-species scaling as used in the 2010 IRIS Toxicological Review would need to be applied to estimate cancer risk for those other tissues. Overall, the U.S. EPA concludes that even

if the current Ramboll PBPK model were accepted at face value and applied to the extent possible, the *total* estimated cancer risk would be reduced by no more than 50%. This factor of 2 difference is well within the generally accepted uncertainty for cancer risk estimation. Hence, EPA concludes that the 2010 Toxicological Review did not over-estimate the human cancer risk by multiple orders of magnitude, as contended by Denka and Ramboll.

EPA Response to Assertion 2 and Assertion 3: Major New Follow-Up Epidemiological Study by Dr. Gary Marsh, et al., Released in 2020, Shows No Increased Cancer Mortality among U.S. Chloroprene Workers; and New Cancer Incidence Data from the Louisiana Tumor Registry Shows the Incidence of Cancers near the Denka Faculty are At or Below State-wide Averages for Cancers of Potential Concern

In addition to the PBPK model discussed above, the RFC referenced a recent update Marsh et al. (2021) to a prior epidemiologic study (Marsh et al., 2007a) described as providing evidence of no increased cancer mortality among a worker cohort exposed to chloroprene. In Exhibit B of the submitted RFC (see Section 4), unpublished analysis of Louisiana Tumor Registry data conducted by Denka (and consultants) concluded there was average or below average cancer incidence near the Denka facility for lung and liver cancer. Exhibit B of the submitted RFC also provides Denka's critique of a community survey that concluded the 23-year period prevalence of all cancer (combined) in the residential area closest to the Denka facility is elevated due to environmental exposures from the Denka facility Nagra et al. (2021).

As part of considering this RFC, the published studies were evaluated using the study evaluation approach undertaken for IRIS assessments (U.S. 2020a) and general comments were provided on Ramboll's unpublished Louisiana Tumor Registry analysis. Importantly, the studies and analyses provided by Denka and Ramboll present some new Nagra et al. (2021). and updated Marsh et al. (2021) epidemiological information, but do not identify errors in the 2010 IRIS assessment. The new epidemiological evidence provided in the 2021 Denka RFC would also not alter the 2010 IRIS conclusion given the study evaluation results presented below.

The Marsh et al. (2021) study is a follow-up analysis of additional person years for a previously published occupational cohort (Marsh et al., 2007a, b) used to examined liver, breast, and respiratory cancer mortality in relation to chloroprene exposures. The results of this study are similar[1] to earlier analyses by Marsh et al. (2007) that were considered in the 2010 IRIS

[1] The two primary cancers of interest identified in the occupational cohort studies by (Marsh et al., 2007a, b) are cancers of the liver and respiratory system. For example, increased risks of respiratory system cancers (inclusive of larynx, bronchus, trachea, lung, and other respiratory cancers) were detected in 3 of 4 plants (all but Plant L in Louisville, KY) reported in the 2007 Marsh internal rate analysis. Their more recent internal rate analysis Marsh et al. (2021) still showed increased risks for 1 of 2 plants (Plant P in Pontchartrain, LA) but without explanation did not include data on the other 2 plants with elevated respiratory system cancer risk. Some of these increased risks detected again in Plant P were strong in magnitude (RRs ranging from 1.42-5.2) across different exposure metrics. Liver cancer rates also remain elevated in Plant L based on the updated Marsh et al. (2021) internal rate analysis, although there was no evidence of an exposure-response relationship (elevated RRs ranged from 1.2-2.5). A new analysis showed that breast cancer rates were also consistently elevated across most exposure categories and metrics based on the internal rate analysis --which is deemed less prone to different biases. Although these risks

Toxicological Review and by the independent peer review committee at that time. For Marsh et al. (2021), several study quality evaluation domains were considered deficient and led to an overall judgment of *low confidence* (Figure 1-1). The epidemiological analyses had not been conducted with optimal exposure, confounder, or outcome data, and several analysis decisions likely led to substantial biases that would largely be expected to bias towards the null (i.e., not finding an association). For example, the extensive amount of healthy worker effect in the standardized mortality ratio (SMR) analysis limits the interpretation and use of these data. The healthy worker effect is a type of selection bias that can impact study validity when inappropriate comparison groups, such as external citizen groups, are compared to occupational cohort studies. This arises from the fact that less healthy individuals from the general population are more likely to be unemployed compared to those in the workforce. The healthy worker effect tends to reduce the association between an exposure and the outcome because workers, as a group, are healthier than general population comparison groups. Exposure misclassification is also anticipated in the Marsh et al. (2021) study given the lack of sampling data to estimate exposures; this reduces confidence that the study can accurately characterize any true effect of exposure. The approach for exposure categorization is also unclear and seems to have been based on cancer deaths and not on an *a priori* exposure distribution targeted to contrast higher exposure groups with an unexposed or lower exposed referent. Limited information on some key potential confounders (e.g., smoking data for respiratory cancer, and alcohol use for liver and breast cancers) precluded their full consideration and likely resulted in residual confounding. Lastly, inclusion of only part of the occupational cohort (i.e., the American plants located in Louisville, KY and in Pontchartrain, LA) raises concern over selective reporting, especially since associations (including some exposure-response relationships) were reported earlier for some outcomes in the European cohorts. These limitations reduce the study sensitivity and the ability to detect an effect that may be present.

The Nagra et al. (2021) analysis is based on a field epidemiology investigation of residents of census tracts 708 and 709 in St. John Parish, LA (within a 2.5-km radius of the Denka facility) conducted by non-profit and local citizen groups. For the Nagra et al. (2021) study, major limitations resulted in several domains that were considered deficient and led to an overall confidence of *uninformative* (Figure 1-1). The study's design and conduct likely resulted in selection of bias given that respondents who were aware of their exposure status (i.e., residential proximity to the plant) may have selectively participated and differentially reported health outcomes. This stems from considerable publicity and lawsuits surrounding these community concerns, as well as community meetings. The health outcome measures were also deficient for various reasons, including self-reported outcome data without medical confirmation and use of proxies to report on the health status of other household members over a 23-year time period. In addition, the small samples not only reduced the study sensitivity, but the examination of total

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were not monotonic, the anticipated exposure misclassification and unclear exposure categorization approaches used likely precluded detection of exposure-response relationships across these outcomes.

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cancer as the primary outcome precluded analyses of more targeted and etiologically-relevant cancer-specific hypotheses related to chloroprene.

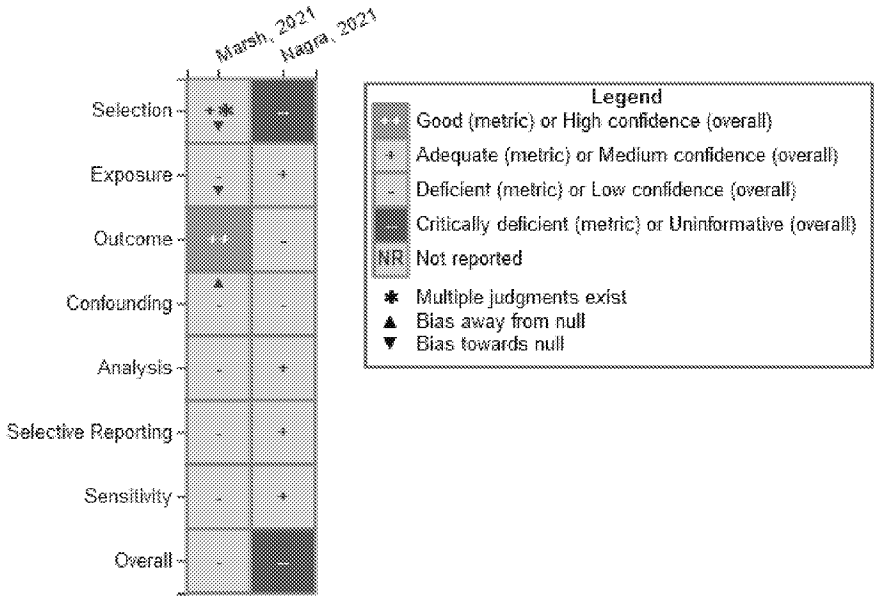

Figure 1-1. Study evaluation results for March et al. and Nagra et al. (see interactive data graphic for rating rationales).

In Exhibit B of the RFC (see Section 4), Denka conducted a tumor registry analysis to estimate cancer rates in St. John the Baptist Parish and its constituent census tracts. Denka propose that if the National Air Toxics Assessment (NATA) risk assessment was accurate, then the tumor registry analysis would identify higher cancer incidence rates in St. John the Baptist Parish than elsewhere. With respect to examining tumor registry analyses in isolation, it is important to emphasize that these data are quite limited for use in evaluating cancer risk for specific exposures, such as chloroprene. In general, and especially when epidemiologically linked with exposure data, tumor registry data are most informative when comparisons are made between local more homogenous populations. This allows for less potential for confounding and other sources of bias due to better comparability across different risk factors, demographics, and socioeconomic status. This is important as lifestyle factors and exposure to other carcinogens that different populations may be exposed to over time and location are not fully considered or controlled for when considering just tumor registry data alone. Tumor registry data may also be subject to notable differences in resources and surveillance rigor and effectiveness across healthcare systems in different regions. Many cancers are also often multifactorial in nature, and examination of tumor registry data by itself doesn't readily inform hypotheses on specific links to certain chemical exposures such as chloroprene. Thus, comparisons based on the tumor registry data alone do not further inform drawing causal inference related to specific exposures such as chloroprene. In the context of a hazard characterization, tumor registry data could be considered more descriptive and does not readily permit the examination of epidemiological associations to evaluate specific etiologic hypotheses. In addition, several limitations were noted by EPA of Denka's statewide tumor registry analysis, including that data on liver cancers are not

available in the Louisiana Tumor Registry at the parish level, which precludes examination of whether liver cancer rates are elevated in the St. John Baptist Parish compared to other relevant areas in Louisiana.

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, was unanimously supported by the external peer review panel for the IRIS Chloroprene Toxicological Review. In particular, the following specific points were evaluated by the peer review panel based on Charge Question 8 (Appendix A, pages A-10 to A-12) which asked: "Under the EPA's 2005 *Guidelines for Carcinogen Risk Assessment* (2005)", 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"*? All six of the peer reviewers commented that the characterization of chloroprene as "likely to be carcinogenic to humans" was appropriate and 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. Two independent peer reviewers further suggested that the strength of the epidemiological evidence was sufficient to change the descriptor to "carcinogenic to humans." The new and updated scientific evidence provided in the 2021 Denka RFC across all the evidence streams would not alter this conclusion, given the study evaluation results presented above

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Appendix B: References

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