HSIA
halogenated
solvents
industry
alliance, inc.

February 28, 2012

Dr. Ruth Linn
Director
Office of the Report on Carcinogens
National Toxicology Program
National Institute of Environmental Health Sciences
P.O. Box 12233, MD K2-14
Research Triangle Park, NC 27709

Re: Request for Public Comment on Nominations to the RoC

Dear Dr. Linn:

The Halogenated Solvents Industry Alliance, Inc. (HSIA) offers these comments on substances that have been nominated for review in future editions of the Report on Carcinogens (RoC), 77 Fed. Reg. 2728 (January 19, 2012). HSIA represents manufacturers and users of trichloroethylene (TCE), a substance that was nominated to be listed as a known human carcinogen as opposed to its current listing of reasonably anticipated to be a human carcinogen.

We strongly believe that TCE does not meet the criteria for listing as a known human carcinogen. We recognize that the Environmental Protection Agency (EPA) did proceed to classify TCE as "carcinogenic to humans" in September 2011. This conclusion is clearly erroneous, however, as it conflicts directly with 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 EPA's own 2005 Guidelines for Carcinogen Risk Assessment).

We briefly address below how the epidemiological data on TCE do not meet the threshold for classification as a known human carcinogen, although this exercise is hampered by the absence of NTP criteria.

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

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TCE Epidemiologic Data

The epidemiologic evidence for TCE is neither "convincing" nor "strong." 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.[2] 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 relied upon in EPA's meta-analysis.[3] While the Kelsh *et al.* meta-analysis produced similar summary results, Kelsh *et al.* recognized the limitations of this body of research. 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. These associations are small, not "convincing" or "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

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[2] 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).

[3] 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).

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 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's meta-analysis 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.[4] 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 in a series of articles that meta-analysis has serious limitations for the purpose of proving a causal relationship. 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.

Camp Lejeune Report

Box 2 of the Academy's Camp Lejeune report, enclosed, 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.[5] 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.

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[4] 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).

[5] Institute of Medicine, Gulf War and Health, Vol. 2, Insecticides and Solvents (National Academies Press) (2003).

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 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.

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.

We urge NTP to give careful consideration to the published reviews and the Camp Lejeune report and not to propose changing the classification of TCE in the 13th Report on Carcinogens.

Very truly yours,

[Redacted]

Fayė Graul
Executive Director

Enclosure

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