



# HSIA

halogenated  
solvents  
industry  
alliance, inc.

December 10, 2010

BY HAND

Honorable Paul T. Anastas, Ph.D.  
Assistant Administrator  
Office of Research and Development  
Environmental Protection Agency  
1200 Pennsylvania Avenue, NW  
Washington, DC 20460

Vanessa Vu, Ph.D.  
Director  
EPA Science Advisory Board Staff  
Suite 31150, Reagan Building  
Environmental Protection Agency  
1300 Pennsylvania Avenue, NW  
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Re: Toxicological Review of Trichloroethylene (October 2009 Draft)

Dear Drs, Anastas and Vu:

The Halogenated Solvents Industry Alliance, Inc. (HSIA) represents producers and users of trichloroethylene (TCE), a chlorinated solvent primarily used to clean materials in applications where aqueous cleaning methods are not acceptable. These include precision parts used in medical, aerospace, defense and other important industries.

The Environmental Protection Agency (EPA) has since 1990 been engaged in an effort to update the health effects assessment for TCE that is reported on its Integrated Risk Information System (IRIS). HSIA participated in a stakeholder process that led to publication of a monograph of 16 articles comprising the "state-of-the-science" on issues relating to the health effects of TCE.<sup>1</sup> It was intended that "[s]taff of the National Center for Environmental Assessment at the U.S. EPA will use these articles to write the health risk assessment for TCE."<sup>2</sup> Regrettably, the 2001 draft Toxicological Review did not accurately reflect the work of many of the "state-of-the-science" authors, and was so flawed that EPA staff spent most of the past decade rewriting it, with the assistance of advice from the EPA Science Advisory Board (SAB) in 2002 and from the National Academy of Sciences in 2006 and 2009.<sup>3</sup> The October 2009 draft

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<sup>1</sup> Trichloroethylene Health Risks – State of the Science, Environ. Health Perspectives 108, Suppl. 2: 159-363 (May 2000).

<sup>2</sup> *Id.* at 159

<sup>3</sup> Review of Draft Trichloroethylene Health Risk Assessment: Synthesis and Characterization: An EPA Science Advisory Board Report (EPA-SAB-EHC-03-002) (December 2002) is available at [http://yosemite.epa.gov/sab/sabproduct.nsf/D14C306CF5482E41852571CE00697543/\\$File/ehc03002.pdf](http://yosemite.epa.gov/sab/sabproduct.nsf/D14C306CF5482E41852571CE00697543/$File/ehc03002.pdf). The Academy's reviews are Assessing the Human Health Risks of Trichloroethylene (National Academies Press) (2006)

which resulted has been the subject of review over the past year by an SAB panel convened for this purpose.

The Chartered SAB will review draft advice prepared by the SAB TCE Panel on December 15, 2010. Enclosed is a written statement submitted by HSIA for consideration by the Chartered SAB. The statement describes how the epidemiological data on TCE fail to meet the threshold for classification as “Carcinogenic to Humans” under EPA’s 2005 Guidelines for Carcinogen Risk Assessment.<sup>4</sup> It also shows how the draft assessment is in conflict with the Academy’s 2009 Camp Lejeune report. These are most serious defects that must be addressed before the assessment is made final.

The purpose of this letter is to bring to your attention two further issues that EPA must deal with as it moves toward a final assessment: (i) the inappropriate reliance on a tainted bioassay; and (ii) a conflict of interest that calls into question the SAB TCE Panel’s recommendations concerning developmental toxicity, an especially important non-cancer endpoint. These issues seem more appropriate for resolution, at least in the first instance, by the EPA program office.

#### I. The Draft TCE Assessment Places Major Reliance on a Study now thought to be Flawed

In April 2010, a team of pathologists from the National Toxicology Program (NTP) conducted a limited assessment of pathology procedures and histopathology for a carcinogenicity bioassay on methanol conducted by the European Ramazzini Foundation in 1990-1992 and published in 2002.<sup>5</sup> The NTP review team found significant discrepancies in the interpretation of the reported results and concluded that an independent pathology review and quality review of the pathology data and specimens were necessary to address the serious discrepancies identified in the reported results of the methanol study.<sup>6</sup> In its summary report, the NTP team stated that: “the diagnosis of leukemia or lymphoma was sometimes difficult to distinguish from the intense, marked lymphocytic infiltrates related to the chronic inflammation of the lung.” Additionally, the NTP pathologists questioned the basic research protocol utilized by Ramazzini in allowing animals to die spontaneously rather than being sacrificed after two years, as is the practice under US Good Laboratory Practices (GLP). They found that advanced autolysis in some tissues “occasionally precluded diagnosis by the NTP pathologists.”

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and Contaminated Water Supplies at Camp Lejeune, Assessing Potential Health Effects (National Academies Press) (2009) (hereinafter “Camp Lejeune report”).

<sup>4</sup> 70 Fed. Reg. 17766-817 (April 7, 2005).

<sup>5</sup> Soffritti, M., Belpoggi, F., Cevolani, D., Guarino, M., Padovani, M. and Maltoni, C., Results of long-term experimental studies on the carcinogenicity of methyl alcohol and ethyl alcohol in rats, *Ann. N.Y. Acad. Sci.* 982: 46-69 (2002).

<sup>6</sup> US Department of Health and Human Services National Toxicology Program, Memo to John R. Bucher re report on visit (4/25/2010 - 4/30/2010) and assessment of the pathology procedures performed at the Ramazzini Institute, Bentivoglio, Italy (June 11, 2010).

The findings of the NTP review team have implications beyond the methanol study. As a result of the review, EPA immediately identified six assessments that rely on Ramazzini data, announced that it is placing on hold four ongoing IRIS assessments pending a full review of the underlying Ramazzini studies, and postponed a pending SAB review of one of those assessments.<sup>7</sup> Regrettably, EPA did not announce similar action with regard to the TCE assessment. Yet the TCE assessment does rely substantially on Ramazzini data for its conclusion that TCE is a kidney carcinogen, the endpoint that drives the cancer risk assessment, and its derivation of the slope factor.

The Ramazzini TCE studies, referenced as Maltoni *et al.* in the draft assessment,<sup>8</sup> account for the only inhalation and one of only two out of 74 total (inhalation and gavage) dose groups of TCE-treated rats reviewed by EPA to have had a statistically significant increase in kidney tumors. This effect (renal adenocarcinomas) was seen by Maltoni *et al.* at the high dose, 600 parts per million (ppm). The other dose group where an increase in renal carcinomas was observed in rats was the high dose group (1000 mg/kg) in an NTP gavage study. There was no statistically significant increase in kidney cancer in any of the 72 other dose groups. Only one statistically significant finding out of 74 is more likely due to chance than to treatment.<sup>9</sup>

Moreover, the draft TCE Toxicological Review recognizes serious weaknesses in the NTP study that preclude its use in the dose-response assessment:

“The NTP (1990) study of TCE exposure in male and female F344/N rats, and B6C3F1 mice (500 and 1,000 mg/kg for rats) is limited in the ability to demonstrate a dose-response for hepatocarcinogenicity. For rats, the NTP (1990) study reported no treatment-related non-neoplastic liver lesions in males and a decrease in basophilic cytological change reported from TCE-exposure in female rats. The results for detecting a carcinogenic response in rats were considered to be equivocal because both groups receiving TCE showed significantly reduced

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<sup>7</sup> “Out of an abundance of caution and to ensure the agency’s chemical assessments are grounded in the soundest possible science, EPA undertook a thorough review of all ongoing and previous chemical assessments to determine which, if any, relied substantially on cancer testing from the Ramazzini Institute. . . . EPA found four ongoing chemical assessments – on methanol, MTBE, ETBE and acrylonitrile – that rely significantly on cancer data from the Ramazzini Institute. EPA has placed those assessments on hold and will determine whether the questions raised by NTP will require EPA to revise the assessments or take additional action to verify the data used in these assessments. EPA also postponed an August 23, 2010 meeting of the agency’s Science Advisory Board, which had been previously scheduled to review the draft methanol assessment.” EPA Press Release at <http://yosemite.epa.gov/opa/admpress.nsf/0/B64D44F06A56D5B285257742007C5002>, posted June 15, 2010.

<sup>8</sup> Maltoni, C, Lefemine, G, Cotti, G, *et al.*, Long-term carcinogenicity bioassays on trichloroethylene administered by inhalation to Sprague-Dawley rats and Swiss and B6C3F1 mice, in Maltoni, C, Selikoff, IJ, eds., *Living in a chemical world*, Ann. N.Y. Acad. Sci (1988), vol. 534; Maltoni, C, Lefemine, G, Cotti, G., *Experimental research on trichloroethylene carcinogenesis*, in Maltoni, C, Mehlman, MA, eds., *Archives of research on industrial carcinogenesis* (Princeton Scientific Publishing, 1986), vol. 5, pp. 316–342.

<sup>9</sup> This information was presented to the SAB TCE Panel by Dr. Michael Dourson on June 24, 2010.

survival compared to vehicle controls and because of a high rate (e.g., 20% of the animals in the high-dose group) of death by gavage error.”<sup>10</sup>

Maltoni *et al.*, on the other hand, was judged by EPA to provide the best data set for its inhalation risk estimate:

“For the inhalation unit risk estimates, the preferred estimate from the most sensitive species and sex was the estimate of  $8.3 \times 10^{-2}$  per ppm for the male rat, which was based on multiple tumors observed in this sex/species but was dominated by the kidney tumor risk estimated with the dose metric for bioactivated DCVC. This estimate was the high end of the range of estimates (see Table 5-32) but was within an order of magnitude of other estimates. . . .”<sup>11</sup>

Accordingly, “[f]rom the inhalation bioassays selected for analysis in Section 5.2.1.1, and using the preferred PBPK model-based dose metrics, the inhalation unit risk estimate for the most sensitive sex/species is  $8 \times 10^{-2}$  per ppm [ $2 \times 10^{-5}$  per  $\mu\text{g}/\text{m}^3$ ], based on kidney adenomas and carcinomas reported by Maltoni *et al.* (1986) for male Sprague-Dawley rats.”<sup>12</sup>

The draft then states that “confidence” in the proposed central estimate of  $2 \times 10^{-2}$  per ppm [ $4 \times 10^{-6}$  per  $\mu\text{g}/\text{m}^3$ ], based on human kidney cancer risks reported by Charbotel *et al.*, “is further increased by the similarity of this estimate to estimates based on multiple rodent data sets.”<sup>13</sup>

On its face, the draft TCE Toxicological Review “relied substantially on cancer testing from the Ramazzini Institute,” and thus would appear to fall within the EPA policy announced on June 15 whereby “EPA has placed those assessments on hold and will determine whether the questions raised by NTP will require EPA to revise the assessments or take additional action to verify the data used in these assessments.” When the Maltoni *et al.* results are excluded, there is no “nonequivocal” animal kidney cancer data supporting either the conclusion that TCE is a kidney carcinogen or the inhalation cancer slope factor.

## II. The TCE Panel Review Has Been Tainted by Active Participation by a Conflicted Member

Regarding non-cancer human health effects, a significant issue for the TCE Panel has been the potential hazard of TCE for the developing fetus, in particular the role of TCE in inducing fetal cardiac defects. Indeed, the Panel’s draft advice makes specific recommendations regarding the studies to be given greatest emphasis in the calculation of the oral reference dose (RfD) and the inhalation reference concentration (RfC). The Panel believed that the non-cancer

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<sup>10</sup> EPA Toxicological Review of Trichloroethylene (October 2009 Draft), at 4-261.

<sup>11</sup> *Id.*, at 5-121.

<sup>12</sup> *Id.*, at 5-145.

<sup>13</sup> *Id.*, at 5-146.

kidney toxicity data are not suitable for calculations of the RfC and RfD. Instead, the Panel advised EPA to give priority to three studies for deriving the RfC and RfD, most particularly Johnson *et al.* (fetal heart malformations in rats).<sup>14</sup> It is the reliance on this and supporting studies from the same laboratory that raises concerns regarding the impartiality and dispassionate judgment of a member of the Panel.

The Overview of the SAB Panel Formation Process states: “If a conflict exists between a panel candidate’s private financial interests and activities and public responsibilities as a panel member, or even if there is the appearance of partiality, as defined by federal ethics regulations, the SAB Staff will, as a rule, seek to obtain the needed expertise from another individual.”<sup>15</sup> Pursuant to the EPA’s Peer Review Handbook (3rd Edition), “each advisory committee member or peer reviewer should be evaluated to ensure that an appearance of lack of impartiality does not preclude their participation.”<sup>16</sup>

The draft TCE assessment clearly has been prepared under EPA’s IRIS program. Consequently, the peer review of the draft assessment is subject to EPA’s NCEA Policy and Procedures for Conducting IRIS Peer Reviews.<sup>17</sup> Under these procedures, a recertification of a peer-review panelist may be requested to determine if there were any changes to the information they previously disclosed that could create either an actual conflict of interest or an appearance of bias or lack of impartiality during the period of performance. EPA may be informed about a potential emerging conflict of interest situation, including an appearance of bias or lack of impartiality, by a person or organization external to EPA.

Most importantly, the Office of Management and Budget (OMB) Final Information Quality Bulletin for Peer Review states that “agencies shall adopt or adapt the NAS policy for committee selection with respect to evaluating conflicts of interest” concerning non-federal employees. The National Academy of Sciences (NAS) Policy on Committee Composition and Balance and Conflicts of Interest for Committees Used in the Development of Reports states that “an individual should not serve as a member of a committee with respect to an activity in which a critical review and evaluation of the individual’s own work, or that of his or her immediate

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<sup>14</sup> Johnson, P, *et al.*, Threshold of trichloroethylene contamination in maternal drinking waters affecting fetal heart development in the rat, *Environ. Health Perspect.*:111: 289-92 (2003).

<sup>15</sup> EPA, Overview of the Panel Formation Process at the Environmental Protection Agency Science Advisory Board. Office of the Administrator, Washington DC (2002) (EPA SAB-EC-02-010), p. 9.

<sup>16</sup> US Environmental Protection Agency Peer Review Handbook (3rd Edition), Science Policy Council, Washington, DC (2009) (EPA/100/B-06/002), p. 67. The Handbook suggests the following question to assess a candidate’s suitability to serve on a peer-review panel: “Do you know of any reason that you might be unable to provide impartial advice on the matter to come before the Panel or any reason that your impartiality in the matter might be questioned?”

<sup>17</sup> EPA, NCEA Policy and Procedures for Conducting IRIS Peer Reviews, Office of Research and Development, Washington, DC (2009).

employer, is the central purpose of the activity, because that would constitute a conflict of interest, although such an individual may provide relevant information to the program activity.”<sup>18</sup>

The conduct at issue here is the active participation of Dr. Ornella Selmin in the discussion of the weight to be given a program of *in vivo* and *in vitro* experiments carried out over the past two decades at the University of Arizona on the relationship between TCE exposure and cardiac malformations. Dr. Selmin is a lead or co-author on a number of papers reporting these results,<sup>19</sup> and has co-authored papers with Dr. Paula Johnson, lead author of the most important and highly criticized of these studies.

Johnson *et al.* reported cardiac effects in rats from research carried out at the University of Arizona and originally published ten years earlier by the same authors.<sup>20</sup> In the earlier-published study, there was no difference in the percentage of cardiac abnormalities in rats dosed during both pre-mating and pregnancy at drinking water exposures of 1100 ppm (9.2%) and 1.5 ppm (8.2%), even though there was a 733-fold difference in the concentrations. The authors reported that the effects seen at these exposures were statistically higher than the percent abnormalities in controls (3%). For animals dosed only during the pregnancy period, the abnormalities in rats dosed at 1100 ppm (10.4%) were statistically higher than at 1.5 ppm (5.5%), but those dosed at 1.5 ppm were not statistically different from the controls. Thus, no meaningful dose-response relationship was observed in either treatment group. Johnson *et al.* republished in 2003 data from the 1.5 and 1100 ppm dose groups published by Dawson *et al.* in 1993 and pooled control data from other studies, an inappropriate statistical practice, to conclude that rats exposed to levels of TCE greater than 250 ppb during pregnancy have increased incidences of cardiac malformations in their fetuses.

Johnson *et al.* has been heavily criticized in the published literature,<sup>21</sup> and the earlier studies were rejected as the basis for minimal risk levels (MRLs) by the Agency for Toxic

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<sup>18</sup> Office of Management and Budget, Final Information Quality Bulletin for Peer Review, Executive Office of the President, Washington, DC (2004).

<sup>19</sup> *E.g.*, Makawana O, *et al.*, Exposure to low-dose trichloroethylene alters shear stress gene expression and function in the developing chick heart, *Cardiovasc Toxicol.* 10(2): 100-7 (2010); Caldwell PT, *et al.*, Gene expression profiling in the fetal cardiac tissue after folate and low-dose trichloroethylene exposure, *Birth Defects Res A Clin Mol Teratol.* 88(2): 111-27(2010); Selmin O, *et al.*, Trichloroethylene and trichloroacetic acid regulate calcium signaling pathways in murine embryonal carcinoma cells p19, *Cardiovasc Toxicol.* 8(2): 47-56 (2008); Caldwell PT, *et al.*, Trichloroethylene disrupts cardiac gene expression and calcium homeostasis in rat myocytes, *Toxicol Sci.* 104(1): 135-43 (2008); Selmin O, *et al.*, Effects of trichloroethylene and its metabolite trichloroacetic acid on the expression of vimentin in the rat H9c2 cell line, *Cell Biol Toxicol.* 21(2): 83-95 (2005); Collier JM, *et al.*, Trichloroethylene effects on gene expression during cardiac development, *Birth Defects Res A Clin Mol Teratol.* 67(7): 488-95 (2003).

<sup>20</sup> Dawson, B, *et al.*, Cardiac teratogenesis of halogenated hydrocarbon-contaminated drinking water, *J. Am. Coll. Cardiol.* 21: 1466-72 (1993).

<sup>21</sup> Hardin, B, *et al.*, Trichloroethylene and cardiac malformations, *Environ. Health Perspect.* 112: A607-8 (2004); Watson, R., *et al.*, Trichloroethylene-contaminated drinking water and congenital heart defects: a critical analysis of the literature, *Repro. Toxicol.*: 21:117-147 (2006).

Substances and Disease Registry (ATSDR).<sup>22</sup> Moreover, the Johnson *et al.* findings were not reproduced in a study designed to detect cardiac malformations; this despite employing an improved method for assessing cardiac defects and the participation of Johnson herself.<sup>23</sup> No increase in cardiac malformations was observed in a guideline, GLP-quality study,<sup>24</sup> despite high inhalation doses and techniques capable of detecting most of the malformation types reported by Johnson *et al.* The dose-response relationship reported in Johnson *et al.* for doses spanning an extreme range of experimental dose levels is considered by many to be improbable, and has not been replicated by any other laboratory. The draft TCE assessment discusses many of the uncertainties regarding the findings of Johnson *et al.*, but the SAB Panel recommended Johnson *et al.* as a preferred basis for the RfD/RfC calculation. It appears that this may be the direct result of strong support for using Johnson *et al.* expressed by Dr. Selmin during the Panel meetings.

As noted above, “Johnson and Dawson, with their collaborators, are alone in reporting that TCE is a ‘specific’ cardiac teratogen,”<sup>25</sup> and Dr. Selmin has been directly involved in this research program for some time. At various stages in the SAB panel discussions, Dr. Selmin indicated her support for the Johnson *et al.* study and expressed her view that recent mechanistic studies made the Johnson *et al.* findings more robust. For example, on May 11, 2010, during the discussions on Charge Question 3, Dr. Selmin indicated her support for EPA’s description of the studies relating to cardiac malformations (and their admitted shortcomings) but then indicated that new studies on mechanism of action make the Johnson *et al.* findings more robust. This theme was then repeated during discussion of Charge Question 8 – derivation of RfC and RfD. During the summary discussions of Charge Question 3, Dr. Selmin proposed that EPA should include recent publications to support conclusions based on Johnson *et al.*: she is co-author of three of those studies.<sup>26</sup>

The concern here is that the findings of Johnson *et al.* have now been elevated to a primary source for hazard assessment and derivation of the RfC and RfD largely at the insistence

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<sup>22</sup> See Letter from Christopher T. DeRosa, Director, ATSDR Division of Toxicology, to Peter E. Voytek, HSEA (February 28, 1996) (enclosed). ATSDR concluded that “[t]he study is limited in that only two widely spaced exposure concentrations were used and that a significant dose-response was not observed for several exposure scenarios.” ATSDR, Toxicological Profile for Trichloroethylene Update (September 1997), p. 88.

<sup>23</sup> Fisher, J, *et al.*, Trichloroethylene, trichloroacetic acid, and dichloroacetic acid: do they affect fetal rat heart development? *Int. J. Toxicol.* 20: 257-67 (2001).

<sup>24</sup> Carney, E, *et al.*, Developmental toxicity studies in Cr1:Cd (SD) rats following inhalation exposure to trichloroethylene and perchloroethylene, *Birth Defects Research (Part B)* 77:405-412 (2006).

<sup>25</sup> Hardin, B, *et al.*, *Repro. Toxicol.*: 21:117-147 (2006), citing several other studies from the University of Arizona, Tucson.

<sup>26</sup> Makawana O, *et al.*, Exposure to low-dose trichloroethylene alters shear stress gene expression and function in the developing chick heart, *Cardiovasc Toxicol.* 10(2): 100-7 (2010); Caldwell PT, *et al.*, Gene expression profiling in the fetal cardiac tissue after folate and low-dose trichloroethylene exposure, *Birth Defects Res A Clin Mol Teratol.* 88(2): 111-27(2010); Caldwell PT, *et al.*, Trichloroethylene disrupts cardiac gene expression and calcium homeostasis in rat myocytes, *Toxicol Sci.* 104(1): 135-43 (2008).

of Dr. Selmin. Despite the recent studies, Johnson *et al.* remains a poor basis for assigning hazard or calculation of exposure limits and the mechanistic studies do not provide information that bridges the gap to support directly the Johnson *et al.* conclusions. Without impugning Dr. Selmin's scientific integrity, the extent of criticisms of the work of the University of Arizona is likely to mean that Dr. Selmin will be drawn to defend the work done by her co-workers; a dispassionate, objective interpretation might not result. The appropriate action would have been for Dr Selmin to have recused herself from discussions of the interpretation of Johnson *et al.* and related studies.

Under the NAS conflicts policy cited above that is required to be adopted or adapted by EPA, "an individual should not serve as a member of a committee with respect to an activity in which a critical review and evaluation of the individual's own work, or that of his or her immediate employer, is the central purpose of the activity, because that would constitute a conflict of interest, although such an individual may provide relevant information to the program activity." Dr. Selmin's active participation in the discourse that has resulted in the SAB recommendation that her laboratory's controversial and unreproducible work be the basis for the RfD/RfC for TCE would seem to constitute a clear conflict of interest under this policy.

It may be possible to deal with this problem by empanelling a small group of perhaps three or four independent developmental toxicologists under the aegis of the SAB to review the cardiac malformation data. This would provide much-needed clarity in a controversial area and allow resolution of the issue to move forward, and could be accomplished while the issue of inconsistency with the EPA Guidelines for Carcinogen Risk Assessment and the Academy's Camp Lejeune report, now pending before the Chartered SAB, is resolved.

### III. Conclusion

In sum, we urge EPA to refrain from reliance on the bioassays by Maltoni *et al.* in the TCE assessment until EPA's review of studies conducted by that laboratory is concluded, and to reconsider the evidence supporting the recommendation that Johnson *et al.* be used to establish the RfC/RfD for TCE.

Very truly yours,

Faye Graul  
Executive Director

Enclosures

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Agency for Toxic Substances  
and Disease Registry  
Atlanta GA 30333

February 28, 1996



Peter E. Voytek, Ph.D.  
Executive Director, HSIA  
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Suite 506A  
Washington, DC 20036

Dear Dr. <sup>Peter</sup>Voytek:

Thank you for your recent correspondence regarding the intermediate duration oral minimal risk level for trichlorethylene chloride. Your concerns as outlined are shared by ATSDR. For this reason we have independently contacted the authors of the studies to further discuss and clarify these issues. ←

Thanks again for your input, and please be assured that it will be carefully considered as we develop the final version of the profile.

Best regards.

Sincerely,

Christopher T. DaRosa, Ph.D.  
Director, Division of Toxicology

## HSIA Statement for Chartered SAB

The Halogenated Solvents Industry Alliance, Inc. (HSIA) represents producers and users of trichloroethylene (TCE). HSIA provides these comments for consideration by the Chartered Science Advisory Board (SAB) in connection with its December 15, 2010 review of draft advice prepared by the Board's TCE Panel. For the past year the TCE Panel has been reviewing EPA's Toxicological Review of Trichloroethylene (October 2009 Draft), which will form the basis for the health effects assessment for TCE that will be reported on the Integrated Risk Information System (IRIS). Regrettably, the TCE Panel failed in its review.

The draft TCE assessment suffers from a serious defect that, if not corrected before publication, will prolong the uncertainty over the central question that has been at the heart of this assessment from the beginning: how likely is TCE to be a human carcinogen? And because the draft takes a position on that question that flatly contradicts a 2009 report by the National Academy of Sciences<sup>1</sup> (and is inconsistent with previous reviews by the International Agency for Research on Cancer, the National Toxicology Program, and, we submit, EPA's own 2005 Guidelines for Carcinogen Risk Assessment), it ensures that the public will continue to be confused by its own government as to the health risk posed by low-level TCE contamination of water supplies, a widespread legacy of disposal practices prior to the 1970s and 1980s.

We briefly address below how the epidemiological data on TCE do not meet the threshold for classification as "Carcinogenic to Humans" and how the draft advice prepared by the SAB TCE Panel conflicts with the Academy's Camp Lejeune report, in the hope that the Chartered SAB can take whatever steps are necessary to achieve a more coherent US Government position on this important question.

### A. The EPA Guidelines

EPA's 2005 Guidelines for Carcinogen Risk Assessment<sup>2</sup> provide the following descriptors as to the weight of evidence for carcinogenicity:

- Carcinogenic to humans,
- Likely to be carcinogenic to humans,
- Suggestive evidence of carcinogenicity,
- Inadequate information to assess carcinogenic potential, and
- Not likely to be carcinogenic to humans.

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<sup>1</sup> Contaminated Water Supplies at Camp Lejeune, Assessing Potential Health Effects (National Academies Press) (2009) (hereinafter "Camp Lejeune report").

<sup>2</sup> 70 Fed. Reg. 17766-817 (April 7, 2005).

According to the Guidelines, “carcinogenic to humans” means the following”

“This descriptor indicates strong evidence of human carcinogenicity. It covers different combinations of evidence.

- “This descriptor is appropriate when there is convincing epidemiologic evidence of a causal association between human exposure and cancer.
- “Exceptionally, this descriptor may be equally appropriate with a lesser weight of epidemiologic evidence that is strengthened by other lines of evidence. It can be used when *all* of the following conditions are met: (a) There is strong evidence of an association between human exposure and either cancer or the key precursor events of the agent's mode of action but not enough for a causal association, *and* (b) there is extensive evidence of carcinogenicity in animals, *and* (c) the mode(s) of carcinogenic action and associated key precursor events have been identified in animals, *and* (d) there is strong evidence that the key precursor events that precede the cancer response in animals are anticipated to occur in humans and progress to tumors, based on available biological information. In this case, the narrative includes a summary of both the experimental and epidemiologic information on mode of action and also an indication of the relative weight that each source of information carries, *e.g.*, based on human information, based on limited human and extensive animal experiments.”

According to the Guidelines, the descriptor “likely to be carcinogenic to humans”

“is appropriate when the weight of the evidence is adequate to demonstrate carcinogenic potential to humans but does not reach the weight of evidence for the descriptor ‘Carcinogenic to Humans.’ Adequate evidence consistent with this descriptor covers a broad spectrum. . . . Supporting data for this descriptor may include:

“An agent demonstrating a plausible (but not definitively causal) association between human exposure and cancer;

- “An agent that has tested positive in animal experiments in more than one species, sex, strain, site or exposure route, with or without evidence of carcinogenicity in humans;
- “A positive tumor study that raises additional biological concerns beyond that of a statistically significant result, for example, a high degree of malignancy or an early age at onset;
- “A rare animal tumor response in a single experiment that is assumed to be relevant to humans; or

- “A positive tumor study that is strengthened by other lines of evidence.”

According to the Guidelines, the descriptor “suggestive evidence of carcinogenicity”

“is appropriate when the weight of evidence is suggestive of carcinogenicity; a concern for potential carcinogenic effects in humans is raised, but the data are judged not sufficient for a stronger conclusion. This descriptor covers a spectrum of evidence associated with varying levels of concern for carcinogenicity, ranging from a positive cancer result in the only study on an agent to a single positive cancer result in an extensive database that includes negative studies in other species. Depending on the extent of the database, additional studies may or may not provide further insights. Some examples include:

- “A small, and possibly not statistically significant, increase in tumor incidence observed in a single animal or human study that does not reach the weight of evidence for the descriptor ‘Likely to Be Carcinogenic to Humans;’
- “A small increase in a tumor with a high background rate in that sex and strain, when there is some but insufficient evidence that the observed tumors may be due to intrinsic factors that cause background tumors and not due to the agent being assessed;
- “Evidence of a positive response in a study whose power, design, or conduct limits the ability to draw a confident conclusion (but does not make the study fatally flawed), but where the carcinogenic potential is strengthened by other lines of evidence; or
- “A statistically significant increase at one dose only, but no significant response at the other doses and no overall trend.”

#### B. Application of the Guidelines to Trichloroethylene

Charge Question 4 indicates that the Panel should address cancer classification “using the approach outlined in the U.S. EPA Cancer Guidelines (US EPA 2005). . . .” and lays down a number of issues for the Panel to consider. Unfortunately, the Panel failed to use the apply the Guidelines in the manner required and only brief lip service was given to the criteria for classification so clearly stated in the Guidelines.

In considering the data in the context of applying the “Carcinogenic to Humans” descriptor, one first considers the weight of the epidemiological evidence. Here, the epidemiologic evidence is neither “convincing” nor “strong,” two key terms in the guidelines. This judgment is based on four recent reviews and meta-analyses of occupational TCE exposures

and cancer as well as other reviews of this literature.<sup>3</sup> The recent review and meta-analysis by Kelsh *et al.*, focuses on occupational TCE exposure and kidney cancer, and includes the Charbotel *et al.* study that is emphasized in the EPA assessment and used by EPA scientists to conduct a quantitative risk assessment.<sup>4</sup> Both the EPA meta-analysis and the recently published Kelsh *et al.* meta-analysis of the TCE kidney cancer epidemiologic literature produced similar summary results. However in Kelsh *et al.*, the limitations of this body of research, namely exposure assessment limitations, potential unmeasured confounding, potential selection biases, and inconsistent findings across groups of studies, did not allow for a conclusion that there is sufficient evidence of a causal association, despite a modest overall association. In addition, Charbotel *et al.* has important limitations that do not permit an appropriate use in quantitative risk assessment.

There are reasonably well-designed and well-conducted epidemiologic studies that report no association between TCE and cancer, some reasonably well-designed and conducted studies that did report associations between TCE and cancer, and finally some relatively poorly designed studies reporting both positive and negative findings. Overall, the summary relative risks or odds ratios in the meta-analysis studies (EPA or published meta-analyses) generally ranged between 1.2 and 1.4. The draft assessment refers to these associations as “small,” a term not typically consistent with “convincing” and “strong.” Weak or small associations may be more likely to be influenced by or be the result of confounding or bias. Smoking and body mass index are well-established risk factors for kidney cancer, and smoking and alcohol are risk factors for liver cancer, yet the potential impact of these factors on the meta-analysis associations was not fully considered. There were suggestions 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). In addition, co-linearity of occupational exposures (*i.e.*, TCE exposure correlated with chemical and/or other exposures) may make it difficult to isolate potential effects of TCE from those of other exposures within a given study, and hinder interpretation across studies. For example, although Charbotel *et al.* reported potential exposure response trends, while controlling for many confounders of concern (which strengthens the weight of evidence), they also reported attenuated associations for cumulative TCE exposure after adjustment for exposure to cutting fluids and other petroleum oils (weakening the weight of the evidence). This study is also limited due to other potential study design considerations such as selection bias, self report of work histories, and residual confounding.

When examining the data for TCE and non-Hodgkin lymphoma, kidney cancer, and liver cancer, associations were inconsistent across occupational groups (summary results differed

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<sup>3</sup> Alexander, D, *et al.*, A meta-analysis of occupational trichloroethylene exposure and multiple myeloma or leukaemia, *Occup Med (Lond)* 56:485–493 (2006); Alexander, D, *et al.*, A meta-analysis of occupational trichloroethylene exposure and liver cancer, *Int Arch Occup Environ Health* 81(2):127–43 (2007); Mandel, J, *et al.*, Occupational trichloroethylene exposure and non-Hodgkin's lymphoma: a meta-analysis and review, *Occup Environ Med* 63:597–607 (2006); Kelsh, M, *et al.*, Occupational trichloroethylene exposure and kidney cancer: a meta-analysis, *Epidemiology* 21(1): 95-102 (January 2010).

<sup>4</sup> Charbotel, B, *et al.*, Case-control study on renal cell cancer and occupational exposure to trichloroethylene, Part II: Epidemiological aspects, *Ann Occup Hyg* 50(8):777–787 (2006).

between aerospace/aircraft worker cohorts compared with workers from other industries), study design, location of the study, quality of exposure assessment (*e.g.*, evaluating studies that relied upon biomonitoring to estimate exposure *vs.* semi-quantitative estimates *vs.* self-report, etc.), and by incidence *vs.* mortality endpoints. Although EPA examined high dose categories, it did not evaluate any potential dose-response relationships across the epidemiologic studies (except for Charbotel *et al.*). Reviews of the epidemiologic data reported in various studies for different exposure levels (*e.g.*, cumulative exposure and duration of exposure metrics) did not find consistent dose-response associations between TCE and the three cancer sites under review.<sup>5</sup> An established dose-response trend is one of the more important factors when making assessments of causation in epidemiologic literature.

The respected epidemiologist Douglas Weed (formerly of NIH) has shown that meta-analysis has serious limitations for the purpose of proving a causal relationship.<sup>6</sup> It is readily apparent that the epidemiological evidence for TCE's association with human cancer is in no way as robust as that relied upon in classifying the current list of "known human carcinogens," and meta-analysis cannot remedy this problem.

Thus, based on an overall weight of evidence analysis of the epidemiologic research, these data do not support the conclusion that there is "strong" or "convincing" evidence of a causal association between human exposure and cancer.

EPA's Guidelines also state that a chemical may be described as "Carcinogenic to Humans" with a lesser weight of epidemiologic evidence that is strengthened by other lines of evidence, all of which must be met. One of these lines of evidence is "extensive evidence of carcinogenicity in animals." Therefore, we must briefly evaluate the animal data.

In weighing the evidence in experimental animals and addressing the impact of the metabolites produced, the draft assessment states (p. 4-233):

"A greater variability of response is expected than from exposure to a single agent making it particularly important to look at the TCE database in a holistic fashion rather than the results of a single study, especially for quantitative inferences."

From this premise, EPA goes on to surmise that evidence for cancer is found in two species (rats and mice) and for more than one tumor endpoint (kidney, liver, lung and immune system).

Starting from the more neutral question of: "Does TCE cause cancer in experimental animals," however, EPA's description of this evidence is unconvincing. The criteria that have to

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<sup>5</sup> Mandel, J, *et al.*, Occupational trichloroethylene exposure and non-Hodgkin's lymphoma: a meta-analysis and review, *Occup Environ Med* 63:597-607 (2006); Alexander, D, *et al.*, A meta-analysis of occupational trichloroethylene exposure and liver cancer, *Int Arch Occup Environ Health* 81(2):127-43 (2007); Kelsh, M, *et al.*, Occupational trichloroethylene exposure and kidney cancer: a meta-analysis, *Epidemiology* 21(1): 95-102 (January 2010).

<sup>6</sup> Weed, D, Meta-analysis and causal inference: a case study of benzene and non-Hodgkin lymphoma, *Ann Epidemiol* 20(5): 347-355 (2010).

be met for animal data to support a "carcinogenic to humans" classification are stated in a sequential manner with an emphasized requirement that all criteria have to be met. Since the Guidelines consider this to be an "exceptional" route to a "carcinogenic to humans" classification, we would expect rigor to have been applied in assessing animal data against the criteria. This suggests that the criteria should have been tested individually, in sequence, by the Panel during a review of classification. This simply was not done.

Of the four primary tissues that EPA evaluates for carcinogenicity, only one or perhaps two rise to the level of biological significance. Discussion of the remaining tumor types appears to presuppose that TCE is carcinogenic. The resulting discussion appears then to overly discount negative data, of which there are many, and to highlight marginal findings. The text does not appear to be a dispassionate rendering of the available data. Specifically, EPA's conclusion that kidney cancer is evident in rats rests on *one* statistically significant finding in over 70 dose/tumor endpoint comparisons and references to exceedances of historical control values. Using a 0.05 p-value for statistical significance, a frequency of 1 or even several statistically or biologically significant events is expected in such a large number of dosed/tumor groups. EPA's overall conclusion based on these flawed studies cannot be that TCE is a known kidney tumorigen. The best that can be said is that the data are inconsistent. Certainly they do not meet the criterion of "extensive evidence of carcinogenicity in animals." Several marginal findings do not constitute "extensive evidence."

For these reasons, EPA's proposed classification of TCE as "Carcinogenic to Humans" is not supported by the evidence and cannot be justified under the 2005 Guidelines.

C. Contrast between EPA Position of 'Convincing Evidence' and NAS Conclusion of 'Limited or Suggestive Evidence'

The draft assessment concludes, "Following U.S. EPA (2005a) guidelines for carcinogen risk assessment, based on the available data as of 2009, TCE is characterized as 'carcinogenic to humans' by all routes of exposure. This conclusion is based on convincing evidence of a causal association between TCE exposure in humans and kidney cancer."

Box 2 of the Academy's Camp Lejeune report, attached, categorizes every cancer outcome reviewed in relation to exposure to TCE, the dry cleaning solvent perchloroethylene, or a mixture of the two. The categories are taken directly from a respected Institute of Medicine (IOM) report.<sup>7</sup> 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 attached.

Looking at Box 2, evidence considered by EPA to be "convincing 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

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<sup>7</sup> Institute of Medicine, Gulf War and Health, Vol. 2, Insecticides and Solvents (National Academies Press) (2003).

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 "convincing evidence of causation." One would expect at the least a detailed explanation in the draft assessment of EPA's very different conclusion. Although the 2009 Camp Lejeune study was already published, and indeed is cited in the references (p. B-358), there is no mention of it in the text of the draft assessment, even though the previous draft had just been the subject of a multi-year review by the Academy.

The Camp Lejeune committee began with a comprehensive review of the epidemiology studies of the two solvents by the IOM for its Gulf War Report. They 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.*). They 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.

EPA, on the other hand, offered the summary conclusion of convincing human evidence, based on the "consistency" of increased kidney cancer across the different studies. The authors of these studies, however, do not agree with EPA's characterization of them. For example, the authors of Charbotel *et al.*, the study EPA 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 EPA assessment is to provide guidance to risk managers about the public health implications of low levels of TCE exposure, it seems remarkable that EPA would ignore the authors' conclusion that the evidence is only suggestive, and fail to mention this caveat, while characterizing the evidence as "convincing."

We urge the Chartered SAB to take whatever steps are necessary to ensure that, whatever the outcome, the US regulatory/scientific establishment speak with one voice on a question of such importance.

**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. . . .

*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. . . .

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  
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**BOX 2** Categorization of Health Outcomes<sup>a</sup> 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*

- Kidney cancer
- Adult leukemia (solvent mixtures)
- Multiple myeloma (solvent mixtures)
- Myelodysplastic syndromes (solvent mixtures)
- 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
- Myelodysplastic 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

<sup>a</sup>Outcomes for TCE and PCE unless otherwise specified\*

\* PCE-only outcomes omitted