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Examining the Scientific and Operational Integrity of EPA's Iris Program

THE IRIS REVIEW PROCESS: CHLOROPRENE AND THE CRITICALITY OF GOOD SCIENCE

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Overview

The US Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS) compiles and evaluates available scientific studies to determine the potential for chemicals to cause human health effects, and to conduct risk assessments that indicate the exposure levels at which risk of health effects is increased. These evaluations are relied upon by federal, state, local as well as international regulatory and public health agencies. Therefore, the validity of the IRIS evaluations is paramount. Over the last decade the methods used in and ultimate quality of IRIS reviews have been criticized by numerous entities, most notably, by expert panels of the National Academy of Sciences (NRC 2011, 2014).

EPA's 2010 IRIS Toxicological Review of Chloroprene (Final Report) (hereafter, "the 2010 Review")[1] serves as one example where several of the more recent concerns expressed by two National Research Council (NRC) Committees of the National Academy of Sciences (NAS) can impact the quality of the scientific evaluation and lead to the derivation and publication of official risk numbers (intended to quantify the relationship between chloroprene exposure and the risk of human cancers), which in the case of chloroprene are not scientifically valid. For example, the Inhalation Unit Risk (IUR) that EPA published for chloroprene appears to be *156 times* greater than a more scientifically accurately derived value. Furthermore, EPA's extreme IUR for chloroprene – a chemical EPA did not even classify as a "known" human carcinogen due to uncertainty - is orders of magnitude higher than the IURs for other chemicals for which the integration of evidence demonstrates carcinogenicity in humans (such as benzene and vinyl chloride) and are classified as "known" human carcinogens. Clearly, EPA's IUR for chloroprene needs to be corrected.

Based on a detailed critical evaluation of the 2010 Review conducted by Ramboll Environ US Corporation (Ramboll Environ), and sponsored by Denka Performance Elastomer LLC ("DPE"), several scientific errors and other problems were identified that likely gave rise to the extreme IUR value that EPA derived. The most important of these scientific issues include the following:

- The 2010 Review failed to critically evaluate the quality of each of the published epidemiological studies on workers highly exposed to chloroprene and apparently gave equal weight to all studies regardless of quality. Workers' exposure to chloroprene is expected to be thousands of times higher than that of the general public. Suggestive associations are reported among the weakest studies (including studies from Armenia, Russia and China); in contrast, the stronger studies (primarily from the US and UK) do not demonstrate increased cancer risks. EPA noted: "In humans, significant increases in liver cancer

[1] U.S. EPA. IRIS Toxicological Review of Chloroprene (Final Report). U.S. Environmental Protection Agency, Washington, DC, EPA/635/R-09/010F, 2010.

mortality were observed in four occupational epidemiology studies (out of nine total studies)." The four studies did not include the highest quality study.

- The 2010 Review ignored the conclusion of the highest quality and most informative epidemiological study published to date: "We conclude that persons exposed to chloroprene or vinyl chloride at the levels encountered in the four study sites 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" (Marsh et al., 2007a, 2007b). Rather, the 2010 Review highlighted out of context statistical results based on small subgroups of workers, even though none of the risk estimates was statistically significant (i.e., likely arose due to chance). EPA noted: "Relative risk estimates for liver cancer (while not statistically significant) increased with increasing exposure, indicating a dose-response trend." However, even the reported "trend" was not statistically significant ($p=0.09$).
- The 2010 Review failed to properly account for large and well-recognized differences between mice and humans in deriving the IUR. The National Toxicology Program (NTP) conducted a study in which male and female mice of a specific strain, as well as male and female rats, were exposed to high concentrations of chloroprene. More tumors were observed in the exposed mice than the unexposed mice, and more in mice compared to rats, with the mouse data then used as the main data for estimating potential cancer risk to humans. However, scientific evidence providing significant and well-documented physiological and metabolic differences between mice and humans were not fully considered. Furthermore, the effects driving the estimates of cancer risk (lung cancer observed in female mice) were not elevated with chloroprene exposure in experiments using rats or hamsters, suggesting that mice are not equivalent to humans and far more sensitive to chloroprene than other animals or humans.

Ramboll Environ, using published data and standard EPA risk assessment methods that properly account for these large differences between female mice and humans (and that EPA has used in IUR calculations for other chemicals), derived a corrected IUR, demonstrating that the EPA IUR was overestimated 156-fold. Other quantitative evaluations in the 2010 Review (e.g., Reference Concentration) also are likely to be incorrect if the interspecies differences are not fully appreciated.

As emphasized in reviews by prominent scientific committees, most notably those of the NAS (NRC 2011, 2014), significant improvements to the IRIS review methods and process are needed, including greater transparency. Additionally, fuller engagement of scientists most knowledgeable about the chemicals under review – including those potentially funded by industry – would contribute to scientific quality and help identify and correct scientific errors before reviews are finalized.

Regardless of future improvements, some IRIS Reviews that are in progress (e.g., formaldehyde) or have been finalized (e.g., chloroprene) need to be validated, with mechanisms for correcting past errors. Regulations and other decisions based on the erroneous IUR for chloroprene, for example, will not be based on sound science, and likely will have serious impacts. Scientifically, the magnitude of this difference

between the published and recalculated IUR is very large, and clearly warrants re-evaluation and correction.

Impetus for Ramboll Environ's evaluation of the 2010 Review

In December 2015, EPA finalized and published the 2011 National Air Toxics Assessment (NATA), which indicated an extremely high off-site air pollution cancer risk from emissions of chloroprene from what is now DPE's Neoprene production facility in LaPlace, Louisiana. The NATA was derived based on the IUR from the 2010 Review and the emission profile of the Neoprene facility. The NATA findings precipitated adverse public opinion, enforcement actions, and a class action lawsuit, all of which potentially have serious economic implications for DPE and the community.

Immediately after the release of the NATA cancer risk conclusions, DPE asked Ramboll Environ to conduct an independent evaluation of the 2010 Review, including a critical review and synthesis of all relevant published epidemiological and toxicological literature, with a focus on validating EPA's cancer IUR as reported in the 2010 Review. DPE recognized Ramboll Environ's scientific work and interaction with the IRIS program regarding the IRIS Draft Formaldehyde Toxicological Review, which was the focus of the NRC 2011 peer review and their criticisms of the IRIS process and methods.

Highlights of the Ramboll Environ evaluation as of one year ago were presented to EPA on August 9, 2016 at an event EPA entitled, "IRIS Assessment of Chloroprene," and attended by 13 EPA representatives – including the Acting Director of EPA's National Center for Environmental Assessment (NCEA) and the Director of IRIS – plus three representatives of the Louisiana Department of Environmental Quality. Ramboll Environ's presentation to the group can be found at the following link: https://cfpub.epa.gov/ncea/iris2/events.cfm. A follow-up letter to Dr. Vandenberg is included as an Attachment. This letter highlights some of the difficulties encountered in seeking a correction of the 2010 Review.

Subsequently, the full Ramboll Environ report was submitted to EPA as part of a request for correction, and is available at the following link: https://www.epa.gov/quality/rfc-17002. This report lays out the exact approach used in calculating an IUR for chloroprene using the best scientific methods used by EPA in other chemical evaluations, and considering the quality of the epidemiological and toxicological evidence used in evaluating chloroprene's carcinogenicity and risk numbers.

Ramboll Environ's evaluation of the 2010 Review

In the 2010 Review, EPA classified chloroprene as "likely to be carcinogenic to humans" and not the more definitive "known to be a human carcinogen," primarily based on EPA's recognition that the evidence was insufficient to classify it as a known human carcinogen. However, even classifying chloroprene as "likely to be carcinogenic to humans" was subject to and influenced by questionable interpretations of the published epidemiological and toxicological evidence.

Nevertheless, EPA proceeded to derive an IUR for chloroprene that is the 5th highest IUR (not including carcinogenic metals or coke oven emissions) EPA ever has developed, even among chemicals EPA or the World Health Organization's (WHO's) International Agency for Research on Cancer (IARC) classifies as "known" or likely/probable human carcinogens. Specifically, the IUR for lifetime exposure to chloroprene derived by EPA is 5×10^{-4} per microgram per cubic meter ($\mu g/m^3$).

The chloroprene IUR is sufficiently large that EPA should have realized prior to publishing the 2010 Review that the value was anomalous. Despite the fact that the 2010 Review underwent several peer-reviews, the large and obvious discrepancy between EPA's IUR for chloroprene and other IURs derived by EPA appears to have gone further unnoticed or unreported. The reasons for this are not clear, but call into question the quality of the peer-review process that IRIS has relied upon to draw conclusions regarding the potential for cancer risk in humans.

The main objective for the Ramboll Environ scientific evaluation of the 2010 Review was to evaluate the IUR for chloroprene as derived by EPA, and to provide improved and transparent scientific methods, interpretations and risk calculations to facilitate scientifically justified corrections for EPA's consideration.

The main elements of the Ramboll Environ assessment are presented below in four sections: Epidemiological Evidence; Toxicological Evidence; Chloroprene Carcinogenicity Classification; and, Deriving the Chloroprene IUR.

Epidemiological Evidence

A critical piece to understanding the potential cancer effects in humans from exposure to chloroprene is a rigorous evaluation of the occupational epidemiological literature. Workers involved in producing and directly using chloroprene are likely the most highly exposed individuals, and the occupational setting facilitates epidemiological methods for enumerating cohorts of workers, estimating levels of exposure and following workers over time to observe the rates at which various outcomes, including cancers, occur. The epidemiological evidence relevant to chloroprene carcinogenicity and that EPA correctly identified includes findings from occupational cohorts from the US, France, Ireland, Armenia, Russia and China. However, the 2010 Review of the epidemiological literature was methodologically irregular, particularly with respect to how individual study quality was assessed and weighted in the overall weight-of-evidence assessment. In fact, it is not clear whether EPA critically evaluated the quality of each of the published epidemiological studies on workers highly exposed to chloroprene and their respective cancer risks, and if so, the methods and rationale for how this was done were not transparent. For example, where suggestive positive associations are seen is among the weakest studies (including studies from Armenia, Russia and China); in contrast, the stronger studies (primarily from the US and UK) do not demonstrate increased cancer risks. The NRC recommendations regarding the IRIS review process (2011, 2014) underscore the importance of considering the quality of individual studies, giving greater weight to high-quality studies in the weight-of-evidence evaluation, and providing transparency in applying and documenting these methods.

A critical review of the same literature cited in the 2010 Review had already been published by Bukowski, as of 2009. The Table below is adapted from a similar table in that publication:

Table: Quality Rankings for Cohort Studies of Cancer Risks from Occupational Chloroprene Exposure

EPA Criteria	Marsh et al. (2007 a,b) Study				Other Studies			
	Kentucky[1]	North Ireland[1]	Louisiana[1]	France-Mort*[1]	Armenia[2]	France-Incid**[3]	Russia[4]	China[5]
Clear objectives	H‡	H	H	H	H	H-M	H	M
Comparison groups	H	H-M	H-M	M	M	M	M-L	L
Exposure	H	H	H	H	M	M	L	L
Follow-up	H	H-M	H	H-M	M-L	M-L	M-L	M-L
Case ascertainment	H	H-M	H-M	H-M	M	M	M	H-M
Control of bias	H-M	H-M	H-M	M	M-L	M	M	M-L
Sample size	H	H	M	L	M-L	L	H-M	M-L
Data collection and evaluation	H	H	H	H	M	M	M-L	M-L
Adequate response	H	H	H	H	M	M	M	H-M
Documentation of results	H	H	H	H	M-L	M	M	L
Overall rank (1=best)	**1**	**2**	**3**	**4**	**5**	**5**	**5**	**6**

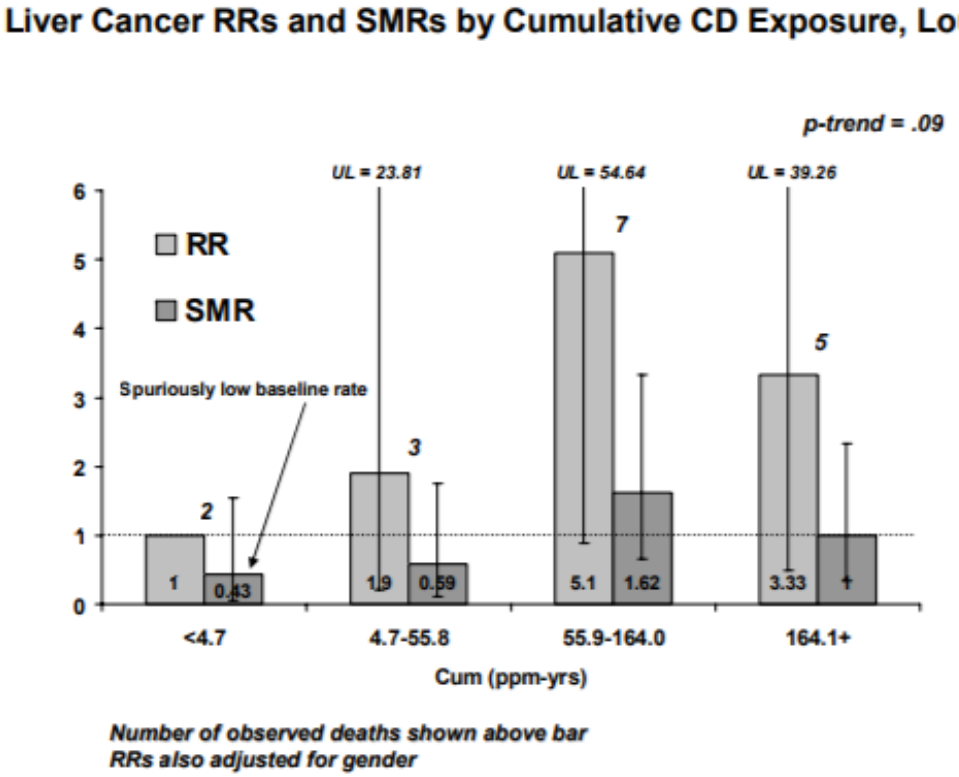
Source: Bukowski 2009 * Mort=Mortality ** Incid=Incidence ‡ Subjective estimate of study quality for each specific criterion H=high, M=medium, L=low; 1 – Marsh et al. 2007; 2 – Bulbulyan et al. 1999; 3 – Colonna and Laydevant 2001; 4 – Bulbulyan et al. 1998; 5 – Li et al. 1989

From this evaluation of individual study quality, it is clear that the first four studies received predominately “high” or “high-medium” ratings, in contrast with the final four studies that received predominately “medium” or lower ratings (Bukowski 2009). The Marsh et al. study (2007a, 2007b) combined the data from these four high-quality studies, and represent the most methodologically rigorous epidemiological evidence available to date. This study has the largest overall cohort size and the most rigorous follow-up, providing the greatest statistical power to detect an increased cancer risk should one exist. In contrast with the low-quality studies, the Marsh et al. study (2007a, 2007b) has the most comprehensive exposure assessment, including assessment and consideration of exposure to other occupational carcinogens (i.e., potentially confounding agents) such as vinyl chloride.

Importantly, the Marsh et al. (2007a, 2007b) study reported no excess occurrence of lung or liver cancers among chloroprene exposed workers when compared to the general population reference group. For all exposed workers at all plants combined, observed liver cancer mortality was 72% of what would be expected based on rates in the unexposed general population (this is expressed by the standardized mortality ratio, or SMR). The comparable finding for all exposed workers in the largest plant

(Louisville) was 90% of expected. Both these values demonstrate no increased risk for liver cancer. By exposure sub-group, none of the SMRs was statistically significantly elevated, and three of the four were below 1.0 (the value when observed and expected are equal). Furthermore, there was no statistically significant trend of increasing risk with increasing exposure (see Figure).

Figure



Source: Figure from comments submitted by Andrea V. Malinowski to EPA, Docket ID No. EPA-HQ-ORD-2009-0217, based on data from Marsh et al. 2007b

For lung cancers – the cancer site that provided the highest incidence in the mouse and was hypothesized to be relevant to chloroprene exposure – the Marsh et al. study (2007a, 2007b) documented a statistically significant 25% *deficit* of lung cancer mortality for all plants combined. Specifically, the pooled study data observed 112 fewer lung cancer deaths than would be expected based on unexposed population rates. Findings for each of the four individual plants were consistent (i.e., suggesting a deficit) although only one – Louisville, the largest plant – had a statistically significant deficit (89 fewer lung cancer deaths observed than expected). In contrast, EPA noted in the IRIS review that several studies reported higher SMRs for lung cancer among workers exposed to chloroprene, although few of the associations were significant and none of the studies controlled for confounding by smoking status, a strong indicator of lung cancer.

Nevertheless, EPA appears to have given no more weight to the most recent and rigorous epidemiological evidence (Marsh et al., 2007a, 2007b) showing no increased occurrence of liver and lung cancer than to the poorer quality Russian, Armenian, and Chinese studies, all of which had significant limitations. These limitations had been identified by others than Bukowski (2009). Rice and Boffetta (2001) conducted a review that included cohorts from the US (Pell 1978), China (Li et al. 1989), Russia (Bulbulyan et al. 1998) and Armenia (Bulbulyan et al. 1999) and noted significant methodological limitations in these studies, including unclear documentation for cohort enumeration, inadequate reference rates for standardized ratios, a lack of detailed histopathology of liver cancer cases, and limited or no information on potential co-exposures. They also remarked that the occupational chloroprene exposure assessment was poor for all published studies at that time, and the statistical power of the available studies was low due to the small number of observed cancers of interest.

In addition to discounting the Marsh et al. (2007a, 2007b) study findings relative to the weaker evidence, EPA also appears to have misinterpreted the Marsh et al. (2007b) results. Specifically, the 2010 Review interpreted a statistical correlation between exposure level and liver cancer risk relative to a comparison subgroup where the comparison group exhibited anomalously fewer cancers than expected, creating the appearance of an increased risk in the higher exposure groups (see Figure). Specifically, note that the 2 observed liver cancer deaths represent less than half the expected number. In turn, using this as the referent or comparison group effectively inflates the other categories by a factor of 2.3. Furthermore, that there were only two liver cancer deaths in this category contributed to large instability in all categories due to chance alone, i.e., the impact of one fewer or one more liver cancer death in this category would spuriously generate conflicting results.

The issues summarized here suggest that EPA's 2010 Review relied on incomplete evaluation and misinterpretation of the published epidemiological evidence. Properly evaluated, interpreted and weighted, the weight of epidemiological evidence does not demonstrate an association between occupational chloroprene exposure and increased incidence of liver or lung cancer.

Separate from the evaluation of the 2010 Review, Ramboll Environ examined cancer incidence data from the Louisiana Tumor Registry, comparing rates for St. John the Baptist Parish where the DPE Neoprene plant is located, with those of the state of Louisiana. For all cancers combined, the rate in the five most recent years in St. John the Baptist Parish was 463.2, compared with 478.7 for the state of Louisiana, that is, cancer rates in St. John the Baptist Parish were about 3% below the state average. For lung cancers, the rate in St. John the Baptist Parish was 60.1 compared with 70.5 for the state of Louisiana, that is, lung cancer rates in St. John the Baptist Parish are 14.7% lower than the state average. Too few liver cancers have occurred in St. John the Baptist Parish to be publically reported.[2] Though these official data are at best an indirect indicator of a population impact of the DPE facility operations, they do not provide evidence that the parish in which the DPE facility operates has elevated cancer rates.

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

Toxicological Evidence

As with the epidemiological studies, the toxicological evidence also should be evaluated in ways that adhere to EPA's own standard risk evaluation methodologies and conform to the NRC recommendations. The 2010 Review relied on the animal toxicological data as basis for deriving the chloroprene IUR, and specifically, the animal studies conducted by the National Toxicology Program (NTP 1998). Overall, this study, which included both mice and rats, demonstrated very little consistency across species in tumor incidence and tumor locations, but also demonstrated a unique sensitivity in a particular strain of female mice in which lung tumors appeared to be the most sensitive endpoint. Findings were specific to mice and not generalizable across the other animal species tested, including rats and hamsters. Given the striking differences in response in mice compared to other laboratory species, it is critically important to identify and evaluate possible differences in pharmacokinetics between animal species and to consider differences between mice and humans. The impact of this on the IUR is substantial, as discussed below.

In addition to revisiting the reliance on the animal dataset for the estimation of the IUR, a more rigorous re-evaluation and integration of the cytotoxic and genotoxic evidence for chloroprene is needed, consistent with NRC (2011, 2014) recommendations. The Ramboll Environ evaluation of the published toxicological literature found that the evidence from these studies indicates that chloroprene acts through a different mode of action (MOA) than 1,3-butadiene, a structurally similar known human carcinogen, but used for comparison and to draw conclusions by EPA in the 2010 Review. Using the NRC (2011, 2014) recommendations as guidelines, review of chloroprene's genotoxicity profile appears to lack several attributes necessary to conclude that there is a mutagenic MOA. Instead, the evidence supports site-specific cytotoxicity as a more likely MOA. This contradicts EPA's conclusion that chloroprene acts *via* a mutagenic MOA, and alone inflated EPA's IUR by about 60%.

Chloroprene Carcinogenicity Classification

The 2010 Review determined that chloroprene was "likely to be carcinogenic to humans" based on EPA's conclusions of (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. As has been demonstrated in this report, three of the five EPA conclusions are not supported by the weight of evidence, and the fourth—structural similarities—has been shown not to be informative, as the evidence available for the chemicals demonstrates different modes of action.

The Ramboll Environ evaluation of the 2010 Review demonstrated considerable misinterpretation of the available science to support the "likely to be carcinogenic to humans" classification. For example, 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. The claim that chloroprene is mutagenic is not supported by the overall evidence. Although there are structural similarities between chloroprene and 1,3-butadiene or vinyl chloride, the toxicological evidence that supports possible modes of action demonstrates substantial differences between chloroprene, vinyl chloride, and 1,3-butadiene. Little discussion of critical uncertainties in relying on the mouse data from NTP (1998) to predict the potential for carcinogenic risk in humans is offered in the 2010 Review, given ample evidence of important pharmacokinetic differences between mice and other species.

The weight-of-evidence evaluation supports a reclassification. Based on the limited evidence remaining to support the potential carcinogenicity of chloroprene, a more appropriate classification of chloroprene would be "suggestive evidence of carcinogenic potential." In any case, a clearer weight-of-evidence narrative is needed that addresses the current uncertainties.

Deriving the Chloroprene IUR

In the 2010 Review, EPA derived the current chloroprene IUR based on a number of assumptions that are not substantiated by the scientific evidence, contributing to overestimation of an already conservative risk estimate *(*i.e., one based on the most sensitive species, gender, and endpoint). Specifically, EPA based the chloroprene IUR on a composite estimate of risk based on multiple tumors observed primarily in mice, instead of relying on just the most sensitive endpoints in mice (lung tumors) which is consistent with standard EPA methods. EPA then assumed that the female mouse-based IUR was representative of continuous human exposure, and that lung tumors were a result of systemic rather than portal-of-entry effects; EPA also rounded up calculations at various stages of adjustment, and these were compounded. Finally, EPA applied an age-dependent adjustment factor (ADAF) based on insufficient data to support a claimed mutagenic MOA. All of these assumptions are not supported by the scientific evidence and contributed to unrealistic increases in the final IUR, as presented in the Ramboll Environ report submitted to EPA as part of DPE's Request for Correction.

The most important correction of the IUR is that it should seek to be predictive of human response. At the time of the 2010 Review, Himmelstein et al. (2004a, 2004b) had published a paper that described a physiologically based pharmacokinetic (PBPK) model for chloroprene. The model provided a means to adjust the exposures associated with tumors in the mouse to corresponding human exposures, and the model integrates the available data that explain why the mouse is the most sensitive species and why humans would be comparatively much less sensitive to the effects of chloroprene exposure. The hypothesis that differences in pharmacokinetics are determinants of the observed species differences has been demonstrated for other chemicals reviewed by EPA, including vinyl chloride. In the 2010 Review, EPA

acknowledged that its results would be improved with the use of a PBPK model, but that all of the required data were not available. However, all of the quantitative data necessary to refine and verify the critical metabolic parameters for the existing peer-reviewed PBPK model for chloroprene were published prior to the publication of the 2010 Review. Since then, additional data have been published, and these newer findings further validate the model and its use in demonstrating consistency with the epidemiological evidence, and its use in deriving the chloroprene IUR (Thomas et al. 2013, Yang et al. 2012, Allen et al. 2014). In particular, Allen et al. (2014) derived an IUR based on consideration of pharmacokinetic differences between mice and humans and estimated an IUR that was 100 times lower than EPA's value, using a method which integrates both the animal and human evidence. Importantly, consideration of the IUR reported by Allen et al. (2014) in comparison with IURs for known human carcinogens, such as vinyl chloride and 1,3-butadiene, is consistent with the stronger and more consistent epidemiological evidence of human carcinogenicity for these compounds compared to chloroprene.

Ramboll Environ performed an updated analysis by applying the peer-reviewed published results from validated PBPK models (Yang et al. 2012) to arrive at an IUR that accounts for the known interspecies differences in pharmacokinetics. Standard EPA methodology and conservative assumptions were applied to estimate the potential cancer risks for chloroprene. The revised IUR is 1.1×10^{-2} per ppm or 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), and which better reflects the scientific understanding of potential chloroprene cancer effects in humans. In contrast, the EPA derived an IUR for lifetime exposure to chloroprene of 5×10^{-4} per microgram per cubic meter ($\mu g/m^3$), a value approximately 156 times higher than what Ramboll Environ considers the best estimate using standard EPA methods and available data. The revised value also is consistent with the results from validated PBPK models and comparisons with other structurally relevant compounds, such as vinyl chloride and 1,3-butadiene, that are recognized as known human carcinogens.

There is little scientific support for each of EPA's conservative assumptions and subsequent adjustments. Combining a fuller understanding of interspecies pharmacokinetic differences and validated PBPK models with the results from the strongest epidemiological data provides the scientific grounds for correcting the 2010 IUR and calls into question the strength of the evidence to support a "likely to be carcinogenic to humans" classification. Similar adjustments should also be considered in estimating the chloroprene inhalation reference concentrations (RfC), as species- and strain-specific differences are noted. This will assure that policies and decisions resting on these toxicity values meet the test of sound science, transparent methods, and reproducible findings.

Conclusions

EPA's 2010 Review of chloroprene offers examples of several broader issues with the quality of IRIS Reviews including those of the NAS (NRC 2011, 2014), including evaluation of individual toxicological and epidemiological studies for quality, and transparency in weight-of-evidence integration to validly determine a chemical's potential carcinogenicity and derive accurate risk numbers. For chloroprene, the IUR

that EPA derived in the 2010 Review appears to be at least 100-fold inflated, and, based on a best-methods approach performed and documented by Ramboll Environ, over-estimated by as much as 156-fold. Risk assessments based on this IUR, such as the National Air Toxics Assessment, incorporate the overestimated value leading to grossly exaggerated human cancer risk predictions. This undoubtedly and unnecessarily triggers regulatory and legal action, as well as incites fear in the workers exposed to chloroprene, as well as those in the surrounding communities who may be exposed at much lower concentrations.

As outlined above, the overestimation of the IUR is the product of several scientific shortfalls or errors, including misreading of the epidemiological evidence, the likely erroneous assumption that chloroprene is mutagenic, an under-appreciation and subsequent incomplete consideration of the large pharmacokinetic differences between the female mice and humans, as well as other issues.

Scientifically, updating the IRIS Review of chloroprene is warranted, possibly including reconsideration of the carcinogenicity classification in light of a more accurate interpretation of the epidemiological evidence. However, and more urgently, a correction to the IUR is needed, based on the Ramboll Environ analysis provided to EPA in DPE's recent Request for Correction. The IUR published in the 2010 Review requires correction to address flaws that are consistent with the critique of the IRIS program by NRC. Specifically, an updated IUR should be based on the best available methodology as well as a valid, transparent, and systematic interpretation of the body of published evidence. Although there are variations in how IURs are derived, proper application of established EPA risk assessment methods – including the PBPK model to account for extreme interspecies differences – should generate an IUR that is 100-150+ times lower than that published in the 2010 Review. The methods presented in the Ramboll Environ report could serve as a starting point, reducing the time and resources EPA otherwise would expend.

Correction additionally is critical given that the IUR published in the 2010 Review is being used by EPA to support enforcement actions and underlies a class action lawsuit. The chloroprene example highlights deficiencies in the IRIS process that need to be addressed as soon as possible.

Respectfully submitted,

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Attachment

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ENVIRONMENT
& HEALTH

John Vandenberg, PhD
Director of Research at NCEA
109 T.W. Alexander Drive
Research Triangle Park, NC 27709

Sent via e-mail

RE: FOLLOW-UP TO THE MEETING AT RTP

Dear Dr. Vandenberg,

August 23, 2016

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Thank you for setting up and orchestrating the "listening session" on Tuesday August 9th, 2016 at your offices. Dr. Gentry and I appreciate the opportunity to present the findings from our independent review of chloroprene's potential carcinogenicity, based on all available data and state-of-the-art methods for critically reviewing and synthesizing epidemiology, toxicology and mechanistic studies, and for integrating evidence across these lines of inquiry.

As discussed after our presentation of the science, we acknowledge and appreciate your explanation of the IRIS Program's resource constraints, the complex procedures in place for selecting substances for IRIS review or re-review, as well as what you described as the "full docket" of current and future IRIS reviews. Based on this feedback, we understand that the IRIS Program will not at this time undertake a new review of chloroprene – or consider any revisions to the risk numbers – primarily due to resource constraints.

This, as you can understand, leaves our client, Denka Performance Elastomer, LLC (DPE), in a very difficult position, and unjustifiably so from a scientific standpoint. During our meeting, we outlined important new information demonstrating that an IRIS chloroprene IUR derived today would be vastly different and more compatible with other IURs for other chemicals. As we demonstrated during our meeting, properly employing validated PBPK models leads to an IUR for chloroprene that is more than 100-fold lower than the 2010 IRIS value. In fact, the 2010 IRIS Review of Chloroprene astutely acknowledged this very flaw: "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" (US EPA, 2010, Section 3) [1]. The information and methods required for chloroprene now have been peer-reviewed, published, and validated, with similar models and methods applied by EPA in comparable risk evaluations (such as vinyl chloride).

[1] US EPA 2010. Toxicological Review of Chloroprene. In support of Summary Information on the Integrated Risk Information System. Washington, DC: U.S. Environmental Protection Agency.

We also noted what we consider a misinterpretation of the body of epidemiological evidence, largely due to discounting the negative results published from the 2007 Marsh et al. study, which is also the strongest epidemiological study, in favor of results from much weaker studies. The integration of the entirety of epidemiological evidence supports the updated toxicology and mechanistic evidence indicating important and substantial differences between humans and mice, specifically in terms of metabolism, which are directly related to estimating the potential cancer risks for chloroprene. This no longer can be ignored. Taking the most up-to-date information into consideration in the context of using science to inform EPA policy and regulation is entirely consistent with the Agency's very public "mission statement" to ensure that "national efforts to reduce environmental risk are based on the best available scientific information." [2]

Without a commitment on the Agency's part to reexamine the 2010 IRIS assessment's IUR derivation in light of the new information, EPA and the Louisiana Department of Environmental Quality have advised DPE that it will be required to meet extremely stringent emissions limits, which may not be attainable, and that are not based on the best available science. We also have seen that the IUR is being used to inform important regulatory and other federal and state government actions, as well as public statements with respect to the possible cancer risks to people who live and work in the community in which our client's facility is located.

Notwithstanding the IRIS Program's resource constraints, we genuinely look forward to any thoughts or ideas you or Dr. Cogliano might have with respect to how we might work collaboratively with you and the program office within EPA that is relying on the 2010 IRIS Assessment, to timely improve and update the IUR. The IUR for chloroprene (as well as actions that are derivative of that IUR) should be more in line with those of other substances, such as vinyl chloride, that provide stronger evidence than chloroprene of carcinogenicity in humans.

We, too, will be exploring various available avenues, and will keep you informed. One possibility would be for us to file a request for correction (RFC). Our ultimate goal, as I initially mentioned to Dr. Cogliano when I first approached him, is to improve the risk calculation based on currently available science and evidence-based processes, which have evolved since the completion of the 2010 Chloroprene Toxicological Review, and to do so in a way that creates the lowest demands on already limited resources. Thank you again, and I look forward to continuing our discussion.

Yours sincerely

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cc: Dr. Vincent Cogliano

[2] https://www.epa.gov/aboutepa/our-mission-and-what-we-do