HSIA
halogenated
solvents
industry
alliance, inc.

August 4, 2014

Dr. Lori White
NTP Designated Federal Official
Office of Liaison, Policy and Review
National Institute for Environmental Health Sciences
P.O. Box 12233, MD K2-03
Research Triangle Park, NC 27709

Re: Draft Report on Carcinogens Monograph on Trichloroethylene

Dear Dr. White:

I write on behalf of the Halogenated Solvents Industry Alliance, Inc. ("HSIA"), which represents producers and users of trichloroethylene ("TCE"). On June 10, 2014, the National Toxicology Program ("NTP") published notice of a meeting to peer review the draft Report on Carcinogens ("RoC") Monograph on Trichloroethylene. 79 Fed. Reg. 33203 (June 10, 2014). The notice indicated that the draft monograph would be available by June 30, 2014, and that the deadline for submission of written public comments would be July 30, 2014. Subsequently, in an email from Dr. John A. Bucher, NTP Associate Director, HSIA was granted an extension of five business days to August 4, 2014.

Introduction

As noted in our request for an extension of at least 60 days, the draft Monograph for TCE only became available on the NTP website on July 2, 2014. It is 378 pages long. Given the obvious impossibility of reviewing the draft Monograph, retaining scientific experts, and preparing and submitting detailed comments in 28 (or 33 days), the comment period you have provided is clearly inadequate. As also noted, the draft monograph is, under NTP policy, to be available "at least 60 days prior to the expert panel meeting." Without the document, the public cannot know the rationale for NTP's listing recommendation.

Moreover, while a 90-day comment period would be difficult for a document of this length and complexity, an effective 33-day comment period virtually ensures that public comment cannot be meaningful, as required by the Administrative Procedure Act ("APA"). The APA provides courts the authority to set aside "agency action" that is "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A). *Synthetic Organic Chemical Manufacturers Association v. Secretary,*

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Department of Health and Human Services, 720 F. Supp. 1244, 1249 (W.D. La. 1989), made clear that the process of publishing the RoC constitutes "agency action" and "fits squarely within the type of decision that Congress intended to be reviewable under the APA." This holding was reaffirmed in *Tozzi v. U.S. Department of Health and Human Services*, 271 F.3d 301 (D.C. Cir. 2001). *See also Styrene Information and Research Center Inc. v. HHS,* 944 F. Supp. 2d 71 (D.C.D.C. 2013).

Upgrading of the RoC classification of TCE qualifies as a rulemaking proceeding under the APA. Because publication of the RoC implements the provisions of the Public Health Service Act and triggers a series of regulatory actions, the decisions cited above held that publication of the 5th and the 10th Reports constituted rulemaking under the APA. Similarly, the process that will lead to the publication of the 13th Report constitutes a rulemaking proceeding. The instant notice is inadequate because the public has not received sufficient notice and opportunity to comment as required by the APA. 5 U.S.C. § 553. When the basis of a rule is a scientific determination, the scientific data which support the rule must be made available to the public during the notice period. *United States v. Nova Scotia Food Products Corp.*, 568 F.2d 240, 252 (2d Cir. 1977*); see also Connecticut Light and Power Co. v. NRC*, 673 F.2d 525, 530-31 (D.C. Cir.), *cert. denied*, 459 U.S. 835 (1982) (stating that "an agency commits serious procedural error when it fails to reveal portions of the technical basis for a proposed rule in time to allow for meaningful commentary").

The last time TCE was proposed for upgrading to "known human carcinogen" (in the 10th RoC) a lengthy peer review process concluded in the determination that TCE "should remain as reasonably anticipated to be a human carcinogen" as a result of a 9-1 vote to that effect by NTP's Board of Scientific Counselors Report on Carcinogens Subcommittee.[1] The changes in procedure since that time (notably, NTP's decision that the Board of Scientific Counselors will no longer vote to approve the listing decision) could be interpreted as a reaction to having a preordained science policy determination overridden by scientific peer review.

In any event, we do believe that there is a compelling case against changing the listing of TCE from reasonably anticipated to known human carcinogen. The latter category requires a level of scientific certainty that simply is not present in the case of TCE.

Criteria for Listing

The criterion for listing an agent, substance, mixture, or exposure circumstance in the RoC as *Known to be Human Carcinogen* is as follows:

> "There is sufficient evidence of carcinogenicity from studies in humans,* which indicates a causal relationship between exposure to the agent, substance, or mixture, and human cancer.

[1] See 66 Fed. Reg. 13334, 13337 (March 5, 2001).

> "Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to, dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub-populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals, but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.
>
> "*This evidence can include traditional cancer epidemiology studies, data from clinical studies, and/or data derived from the study of tissues or cells from humans exposed to the substance in question that can be useful for evaluating whether a relevant cancer mechanism is operating in people."

As shown above, the listing criterion indicates that conclusions regarding carcinogenicity in humans should consider *all* relevant information. Given that TCE is a data-rich chemical which has recently undergone both EPA[2] and IARC[3] evaluations, consideration of all relevant information is an onerous task. Nonetheless, the draft NTP monograph focused on the potential carcinogenicity of TCE for kidney cancer, non-Hodgkin lymphoma (NHL), and liver cancer and came to the following conclusions:

1. "Trichloroethylene is *known to be a human carcinogen* based on *sufficient* evidence (emphasis added) of carcinogenicity from studies in humans. This conclusion is based on evidence from human epidemiological studies together with toxicokinetic, toxicological, and mechanistic studies that show trichloroethylene causes kidney cancer in humans;"

2. "Epidemiological studies provide *limited* evidence (emphasis added) for an association between exposure to trichloroethylene and NHL, based on positive associations in several studies and evidence of a combined increased risk for NHL across studies. The evidence across studies was less consistent than for kidney cancer, and alternative explanations such as chance or confounding could not reasonably be ruled out;" and

3. "The data available from studies in humans are *inadequate* (emphasis added) to evaluate the relationship between liver cancer and exposure to trichloroethylene. A

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[2] Environmental Protection Agency, Toxicological Review of Trichloroethylene (CAS No. 79-01-6) In Support of Summary Information on the Integrated Risk Information System (IRIS) (EPA/635/R-09/011F) (2011).

[3] International Agency for Research on Cancer, Trichloroethylene, tetrachloroethylene and some other chlorinated agents, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans vol. 106 (Lyon, France) (2014).

few studies, including two meta-analyses, found modest increases in the risk of liver cancer; however, findings were inconsistent across studies and there was little evidence of exposure-response relationships in the individual studies or the meta-analyses."

Therefore, based on NTP's listing criteria, the decision to change the listing of TCE from *Reasonably Anticipated to be Human Carcinogen* to *Known to be Human Carcinogen* appears to rest on the Agency's evaluation of the available kidney data. This seems consistent with the recommendation from the National Academy of Sciences in its review of the 2001 draft EPA IRIS assessment, released in 2006, to accord greater weight to kidney toxicity and tumorigenesis than to liver responses in the mouse.[4] In general, HSIA supports the change in emphasis recommended by the Academy. We believe, however, that the 2011 EPA IRIS assessment applied faulty, and sometimes unbalanced, interpretation of the data from epidemiological and toxicity studies to generate unfounded concerns about exposure to TCE and effects on the kidney. Unfortunately, many of these same flaws can be found in the draft NTP Monograph.

As the draft Monograph is nearly 400 pages long, and given the truncated period for public comment, we did not review the document section by section to address NTP's interpretation of isolated scientific points. Instead we will focus on several concerns relating specifically to the sufficiency of the kidney data which led NTP to conclude that TCE should be classified as a known carcinogen in humans. The epidemiological evidence for TCE and kidney cancer is far too weak to be considered "sufficient." The animal cancer bioassay data are equivocal and inconsistent, TCE genotoxicity is probably significant, if at all, only after nephrotoxicity has occurred, and there is little support for glutathione conjugation as a relevant metabolic pathway. Thus, the toxicokinetic, toxicological, and mechanistic data for TCE do not add support for the known human carcinogen designation. Indeed, making any assumptions as to kidney cancer in humans based on the rodent data would be highly speculative.

These points are amplified below.

<u>NTP's Assessment of the Epidemiological Data Conflicts with that of the National Academy</u>

In addition to the EPA IRIS and IARC evaluations of TCE, the National Academy of Sciences evaluated the relationship between exposure to TCE (and/or perchloroethylene) in contaminated water supplies at Camp Lejeune, North Carolina, and a variety of health outcomes.[5] For kidney cancer, the report concluded that there was only limited/suggestive evidence of an association with solvent exposure. Surprisingly, the draft Monograph devotes

[4] National Research Council, Assessing the human health risks of trichloroethylene: Key scientific issues (National Academies Press) (2006).

[5] National Research Council, Contaminated water supplies at Camp Lejeune: Assessing potential health effects, (National Academies Press) (2009).

little attention to the results of that study or of a follow-up study conducted by the Agency for Toxic Substances and Disease Registry ("ATSDR")[6] which was judged by NTP to be of low quality (See draft Monograph Section 4.1.4).

Box 2 of the Academy's Camp Lejeune report, enclosed, categorizes every cancer outcome reviewed in relation to exposure to TCE, perchloroethylene, or a mixture of the two. The categories are taken directly from a respected Institute of Medicine ("IOM") report.[7] These categories are "sufficient evidence of a causal relationship," "sufficient evidence of an association," "limited or suggestive evidence of an association," "inadequate evidence to determine an association," and "limited or suggestive evidence of no association," all as defined in Box 1, also enclosed.

Looking at Box 2, evidence considered by NTP to be sufficient evidence of a causal association between TCE exposure in humans and kidney cancer would seem to be considered "sufficient evidence of a causal relationship." Yet the Academy found no outcomes in that category. It would at least be "sufficient evidence of an association." Again, the Academy found no outcomes in that category. Only in the third category, "limited or suggestive evidence of an association," does one find kidney or any other cancer outcome associated with TCE. "Limited evidence of an association" is far from "sufficient evidence of a causal relationship."

The Camp Lejeune committee began with a comprehensive review of the epidemiological studies of the two solvents by the IOM for its Gulf War Report. It then identified new studies published from 2003 to 2008 and considered whether these changed the conclusions in the IOM report. In the case of TCE and kidney cancer, this was the case. The Camp Lejeune committee considered six new cohort studies and two case-control studies (including Charbotel *et al.* (2006), a principal study in the draft NTP Monograph). It concluded that several of these studies reported an increased risk of kidney cancer, but observed that the results were often based on a relatively small number of exposed persons and varied quality of exposure data and methodology. Given these data, the committee raised the classification for TCE to match the IOM conclusion of "limited" evidence for perchloroethylene.

One would expect at the least a detailed explanation in the draft Monograph of NTP's very different conclusion from that of the National Academy of Sciences, but there is no discussion at all of this important question.

Meta-Analysis of Epidemiology Data Cannot Establish a Causal Relationship

There are reasonably well-designed and well-conducted epidemiologic studies that

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[6] Bove FJ, Ruckart PZ, Maslia M, Larson TC, Evaluation of mortality among marines and navy personnel exposed to contaminated drinking water at USMC base Camp Lejeune: a retrospective cohort study, Environ Health 13(1): 10 (2014).

[7] Institute of Medicine, Gulf war and health, vol. 2, insecticides and solvents (National Academies Press) (2003).

report no association between TCE and kidney cancer, some reasonably well-designed and conducted studies that do report associations between TCE and kidney cancer, and finally some relatively poorly designed studies reporting both positive and negative findings. In all, over 80 cohort, case-control, and ecological studies have evaluated TCE exposure and kidney cancer.

The draft Monograph relies on three meta-analyses in an effort to provide additional statistical power to the evaluation of these often disparate study results, as described in the enclosed comments. Kelsh *et al.* (2010) argued that a more careful analysis of subgroups indicated no association or, at best, only moderately elevated associations between TCE exposure and kidney cancer.

In the draft monograph, NTP raises concerns about the Kelsh *et al.* (2010) results, claiming that the meta-analysis contained "a number of studies that were considered non-specific for trichloroethylene exposure." NTP marginalizes these results despite the adherence of Kelsh *et al.* (2010) to recommendations from the National Academy review (2006) for conducting a meta-analysis of TCE and cancer. Focusing only on the two remaining meta-analyses (Scott and Jinot, 2011 and Karami *et al.*, 2012), NTP describes the results as being comparable and yielding "robust and statistically significant but *modest* (emphasis added) increases in meta-relative risks (mRRs) for kidney cancer. . . ."

NTP, on the other hand, concludes that the data are "sufficient" based on the "consistency" of increased kidney cancer across the different studies. The authors of these studies, however, do not agree with NTP's characterization of them. For example, the authors of Charbotel *et al.* (2006), the study NTP finds most compelling, state that the "study suggests an association between exposures to high levels of TCE and increased risk of [renal cell carcinoma]. Further epidemiological studies are necessary to analyze the effect of lower levels of exposure." Given that a primary purpose of the RoC is to provide definitive guidance about the carcinogenicity of TCE, it seems remarkable that NTP would ignore the authors' conclusion that the evidence is only suggestive.

Weak associations are more likely to be influenced by or be the result of confounding or bias. For example, smoking and body mass index are well-established risk factors for kidney cancer, yet the full potential impact of all potential confounding factors on the studies selected for meta-analyses was, in our judgment, not fully considered. There are indications that these factors may have impacted findings (*e.g.*, in the large Danish cohort study of TCE exposed workers, the researchers noted that smoking was more prevalent among the TCE exposed populations, however little empirical data were provided).

An even more troubling issue is that rarely, if at all, is consideration given to multiple chemical exposures in occupational epidemiology studies. More often than not, exposure to TCE is assumed based on a job exposure matrix ("JEM") without actual exposure measurements or confirmation that TCE is the only chemical associated with a particular job classification. Given the weak associations between assumed TCE exposures and kidney cancer, the potential confounding associated with co-exposure to other chemicals may make

it difficult to isolate potential effects of TCE from those of other exposures within a given study, and that exposure uncertainty could hinder interpretation across studies.

The respected epidemiologist Douglas Weed (formerly of the National Institutes of Health) has shown that meta-analysis has serious limitations for the purpose of proving a causal relationship.[8] It is readily apparent that the epidemiological evidence for TCE's association with human kidney cancer is in no way as robust as that relied upon in classifying the current RoC list of "known human carcinogens," and meta-analysis cannot remedy this problem. An overall weight-of-evidence analysis of the available epidemiologic research simply does not support the conclusion that there is "sufficient" evidence of a causal association between human exposure to TCE and kidney cancer.

Even Accepting the Meta-Analyses at Face Value, the Relative Risks Shown Cannot Support a Known Human Carcinogen Classification

The summary relative risks or odds ratios in the three most recent meta-analyses relied upon by NTP (Kelsh *et al.,* 2010; Scott and Jinot, 2011; Karami *et al.*, 2012) generally range between 1.2 and 1.4 for combined case-control and cohort studies. We submit that these relative risks are only suggestive of a weak association, and cannot serve as the basis for a known human carcinogen classification under the listing criterion: "There is sufficient evidence of carcinogenicity from studies in humans, which indicates *a causal relationship* between exposure to the agent, substance, or mixture, and human cancer" (emphasis added).

"Cause" is defined as "something that brings about an effect or a result."[9] It is well established in common law that small relative risks (generally less than 2) are not sufficient evidence of causation. *See In re Agent Orange Product Liab. Litig., 597 F. Supp.* 740, 785, 817 (E.D.N.Y. 1984) (plaintiffs must prove at least a two-fold increase in rate of disease allegedly caused by the exposure), *aff'd*, 818 F.2d 145, 150-51 (2d Cir. 1987) (approving district court's analysis), *cert. denied sub nom. Pinkney v. Dow Chemical Co.*, 484 U.S. 1004 (1988); *see also In re "Agent Orange" Prod. Liab. Litig.,* 611 F. Supp. 1223, 1240, 1262 (E.D.N.Y. 1985) (excluding plaintiffs' expert witnesses), *aff'd*, 818 F.2d 187 (2d Cir. 1987), cert. denied, 487 U.S. 1234 (1988).

The reasoning here is straightforward: a relative risk of 2 means that it is more likely than not (a probability of more than 50 percent) that the agent caused the disease. Not certain, but more likely than not. We submit that any lesser degree of certainty cannot be considered sufficient to establish "a causal relationship," as specified in the listing criterion.

We recognize that the law of toxic torts does not apply to decisions to regulate a substance, which may be precautionary and based on a lower probability of a causal

[8] Weed, D., Meta-analysis and causal inference: a case study of benzene and non-Hodgkin lymphoma, Ann. Epidemiol. 20(5): 347 (2010).

[9] Webster's New Collegiate Dictionary (1977).

relationship. The instant case, however, is not one of a government agency regulating or prohibiting the use of a toxic substance. Rather, the RoC is a compilation of information intended to address a single question: whether and to what extent a compound qualifies for listing as known or reasonably anticipated to be human carcinogen. Epidemiological evidence showing a relative risk of 1.2 to 1.4 cannot, without more, satisfy NTP's own criterion for classification as a known human carcinogen.

The Evidence that TCE is a Renal Carcinogen in Rodents is Problematic

Many of the arguments used in the draft Monograph to justify classification of TCE as a known carcinogen are based on the results of rodent cancer bioassay studies. However, the results from these studies are equivocal and many of the studies were plagued by methodological problems.

The earliest long-term oral study to evaluate TCE was conducted in mice and rats.[10] The study found no significant difference in kidney tumor incidence between control and treated animals. Two long-term NTP studies were conducted in 1988 and 1990.[11] The 1988 study used four strains of rats, both male and female, and when the overall rates of adenocarcinomas were combined based on sex and dose, the highest rate was only 2.1% (in the high dose males). In the report, the authors state that "trichloroethylene administration caused renal tubular cell cytomegaly and toxic nephropathy in both sexes of the four strains. However, these are considered to be inadequate studies of carcinogenic activity." The 1990 study tested one strain of rats and one strain of mice and renal tubular cell adenocarcinomas were detected in three high dose male rats (1,000 mg/kg) and one high dose female rat. Renal tubular cell adenocarcinomas were found in one male mouse (1,000 mg/kg); none was found in female mice. It is important to note that the study authors concluded that although these results were significant, they should be considered equivocal due to the high excess mortality observed in both dose groups. In all three of these studies the incidence of renal tumors was very low, despite exposure to TCE doses that were either at or exceeded the maximum tolerated dose (MTD).

Maltoni *et al.* conducted a series of controversial oral and inhalation studies with two strains of mice and one strain of rat.[12] Although significant numbers of renal

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[10] National Cancer Institute, Carcinogenesis bioassay of trichloroethylene (CAS No. 79-01-6), National Technical Information Service (NTIS) PB-264122, NCI-CG-TR-2 (1976).

[11] NTP, Toxicology and carcinogenesis studies of trichloroethylene (CAS No. 79-01-6) in four strains of rats (ACI, August, Marshall, Osborne-Mendel) (Gavage Studies), NTIS PB88-218896, NTP Technical Report Series No. 273 (1988). NTP, Carcinogenesis studies of trichloroethylene (without epichlorohydrin) (CAS No. 79-01-6) in F344/N Rats and B6C3F1 Mice (Gavage Studies), NTP TR 243, NIH Publication No. 90-1779 (1990).

[12] Maltoni, C, Lefemine, G, Cotti, G, eds. Experimental research on trichloroethylene carcinogenesis, Princeton Scientific Publishing Co. (Princeton, NJ) Archives of Research on Industrial Carcinogenesis: Volume 5 (1986); Maltoni, C, Lefemine, G, Cotti, G, Perino, G., Long-term carcinogenicity bioassays on trichloroethylene administered by inhalation to Sprague-Dawley rats and Swiss and B6C3F1 mice, Ann. NY Acad. Sci. 534:316-342 (1988).

adenocarcinomas were reported, the reliability of the results has been widely challenged due to the use of non-standard methodology. In a scathing comment, ATSDR[13] stated that:

> "[o]ther problems were found in the study methodology: use of an unconventional technique of holding the animals until spontaneous death, use of an unorthodox method of reporting results (percentage of animals with tumors reported, but not the number of surviving animals), a lack of appropriate pathological data on the types of tumors observed, and a lack of a complete report on methodology. Finally, inadequate laboratory operation procedures were used; there was a lack of independent pathology reviewers; and the use of Good Laboratory Practices was not confirmed."

In summary, although the overall tumor incidence in rodents is very low, with no reliable studies reporting statistically significant increases, there is some consistency across the studies that suggests TCE is capable of producing renal cell adenocarcinomas at high chronic doses ($\geq$ 500 ppm via inhalation and $\geq$ 500 mg/kg via ingestion), primarily in male rats. Even at high doses (in most cases, above the MTD), the incidence rate for these tumors is consistently low across studies at between 1-3%. The incidence is even rarer and more inconsistent in female rats and mice of both sexes.

The Presumed Mode of Action – GSH Conjugation – Is Based on Flawed Research

The listing criteria state that "[c]onclusions regarding carcinogenicity in humans ... are based on scientific judgment, with consideration given to all relevant information." Typically, the approach followed is to enlist animal data from toxicology studies to support a common mode of action between laboratory animals and man.

In terms of mechanistic data for kidney carcinogenesis, Section 4.2 of the draft Monograph addresses the assumed mode of action ("MoA") for TCE. Products of the glutathione conjugation pathway involved in the metabolism of TCE are deemed to be responsible for kidney toxicity and carcinogenicity in mice, rats and man. In this hypothesis, the initial product in this path, DCVG, is converted to DCVC which, in turn, may be activated in the kidney (to produce toxicity) or detoxified and excreted following acetylation. Interestingly, despite claims of a common mechanism TCE exposure has not been associated with kidney cancer in mice.

As with oxidative metabolism, the primary pathway for metabolism of TCE, *in vitro* studies of GSH conjugation of TCE in mice, rats, and humans show considerable intra- and interspecies variability. Reported conjugation rates also differ by several orders of magnitude between laboratories. According to the draft Monograph, the reasons for the discrepancies have not been fully resolved, thus there is considerable uncertainty in

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[13] ATSDR. Addendum to the Toxicological Profile for Trichloroethylene (January 2013) http://www.atsdr.cdc.gov/ToxProfiles/tce_addendum.pdf

quantitative estimates associated with this pathway. However, in order for the above MoA to be relevant in man, there must be a significant capacity to form glutathione conjugates in the kidney. In our view, this has not been demonstrated.

This notion of a high proportion of TCE being metabolized via the glutathione conjugation pathway is based upon the work of Lash and co-workers utilizing a questionable analytical technique.[14] Substantial and credible information from three other laboratories (Dekant, Green, and Kim/Rusyn and co-workers[15]) indicate a *very* low level of metabolism of TCE via the glutathione conjugation pathway. According to these researchers, the extent of TCE metabolism via the glutathione conjugation pathway (and DCVC activation) in humans is lower than the already low levels in rodents, in contrast to the Lash findings.

The incorrect assumption of a high rate of formation of DCVG/DCVC in humans leads to false interpretations of rodent kidney toxicity and carcinogenicity, both qualitatively and quantitatively. From the known potency of DCVC administered directly to rats, the toxicity of TCE in chronic or long term experiments in rats cannot be explained solely on the extent of DCVC production and activation. The generation of formic acid through the kidneys of rats exposed to TCE does, however, lead to recognizable kidney damage. In mice, less formic acid is released following TCE administration and DCVC activation is greater in mouse kidney, which suggests that DCVC may play a greater role in mouse kidney toxicity. Since DCVC is not a highly potent kidney toxicant, the very low levels generated in man are unlikely to cause kidney toxicity. Those studies in which markers of kidney damage have been examined have not provided clear evidence of an effect of TCE in man. The conclusion must be that kidney damage is highly unlikely to occur at current occupational exposure levels and is of no concern for the general population.

Genotoxicity Is Not a Likely Mechanism for Kidney Carcinogenicity

Kidney tumors in rats following TCE exposure are hypothesized to be the result of genotoxicity following DCVC activation, and this purportedly provides a plausible and relevant mechanism for kidney cancer in man. Reasons to consider this to be improbable include: (i) DCVC, although positive in *in vitro* bacterial mutagenicity tests (following activation by endogenous bacterial enzymes or enhanced by exogenous rat kidney preparations), has not been found, in credible studies, to be anything more than weakly genotoxic *in vivo*; (ii) combining the weak genotoxicity with the low levels generated in rats does not indicate a primary role for generation of tumors by a genotoxic mechanism; (iii) long-term direct administration of DCVC to rats did not generate tumors using a protocol

[14] Lash, L, Lipscomb, J, Putt, D, Parker, J, Glutathione conjugation of trichloroethylene in human liver and kidney: Kinetics and individual variation, Drug Metab Dispos 27: 351-359 (1999); Lash, L, Putt, D, Brashear, W, Abbas, R, Parker, J, Fisher, J., Identification of S-(1,2-dichlorovinyl)glutathione in the blood of human volunteers exposed to trichloroethylene, J Toxicol Environ Health 56: 1-21 (1999).

[15] *E.g.*, Green, T., Pulmonary toxicity and carcinogenicity of trichloroethylene: Species differences and modes of action, Environ Health Perspect 108: 261-264 (2000).

which would have been expected to show induction of tumors by a genotoxic mechanism;[16] and (iv) DCVC activation in the mouse kidney is greater than in rat kidney but kidney tumors have not been induced in mice by TCE in any study.

On balance, rat kidney tumors are unlikely to have arisen via a genotoxic mechanism following TCE administration. Since tumors have only been induced at dose levels of TCE that cause frank kidney toxicity, and male rats have a recognized tendency to develop kidney tumors under circumstances of repeated damage-repair cycles, this seems to be a more-plausible mechanism for induction of kidney cancer than genotoxicity. In its review of the draft IRIS document, the Science Advisory Board critiqued EPA's conclusion that a mutagenic mode of action was operative in kidney tumorigenesis, commenting that the Panel concluded that "the available evidence also supports MOAs involving cell death and compensatory cell proliferation."[17] If the evidence for genotoxicity in rodents is equivocal, it should raise serious doubts that TCE induces kidney cancer in man through a genotoxic mechanism. Certainly such equivocal evidence at most should be considered limited and not sufficient.

Conclusion

In spite of a great deal of effort, the draft Monograph fails to demonstrate anything other than a weak association between TCE exposure and kidney cancer in man, which is not supported by the inconsistent and equivocal toxicological data. Under the applicable listing criteria, the evidence for the carcinogenicity of TCE in humans at most supports the current "reasonably anticipated" classification. The evidence cannot be stretched to be considered "sufficient," and thus there is no basis for the designation of TCE as a known human carcinogen.

Very truly yours,

[Redacted]

Faye Grau
Executive Director

Enclosures

[16] Terracini, B. and Parker,V.H, A pathological study on the toxicity of s-dichlorovinyl-l-cysteine, Food Cosmet Toxicol 3, 67-74 (1965).

[17] EPA Science Advisory Board, Review of EPA's draft assessment entitled Toxicological Review of Trichloroethylene (October 2009) (EPA-SAB-11-002) (2011).

Contaminated Water Supplies at Camp Lejeune, Assessing Potential Health Effects National Research Council of the National Academy of Sciences (2009)

BOX 1 Five Categories Used by IOM to Classify Associations

Sufficient Evidence of a Causal Relationship

Evidence from available studies is sufficient to conclude that a causal relationship exists between exposure to a specific agent and a specific health outcome in humans, and the evidence is supported by experimental data. The evidence fulfills the guidelines for sufficient evidence of an association (below) and satisfies several of the guidelines used to assess causality: strength of association, dose-response relationship, consistency of association, biologic plausibility, and a temporal relationship.

Sufficient Evidence of an Association

Evidence from available studies is sufficient to conclude that there is a positive association. A consistent positive association has been observed between exposure to a specific agent and a specific health outcome in human studies in which chance and bias, including confounding, could be ruled out with reasonable confidence. For example, several high-quality studies report consistent positive associations, and the studies are sufficiently free of bias, including adequate control for confounding.

Limited/Suggestive Evidence of an Association

Evidence from available studies suggests an association between exposure to a specific agent and a specific health outcome in human studies, but the body of evidence is limited by the inability to rule out chance and bias, including confounding, with confidence. For example, at least one high-quality study reports a positive association that is sufficiently free of bias, including adequate control for confounding. Other corroborating studies provide support for the association, but they were not sufficiently free of bias, including confounding. Alternatively, several studies of less quality show consistent positive associations, and the results are probably not due to bias, including confounding.

Inadequate/Insufficient Evidence to Determine Whether an Association Exists

Evidence from available studies is of insufficient quantity, quality, or consistency to permit a conclusion regarding the existence of an association between exposure to a specific agent and a specific health outcome in humans.

Limited/Suggestive Evidence of No Association

Evidence from well-conducted studies is consistent in not showing a positive association between exposure to a specific agent and a specific health outcome after exposure of any magnitude. A conclusion of no association is inevitably limited to the conditions, magnitudes of exposure, and length of observation in the available studies. The possibility of a very small increase in risk after exposure studied cannot be excluded.

Source: IOM (Institute of Medicine). 2003. Gulf War and Health, Vol. 2, Insecticides and Solvents. Washington, DC: National Academies Press.

Contaminated Water Supplies at Camp Lejeune, Assessing Potential Health Effects National Research Council of the National Academy of Sciences (2009)

BOX 2 Categorization of Health Outcomes[a] Reviewed in Relation to TCE, PCE, or Solvent Mixtures

Sufficient Evidence of a Causal Relationship

- No outcomes

Sufficient Evidence of an Association

- No outcomes

Limited/Suggestive Evidence of an Association

- Esophageal cancer (PCE)
- Lung cancer (PCE)
- Breast cancer (PCE)
- Bladder cancer (PCE)
- Kidney cancer
- Adult leukemia (solvent mixtures)
- Multiple myeloma (solvent mixtures)
- Myleodysplasic syndromes (solvent mixtures)
- Renal toxicity (solvent mixtures)
- Hepatic steatosis (solvent mixtures)
- Female infertility (with concurrent exposure to solvent mixtures)
- Miscarriage (with exposure to PCE during pregnancy)
- Scleroderma (solvent mixtures)
- Neurobehavioral effects (solvent mixtures)

Inadequate/Insufficient Evidence to Determine Whether an Association Exists

- Oral/pharyngeal cancer
- Nasal cancer
- Laryngeal cancer
- Esophageal cancer (TCE)
- Stomach cancer
- Colon cancer
- Rectal cancer
- Pancreatic cancer
- Hepatobiliary cancer
- Lung cancer (TCE)
- Bone cancer
- Soft tissue sarcoma
- Melanoma
- Non-melanoma skin cancer
- Breast cancer (TCE)
- Cervical cancer
- Ovarian/uterine cancer
- Prostate cancer
- Bladder cancer (TCE)
- Cancer of the brain or central nervous system
- Non-Hodgkin lymphoma
- Hodgkin disease
- Multiple myeloma
- Adult leukemia
- Myelodysplasic syndromes
- Childhood leukemia
- Childhood neuroblastoma
- Childhood brain cancer
- Aplastic anemia
- Congenital malformations
- Male infertility
- Female infertility (after exposure cessation)
- Miscarriage, preterm birth, or fetal growth restriction (from maternal preconception exposure or paternal exposure)
- Preterm birth or fetal growth restriction (from exposure during pregnancy)
- Cardiovascular effects
- Liver function or risk of cirrhosis
- Gastrointestinal effects
- Renal toxicity
- Amyotrophic lateral sclerosis
- Parkinson disease
- Multiple sclerosis
- Alzheimer disease
- Long-term reduction in color discrimination
- Long-term hearing loss
- Long-term reduction in olfactory function

Limited/Suggestive Evidence of No Association

- No outcomes

[a]Outcomes for TCE and PCE unless otherwise specified.