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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[1] (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[2] 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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[1] Contaminated Water Supplies at Camp Lejeune, Assessing Potential Health Effects (National Academies Press) (2009) (hereinafter "Camp Lejeune report").

[2] 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.[3] 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.[4] 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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[3] 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).

[4] 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.[5] 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.[6] 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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[5] 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).

[6] 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.[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 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

[7] 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 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

- Kidney cancer
- Adult leukemia (solvent mixtures)
- Multiple myeloma (solvent mixtures)
- Myleodysplasic 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
- 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**

* PCE-only outcomes omitted