HSIA
halogenated
solvents
industry
alliance, inc.

March 16, 2015

Division of Toxicology and Human Health Services
Agency for Toxic Substances & Disease Registry
1600 Clifton Road, NE (MS F57)
Atlanta, GA 30333

Re: ATSDR-2014-0001 (Trichloroethylene)

Dear Sir or Madam:

The Agency for Toxic Substances & Disease Registry ("ATSDR") recently announced the availability for review of a draft updated Toxicological Profile for Trichloroethylene (CAS No. 79-01-6) (the "TCE Update"). 79 Fed. Reg. 74094 (December 15, 2014). These comments on the TCE Update are offered on behalf of the Halogenated Solvents Industry Alliance, Inc. ("HSIA"), which represents producers and users of TCE and other chlorinated solvents.

HSIA has a long history of cooperation with ATSDR, including voluntary development of test data to meet Priority Data Needs ("PDNs") identified by ATSDR pursuant to our Agreement effective July 1, 2002. HSIA commented on the original Toxicological Profile for Trichloroethylene and several updates thereto.

Our comments on the TCE Update will be divided between non-cancer and cancer effects, with some general comments that follow.

A. Non-cancer Effects

1. Basis for MRLs

A primary purpose of the Toxicological Profiles is to establish estimates of exposure levels posing minimal risk to humans ("MRLs"). An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse non-cancer effects over a specified duration of exposure.

In previous Toxicological Profiles, ATSDR has properly assessed all the available evidence and derived sound, science-based MRLs. In the TCE Update, however, ATSDR has abdicated its responsibility to review and judge the relevant evidence and instead relies entirely upon a flawed

TCE assessment produced by the Environmental Protection Agency ("EPA") in 2011.[1] The IRIS Assessment contains a reference concentration ("RfC") of 0.0004 ppm (0.4 ppb or 2 μg/m^3) and a reference dose ("RfD") of 0.0005 mg/kg/day for TCE.[2] These are values that are considered by EPA to be protective for all of the candidate critical effects. EPA's derivation of the RfC/RfD for TCE is based, in part, on Johnson *et al.*, Threshold of Trichloroethylene Contamination in Maternal Drinking Waters Affecting Fetal Heart Development in the Rat, Environmental Health Perspectives 111: 289-92 (March 2003). It is one of the few studies cited in support of both the RfC and the RfD.

Given the recognized deficiencies of Johnson *et al*. (2003), it (and the EPA RfC/RfD) should not be the basis for the MRLs. At least two GLP-compliant studies conducted under EPA guidelines to support pesticide registration (40 CFR § 870.3700) and OECD guidelines (414), one of which was sponsored by HSIA under the Agreement with ATSDR, have been unable to reproduce the effect seen by Johnson *et al.*, as described below.

Ignoring for the moment the deficiencies in the Johnson *et al.* study, ATSDR's reliance on that study as the basis for the MRLs appears to be in direct conflict with information contained on the ATSDR MRL[3] webpage which states that "**ATSDR does not use serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) as a basis for establishing MRLs**" [emphasis added].

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.[4] 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

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[1] EPA/635/R-09/011F (September 2011) (hereafter "IRIS Assessment").

[2] The TCE Update states (pp. 22-26) "these values have been adopted as the ATSDR chronic-duration oral MRL and chronic-duration inhalation MRL[and the intermediate-duration oral and inhalation MRLs], respectively."

[3] See http://www.atsdr.cdc.gov/mrls/index.asp

[4] Dawson, B, *et al.*, Cardiac teratogenesis of halogenated hydrocarbon-contaminated drinking water, J. Am. Coll. Cardiol. 21: 1466-72 (1993).

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.[5] Indeed, the Arizona studies were expressly rejected as the basis for MRLs by ATSDR in its last TCE Toxicological Profile Update.[6] Moreover, the Johnson *et al.* findings were not reproduced in a study designed to detect cardiac malformations; this despite employing an improved staining method for assessing cardiac defects, the tissue dissection method used in Johnson *et al.* and the participation of Johnson herself.[7] No increase in cardiac malformations was observed in the guideline study sponsored by HSIA,[8] 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.[9]

One of the principal criticisms of Johnson *et al.* is that it employed an inappropriate statistical practice:

> "Johnson *et al.* (2003) provided no rationale for designing their study with a concurrent control five times larger than the treatment groups, which leads us to ask whether the control group reported here is, in fact, a composite of controls from multiple, perhaps five, different studies.. The immediate impact of this large control

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[5] 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: 117-47 (2006).

[6] 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." Toxicological Profile for Trichloroethylene Update (September 1997), at 88.

[7] Fisher, J, *et al.*, Trichloroethylene, trichloroacetic acid, and dichloroacetic acid: do they affect fetal rat heart development? Int. J. Toxicol. 20: 257-67 (2001).

[8] Carney, E, *et al.*, Developmental toxicity studies in Crl:Cd (SD) rats following inhalation exposure to trichloroethylene and perchloroethylene, Birth Defects Research (Part B) 77: 405−412 (2006).

[9] "Johnson and Dawson, with their collaborators, are alone in reporting that TCE is a 'specific' cardiac teratogen." Hardin, B, *et al.*, Trichloroethylene and cardiac malformations, Environ. Health Perspect. 112: A607-8 (2004).

> group is that the very cardiac 'abnormalities' at the 1.5 ppm dose that did not differ significantly from controls in 1993 become statistically significant in 2003."[10]

We are hard pressed to find a better summary of Johnson *et al.* than the following statement by the California Office of Environmental Health Hazard Assessment (OEHHA) rejecting the study as deficient:

> "Johnson et al. (2003) reported a dose-related increased incidence of abnormal hearts in offspring of Sprague Dawley rats treated during pregnancy with 0, 2.5 ppb, 250 ppb, 1.5 ppm, and 1,100 ppm TCE in drinking water (0, 0.00045, 0.048, 0.218, and 128.52 mg/kg-day, respectively). The NOAEL for the Johnson study was reported to be 2.5 ppb (0.00045 mg/kg-day) in this short exposure (22 days) study. The percentage of abnormal hearts in the control group was 2.2 percent, and in the treated groups was 0 percent (low dose), 4.5 percent (mid dose 1), 5.0 percent (mid dose 2), and 10.5 percent (high dose). The number of litters with fetuses with abnormal hearts was 16.4 percent, 0 percent, 44 percent, 38 percent, and 67 percent for the control, low, mid 1, mid 2, and high dose, respectively. The reported NOAEL is separated by 100-fold from the next higher dose level. The data for this study were not used to calculate a public-health protective concentration since a meaningful or interpretable dose-response relationship was not observed. *These results are also not consistent with earlier developmental and reproductive toxicological studies done outside this lab in mice, rats, and rabbits: The other studies did not find adverse effects on fertility or embryonic development, aside from those associated with maternal toxicity (Hardin et al., 2004)*."[11]

Moreover, reliance upon an irreproducible study result is a significant scientific deficiency in itself. This particular problem was illustrated most vividly during a recent EPA-empanelled peer review.[12] The comments of the peer reviewers include the following critique of EPA's reliance on Johnson *et al.*:

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[10] Hardin, B, *et al*., Trichloroethylene and cardiac malformations, Environ. Health Perspect. 112: A607-8 (2004).

[11] California EPA Public Health Goal for Trichloroethylene in Drinking Water (July 2009), at 21 (emphasis added).

[12] Peer Review Meeting for EPA's Draft TSCA Work Plan Chemical Risk Assessment for Trichloroethylene: Degreaser and Arts/Crafts Uses (CASRN: 79-01-6) 1,1,2-Trichloethene (July 9 – August 21, 2013).

"It is not clear why OPPT relied on the results of the Johnson et al. (2003) study to the exclusion of all other inhalation and oral developmental toxicity studies in rodents and rabbits. If in fact the OPPT is reliant upon only the inhalation data, why is it the Carney et al. (2001), the Schwetz et al. (1975), the Hardin et al. (1981), the Beliles et al. (1980) or the Dorfmueller et al. (1979) study was not used? Why is there no discussion of all of the available developmental toxicity inhalation bioassays in the present analysis?

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"As submitted, the exposure parameters appear arbitrary (e.g., 0.5 and 1 hr/day) and may have been selected for sake of convenience. The data upon which conclusions put forward by OPPT on risk for developmental toxicity associated with arts and crafts use of TCE are not reliable. Nearly all developmental toxicity studies with TCE in rodents find no sign of teratogenicity (*e.g.*, Beliles et al., 1980) or find only slight developmental delay (Dormueller et al., 1979). Chiu et al. (2013) cite the NRC (2006) report as verification of their risk assessment for TCE developmental toxicity, but actually the NRC (2006) concluded:

> "Additional studies evaluating the lowest-observed-adverse-effect-level and mode of action for TCE-induced developmental effects are needed to determine the most appropriate species for human modeling."

"In its present assessment, the OPPT ignored the serious deficiencies already identified in conduct of the Johnson et al. (2003) rat drinking water study upon which the BMD01 was based (Kimmel et al., 2009; Watson et al., 2006) [Attachments 1 and 2]. In their weight-of-evidence assessment, Watson et al. (2006) concluded:

> "…application of Hill's causality guidelines to the collective body of data revealed no indication of a causal link between gestational TCE exposure at environmentally relevant concentrations and congenital heart defects."

"Those conclusions were consistent with Hardin et al. (2005). Perhaps most disturbing of all in US EPA's reliance upon Johnson et al. (2003) as the key study (which for the basis for their lowest non-cancer TCE hazard index and margin of exposure) is the observation by Hardin and associates (2004):

> "Conventional developmental and reproductive toxicology assays in mice,

> rats and rabbits consistently fail to find adverse effects of TCE on fertility or embryonic development aside from embryo- or fetotoxicity associated with maternal toxicity. Johnson and Dawson, with their collaborators, are alone in reporting that TCE is a "specific" cardiac teratogen."

"One of the fundamental tenants in science is the reliability and reproducibility of results of scientific investigations. In this regard, one of the most damning of the TCE developmental toxicity studies in rats is that by Fisher et al. (2005) who stated:

> "The objective of this study was to orally treat pregnant CDR(CD) Sprague-Dawley rats with large bolus doses of either TCE (500 mg/kg), TCA (300 mg/kg) or DCA (300 mg/kg) once per day on days 6 through 15 of gestation to determine the effectiveness of these materials to induce cardiac defects in the fetus. All-trans-retinoic acid (RA) dissolved in soybean oil was used as a positive control."
>
> "The heart malformation incidence for fetuses in the TCE-, TCA- and DCA-treated dams did not differ from control values on a per fetus or per litter basis. The RA treatment group was significantly higher with 33% of the fetuses displaying heart defects."

"Unfortunately, Johnson et al. (2005) failed to report the source or age of their animals, their husbandry or provide comprehensive historical control data for spontaneous cardiovascular malformations in their colony. The Johnson study with 55 control litters compared to 4 affected litters of 9 treated was apparently conducted over a prolonged period of time (perhaps years); it is possible this was due to the time required to dissect and inspect fresh rodent fetuses by a small academic research group. However, rodent background rates for malformations, anomalies and variants show temporal fluctuations (WHO, 1984) and it is not clear whether the changes reported by Johnson et al. (2005) were due to those fluctuations or to other factors. Surveys of spontaneous rates of terata in rats and other laboratory animals are common particularly in pharmaceutical and contract laboratory safety assessment (e.g., Fritz et al., 1978; Grauwiler, 1969; Palmer, 1972; Perraud, 1976). The World Health Organization (1984) advised:

> "Control values should be collected and permanently recorded. They provide qualitative assurance of the nature of spontaneous malformations that occur in control populations. Such records

> also monitor the ability of the investigator to detect various subtle structural changes that occur in a variety of organ systems."

> "Rates of spontaneous congenital defects in rodents can vary with temperature and housing conditions. For example, depending on the laboratory levocardia and cardiac hypertrophy occur in rats at background rates between 0.8-1.25% (Perraud, 1976). Laboratory conditions can also influence study outcome; for instance, maternal hyperthermia (as a result of ambient elevated temperature or infection) can induce congenital defects (including cardiovascular malformations) in rodents and it acts synergistically with other agents (Aoyama et al., 2002; Edwards, 1986; Zinskin and Morrissey, 2011). Thus while the anatomical observations made by Johnson et al. (2003) may be accurate, in the absence of data on maternal well-being (including body weight gain), study details (including investigator blind evaluations), laboratory conditions, positive controls and historical rates of cardiac terata in the colony it is not possible to discern the reason(s) for the unconventional protocol, the odd dose-response and marked differences between the Johnson et al. (2003) results and those of other groups.

> "As noted by previous investigators, the rat fetus is 'clearly at risk both to parent TCE and its TCA metabolite' given sufficiently high prenatal TCE exposures that can induce neurobehavioral deficits (Fisher et al., 1999; Taylor et al., 1985), but to focus on cardiac terata limited to studies in one laboratory that have not been reproduced in other (higher dose) studies and apply the BMD01 with additional default toxicodynamic uncertainty factors appears misleading."[13]

2. Information Quality Act Issues

Congress passed the Information Quality Act ("IQA") in 2000 to ensure the quality, objectivity, utility, and integrity of the scientific, technical, and statistical information that federal agencies adopt and disseminate to the public.[14] As a sister agency of the Centers for Disease Control ("CDC"), ATSDR follows the IQA Guidelines of the Department of Health and Human

[13] http://www.scgcorp.com/tcl2013/prcomments.asp, pp. 56-73. Attachments containing more detailed critiques of Johnson *et al.* are also available via this link.

[14] Section 515(a) of the Treasury and General Government Appropriations Act for Fiscal Year 2001, P.L. 106-554; 44 U.S.C. § 3516 (notes).

Services.[15] CDC's "policies and procedures are designed to ensure and maximize the quality of its information products with regard to their utility, objectivity, and integrity." For the Toxicological Profiles, which are considered "influential scientific information," these Guidelines require that ATSDR use:

> "a. the best available science and supporting studies conducted in accordance with sound and objective scientific practices, including peer-reviewed science and supporting studies when available
>
> b. data collected by accepted methods (if reliability of the method and the nature of the decision justify use of the data)."

The "objectivity," "utility," and "integrity" criteria are all implicated by ATSDR's reliance on Johnson *et al*. as a basis for its MRLs (just as they are by EPA's reliance on Johnson *et al*. as a basis for its RfC/RfD). The IQA Guidelines provide that it is ATSDR's "policy to ensure and maximize the quality, objectivity, utility, and integrity of information that it disseminates to the public." These terms are defined as follows:

- **Utility** CDC [ATSDR] addresses utility, a measure of the usefulness of information products to its intended users, by staying informed of user needs through information product research and user needs assessment, user feedback, consultation with advisory committees, and conference participation.

- **Objectivity** CDC [ATSDR] provides assurance that information is accurate, reliable, and unbiased. Objectivity is achieved through existing review and clearance procedures and, in many cases, the peer review of disseminated information.

- **Integrity** CDC [ATSDR] assures the integrity of its data and information products through the enforcement of rigorous controls that protect against unauthorized access, revision, or corruption.

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[15] Guidelines for Ensuring the Quality of Information Disseminated to the Public D. Centers for Disease Control and Prevention and Agency for Toxic Substances and Disease Registry ("Unless otherwise specified, all subsequent references to CDC also include ATSDR and all practices and procedures described in this document apply to both agencies"). http://aspe.hhs.gov/infoquality/Guidelines/cdcinfo2.shtml

While not covered expressly in the HHS Guidelines, guidance published by the IQA lead agency, the Office of Management and Budget, indicates that "reproducibility" means that the information is capable of being substantially reproduced, *i.e.*, "that independent analysis of the original or supporting data using identical methods would generate similar analytic results."[16]

Johnson *et al.* (2003) does not meet the applicable IQA objectivity, integrity, or reproducibility criteria. On November 5, 2013, HSIA submitted to EPA a request for the correction of information ("Request for Correction") in the IRIS Assessment under the IQA. HSIA explained that EPA's exclusive reliance on a single inappropriate and unreproducible study, as well as an RfC/RfD based on that study, constitutes erroneous information, the dissemination of which contravenes the IQA. More recently, on July 3, 2014, HSIA supplemented its Request for Correction in light of an erratum published in the spring of 2014 by Johnson *et al.*[17] Still more recently, on September 8, 2014, HSIA further supplemented its Request for Correction to identify how EPA's reliance on Johnson *et al.* in its TCE IRIS Assessment conflicted with its interpretation of the same body of evidence in an earlier IRIS assessment of vinylidene chloride. All of the points made in the Request for Correction and its supplements, which are enclosed, apply equally to ATSDR's reliance on Johnson *et al.* and the EPA RfC/RfD.

An important indicator that the MRLs fail to meet the standard of the IQA appears in a recent article by the authors of the IRIS assessment, which states:

> "Interpretation of these data has been controversial because many of the studies are limited by small numbers of cases, insufficient exposure characterization, chemical coexposures, and other methodological deficiencies. In addition, these studies aggregate a broad array of TCE-associated cardiac malformations and have inadequate statistical power to identify any particular kind(s) of defect that may be

[16] OMB Guidelines, 67 Fed. Reg. at 8460.

[17] Johnson *et al.,* Environ Health Perspect 122: A94 (2014): erratum to Environ Health Perspect 113:A18 (2005), which is an erratum for Johson *et al.,* Threshold of Trichloroethylene Contamination in Maternal Drinking Waters Affecting Fetal Heart Development in the Rat. Environ Health Perspect 111:289–292 (2003). The previously published articles covered by the Johnson *et al*., 2014 erratum are: Dawson BV, Johnson PD, Goldberg SJ, Ulreich JB, Cardiac Teratogenesis of Halogenated Hydrocarbon-contaminated Drinking Water, J Am Coll Cardiol 21(6):1466–1472 (1993); Johnson PD, Dawson BV, Goldberg SJ., Cardiac Teratogenicity of Trichloroethylene Metabolites, J Am Coll Cardiol 32(2):540–545 (1998); Johnson PD, Dawson BV, Goldberg SJ., A Review: Trichloroethylene Metabolites: Potential Cardiac Teratogens. Environ Health Perspect 106 (Suppl 4):995–999 (1998); Johnson PD, Dawson BV, Goldberg SJ, Mays MZ., Trichloroethylene: Johnson *et al*.'s Response [Letter], Environ Health Perspect 112:A608–A609 (2004).

> more susceptible to induction by TCE. . . . The approaches and conclusions of the U.S. EPA's analyses (U.S. EPA 2011d) are consistent with the recommendations of the NRC (2006)."[18]

Reference to the National Research Council report cited reveals a very different understanding of the studies in question, one that is quite inconsistent with those studies being the basis for the MRLs:

> "Although some rodent studies have shown effects (Smith et al. 1989, 1992; Dawson et al. 1993; Epstein et al. 1992), other studies have not (NTP 1985, 1986b; Fisher et al. 2001), suggesting either methodological or strain differences. The committee noted that the *rodent studies showing trichloroethylene-induced cardiac teratogenesis at low doses were performed by investigators from a single institution. Also noted were the unusually flat dose-response curves in the low-dose studies from these investigators. For example, the incidences of heart malformations at trichloroethylene concentrations of 1.5 and 1,100 ppm (almost three orders of magnitude greater) were 8.2% to 9.2% (prepregnancy and during pregnancy) to 10.4% (during pregnancy only) (Dawson et al. 1993). The same pattern occurred with dichloroethylene. Thus, the animal data are inconsistent, and the apparent species differences have not been addressed*."[19]

This damning indictment of EPA's reliance on an irreproducible study as the basis for its RfC/RfD by its own external peer reviewers applies equally to ATSDR's reliance on EPA's assessment for its TCE MRLs.

3. Epidemiological Evidence Relating to Cardiac Anomalies

HSIA recently sponsored a critical review of the epidemiologic literature regarding the association between congenital heart defects ("CHD") and exposure to trichloroethylene.[20] It

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[18] Chiu, W., *et al.,* Human Health Effects of Trichloroethylene: Key Findings and Scientific Issues, Environ Health Perspect. 121(3): 303–311 (2013).

[19] National Academies Press, Assessing the Human Health Risks of Trichloroethylene: Key Scientific Issues (2006), at 211 (emphasis added).

[20] Bukowski, J., Critical Review of the Epidemiologic Literature Regarding the Association between Congenital Heart Defects and Exposure to Trichloroethylene, Crit Rev Toxicol, 2014; Early Online: 1–9. (All references in text in this section are cited in this review.)

concluded that overall, the reviewed studies provide no substantive or consistent epidemiologic evidence of a causal relationship between TCE exposure and CHD. The literature assessing this association is relatively sparse, consisting of only about a dozen studies covering eight different populations. A positive association with exposure was reported for four of these, but these positive studies contained substantial design or analytic limitations that could easily have explained the elevated results.

The strongest associations were reported by Yauck *et al.* (2004) and Forand *et al*. (2012), each finding a significant 5- to 6-fold increase among certain subgroups. However, the former finding was the result of *post-hoc* model shopping for interaction, with no main effect reported for TCE exposure (OR: 1.0). The latter finding was based on only three CHD cases using models adjusted for nine strata from six covariates, suggesting sparse-data concerns and model over-fitting. The 3-fold increased risk reported by Goldberg *et al*. (1990) was unadjusted for confounding despite the fact that several risk factors were 2- to 3-fold more common among exposed cases than among either controls or cases without exposure. Finally, the marginally increased CHD risk (OR: 1.2 – 1.3) reported by Bove *et al*. (1995) was not statistically significant and was not an *a priori* study focus.

Bove *et al.* (1995) suggest that the marginal nature of their reported increase might have been due to the relatively low-level TCE exposures found in NJ water. Yet this logic is not consistent with the 2- to 6-fold increased risks reported by other positive studies in which exposure estimates were in the same general range (Table 1). Furthermore, some negative studies had higher TCE exposures (Table 1) but reported fewer CM/CHD cases than expected. Such results suggest that risk is unrelated to level of exposure, and that positive findings might be better explained by analytical flaws or study bias.

Several of the studies were highly exploratory, making dozens to a hundred or more comparisons in search of positive findings. Chief among these was Bove *et al.* (1995) and Bove (1996), which explored 117 planned comparisons in addition to *post-hoc* analyses. In such an instance, a non-significant 20 – 30% increase is inconsequential. Forand *et al*. (2012) reported dozens of tests of association, and likely explored other unreported associations as well. Indeed, ATSDR acknowledged more than 200 tests of exposure/disease associations in its assessment of the Endicott population.

Similarly, the finding by Yauck *et al.* (2004) of significant effect modification is not unusual given that main effects were ignored, thereby reducing the model building to a shotgun approach

looking for all possible interactions with exposure. The highly unlikely finding of a 6-fold increase in risk among older women with exposure, despite no overall effect of exposure and a protective effect among younger exposed women (OR: 0.90), is highly suggestive of a chance or spurious result (Yauck *et al.* 2004).

Uncontrolled/residual confounding was also an issue in this literature. This concern was paramount in Goldberg *et al.* (1990), given the strong propensity for exposed subjects to be both Hispanic and lower SES. However, residual confounding was also a concern for both Forand *et al.* (2012) and Bove *et al.* (1995), given that these studies could adjust only for variables available on birth/death certificates. This precluded adjustment for more established risk factors such as maternal diabetes or alcohol consumption. Furthermore, all studies were confounded by coexposures to various chemicals such as benzene, chromium, vinyl chloride, methylene chloride, etc., making it virtually impossible to reliably tease specific effects of TCE out of this chemical mélange.

4. Methodological Concerns with MRL

Ignoring for the moment the data quality issues associated with Johnson *et al.,* discussed above, it appears that EPA used an inappropriate level of conservatism in deriving the RfC for TCE based on that study. In adopting the RfC as its inhalation MRL, ATSDR has failed to acknowledge and address this issue.

In its evaluation of dose-response data from Johnson *et al*. (2003), EPA used the Agency's Benchmark Dose Software (BMDS) to calculate a BMDL (Benchmark Dose Low).[21] In order to calculate the BMDL, a Benchmark Response (BMR) has to be selected and, according to the EPA IRIS document, "a 1% extra risk of a pup having a heart malformation was used as the BMR because of the severity of the effect, since, for example, some of the types of malformations observed could have been fatal."

The following language from the BMDS training module for nested benchmark dose modeling, which was the approach used by EPA to evaluate Johnson *et al.*, indicates that a 1% BMR may be inappropriately conservative for a developmental study:

> "Although, an extra risk of 10% is usually used as a default BMR for regular dichotomous data, an extra risk of 5% is used to approximate the NOAEL for many

[21] Environmental Protection Agency (EPA), Benchmark Dose Technical Guidance, Risk Assessment Forum, Environmental Protection Agency, Washington, DC 20460: EPA/100/R-12/001 (June 2012).

> developmental studies. A developmental study will provide extra statistical power because the sample size has increased by use of pups as the observation subject. Therefore, a 5% response increase in risk in those pups actually corresponds to a NOAEL from a regular developmental study as shown by Allen *et al*. 1994. This is why for nested data from a developmental study, we may chose 5% instead of 10% as our BMR."[22]

This subjective decision by EPA resulted in a BMDL of 0.021 mg/kg/day in drinking water, rather than 0.108 mg/kg/day in drinking water had the agency used the recommended BMR of 5%.[23] As the calculated BMDL formed the basis for EPA's development of the RfC, that decision has a trickle-down impact on the inhalation MRLs proposed for trichloroethylene in the draft Toxicological Profile. It should be noted that EPA's dose-response evaluation of Johnson *et al.* was also used in development of the RfD selected by ATSDR as the basis for its proposed oral MRL.

Another concern is that, although suitable inhalation studies exist, ATSDR has followed EPA's lead in basing inhalation criteria on oral studies. In the draft TCE Update, ATSDR proposes to adopt EPA's chronic RfC to serve as the chronic and intermediate inhalation MRL. As five of the six candidate studies selected by EPA for development of the RfC are actually oral studies, ATSDR should conduct an evaluation of the appropriateness of oral to inhalation route-to-route extrapolation, as well as the suitability of study selection.

Although this comment is a criticism of ATSDR's proposed approach, the underlying criticism is focused on EPA's derivation of the RfC for trichloroethylene. In Table 5-24 of its IRIS document, EPA presents 18 candidate RfC values (comprising p-cRfCs based on PBPK modeled internal dose metrics and cRfCs based on applied dose). The values in Table 5-24 reflect the lowest candidate RfCs for six different effect domains (*i.e*., neurologic, kidney, liver, immunologic, reproductive and developmental). Although, ultimately, the RfC was based on only two studies [*i.e*., Keil *et al*. (2009)[24] and Johnson *et al*. (2003)], the evaluation process initially considered six critical effects/studies. Interestingly, five of the six selected candidate RfCs were actually derived from oral studies and were based on PBPK modeled internal dose metrics. The sixth candidate RfC was based

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[22] *See* http://www.epa.gov/ncea/bmds/training/captivate/nested-benchmark-dose-models/nested-benchmark-dose-models.html.

[23] *See* Table F-6 in IRIS Assessment.

[24] Keil *et al.*, Assessment of trichloroethylene (TCE) exposure in murine strains generically-prone and non-prone to develop autoimmune disease, J Env Sci Hlth Part A. 44: 443-453 (2009).

on an inhalation study (Woolhiser *et al*. 2006).[25] The range of the six candidate RfCs, as selected by EPA, spans 3,000-fold (from 0.0003 to 0.9 ppm).

The derivation and consideration of a range of candidate RfCs to develop an RfC is a sound approach, however, choosing the lowest range of RfCs, without a sufficient weight-of-evidence evaluation of the RfCs in that range, and including only one inhalation study, raises serious issues. Several of the identified problems include: (i) the fact that the significance of the observed effect in the Woolhiser inhalation study (*i.e*., increased kidney weight) was weak and based on a small sample size; (ii) uncertainty in the oral to inhalation route-to-route extrapolation for the five other RfCs (p-cRfCs) in the range; and (iii) uncertainty in the PBPK model reflecting a higher DCVC bioactivation in humans than in rodents (potentially impacting PBPK modeling for three of the p-cRfCs).

Although we did not conduct an evaluation of the quality of the studies used by EPA to derive the candidate RfCs in Table 5-24, an examination of the table suggests that consideration of an alternate RfC range might be appropriate. There are six inhalation studies that represent another relatively narrow range of cRfCs (from 0.013 to 0.12 ppm), two representing reproductive effects (0.013 and 0.017 ppm), one representing a neurological effect (0.016 ppm), one representing a developmental effect (0.062 ppm), and two representing immunological effects (0.11 and 0.12 ppm). In fact, toxicity in the inhalation studies is largely seen at higher doses, at least on an applied-dose basis, compared to the doses causing toxicity in oral studies. This casts doubt on the appropriateness of the PBPK-modeled route-to-route extrapolations upon which EPA's RfC relies.

B. Carcinogenicity

As in the case of developmental effects, the discussion of carcinogenicity in the TCE Update suffers from an inappropriate reliance on EPA's IRIS Assessment. The IRIS Assessment classifies TCE as "Carcinogenic to Humans." It fails to discuss (or even to recognize) that such classification is inconsistent with a recent report by the National Academy of Sciences.[26] Thus, 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

[25] Woolhiser *et al.*, Trichloroethylene (TCE): Immunotoxicity potential in CD rats following a 4-week vapor inhalation exposure. Midland, MI: Unpublished Report (2006). Subsequently published as: Boverhof *et al.,* Assessment of the immunotoxic potential of trichloroethylene and perchloroethylene in rats following inhalation exposure. J Immunotoxicol 10(3): 311-320 (2013).

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

and 1980s. We briefly address below how the epidemiological data on TCE do not meet the threshold for classification as "Carcinogenic to Humans."

1. Guidelines for Carcinogen Risk Assessment

EPA's 2005 Guidelines for Carcinogen Risk Assessment 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.[27]

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

[27] 70 Fed. Reg. 17766-817 (April 7, 2005).

> 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."

2. Application of the Guidelines to TCE

In considering the data in the context of applying the "Carcinogenic to Humans" descriptor, one first considers the weight of the epidemiological evidence. We judge the epidemiologic evidence to be 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.[28] 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.[29] Both the EPA meta-analysis and the Kelsh *et al.* meta-analysis of the TCE kidney cancer epidemiologic literature produced similar summary results.

[28] 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).

[29] 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).

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.

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-reporting 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 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.[30] An established dose-response trend is one of the more important factors when making assessments of causation in epidemiologic literature. 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.

The criteria that have to 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 simply was not done.

Of the four primary tissues that EPA evaluated 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.[31] 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."

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[30] 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).

[31] And that bioassay, as discussed below, is from a laboratory whose studies EPA is reviewing and has placed on hold other ongoing IRIS assessments as a result.

Finally, the TCE Update alludes to shortcomings associated with several of the studies described in the Health Effects section yet fails to provide a further discussion of those shortcomings. For example, in describing potential renal effects on page 62, the Update states that "[m]ale rats, but not female rats, that were exposed to 300 ppm trichloroethylene in a chronic study showed renal tubular meganucleocytosis (Maltoni *et al*. 1986, 1988). The study authors considered that this histopathological change might be a precancerous lesion; however, no kidney tumors were observed. The serious shortcomings of these chronic studies are discussed in Section 3.2.1.7." Despite the controversy surrounding the Maltoni studies, there is no elaboration provided in Section 3.2.1.7. Given the importance of these studies to EPA's determination that TCE is a renal carcinogen, the TCE Update should provide a more balanced evaluation of their quality.

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 Ramazzini Foundation in 1990-1992. The NTP review team found significant discrepancies in the interpretation of the reported results and concluded that an independent review of the pathology data and specimens was necessary to address the serious discrepancies identified in the reported results of the methanol study. 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 Practice. They found that advanced autolysis in some tissues "occasionally precluded diagnosis by the NTP pathologists."

The findings of the NTP review team had implications beyond the methanol study. As a result of the review, EPA immediately identified six assessments that relied on Ramazzini data, announced that it was 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. Regrettably, EPA did not announce similar action with regard to the TCE IRIS Assessment ongoing at the time. Yet the TCE IRIS Assessment did rely substantially on the Ramazzini data[32] for its conclusion that TCE is a kidney carcinogen, the endpoint that drives the cancer risk assessment.

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

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[32] Maltoni, C *et al*., Experimental research on trichloroethylene carcinogenesis (Vol. 5), Princeton, NJ: Princeton Scientific Publishing (1986); Maltoni, C et al., Long-term carcinogenicity bioassays on trichloroethylene administered by inhalation to Sprague-Dawley rats and Swiss and B6C3F1 mice, Ann N Y Acad Sci 534: 316-342 (1988).

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

The IRIS Assessment states that "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, 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.[33] 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 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 of EPA's very different conclusion. Although the 2009 Camp Lejeune study was already published, and indeed is cited in the references, there is no mention of it in the text of the IRIS 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

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

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 the flaws in the IRIS Assessment, and the very different conclusion reached by the Academy in its Camp Lejeune report on the same body of data, we urge ATSDR to make its own assessment of the evidence relevant to the classification of TCE as a carcinogen.

C. General Comments

ATSDR should utilize emerging tools for systematic review in development of its Toxicological Profiles. Systematic review methodologies provide objectivity and transparency to the process of collecting and evaluating scientific data; however, it does not appear that ATSDR has utilized systematic review in the development of the TCE Update. In fact, nowhere in the document is 'systematic review' even acknowledged. Although well established in clinical medicine,[34] systematic review has recently become popular in the evaluation of environmental health data which can typically involve human, animal and mechanistic data. In its recent evaluation of EPA's IRIS process, the National Research Council made a series of recommendations for conducting a systematic review.[35] Many of those recommendations mirror approaches contained in systematic review methodology developed by NTP's Office of Health Assessment and Translation (OHAT).[36] In its recommendations to EPA on overall evidence integration, the NRC states that "if EPA does move to a structured evidence-integration process, it should combine resources with NTP to leverage the intellectual resources and scientific experience in both organizations."

[34] Institute of Medicine (IOM), Finding what works in health care: standards for systematic review, National Academies Press, Washington, DC (2011).

[35] National Research Council (NRC), Review of EPA's Integrated Risk Information System (IRIS) Process, National Academies Press, Washington, DC (2014).

[36] National Toxicology Program (NTP), Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration, National Institute of Environmental Health Sciences, Office of Health Assessment and Translation (OHAT), Research Triangle Park, NC (2015).

In a recent publication, ATSDR indicated that the agency has "entered into a collaborative effort with NTP OHAT to implement [systematic review] for updating and evaluating the scientific literature used to develop ATSDR Toxicological Profiles and Addenda."[37] As ATSDR has already used systematic review in at least one other profile/addendum,[38] it would be our recommendation that the TCE Update be revised to demonstrate, at a minimum, that it conforms with the NTP/OHAT systematic review paradigm.

Several key components of the recommended systematic review process are common to both the NRC and NTP approaches:

1. Problem Formulation and Protocol Development

NRC recommends a three-step process for problem formulation:

- Utilize a trained information specialist to conduct a broad literature search to identify possible health outcomes [Not to be confused with the comprehensive literature search conducted as part of evidence identification. No results are extracted or summarized during this stage];

- Construct a table to guide the formulation of specific questions that would be the subject of the systematic review [Organized by lines of evidence and various health outcomes to investigate]; and

- Determine from the table which outcomes warrant a systematic review and how to define the systematic review question(s). [The decision process should be documented and reviewed by relevant experts].

After the systematic review questions are defined, protocols for conducting the reviews to address the questions need to be developed. According to the NRC, the protocol "makes the methods and the process of the review transparent, can provide the opportunity for peer review of the methods, and stands as a record of the review. It also minimizes bias in evidence identification by ensuring that inclusion of studies in the review does not depend on the studies' findings. Any changes made after the protocol is in place should be transparent, and the rationale for each should

[37] See: Murray HE and Thayer KA, Implementing systematic review in toxicological profiles: ATSDR and NIEHS/NTP collaboration, J Env Hlth 76(8):34-35 (2014).

[38] See: ATSDR, Addendum to the toxicological profile for titanium tetrachloride (2014).

be stated." The protocol is developed *a priori* and forms the basis for scientific judgments throughout the evaluation. Protocols should be included as appendices to the final document.

No documentation is provided in the TCE Update to indicate that ATSDR has developed or has utilized a protocol which delineates the steps *a priori* that were followed in its review. It appears that the agency has relied heavily on the EPA IRIS Assessment rather than conducting its own systematic review of the available literature. Unfortunately, the IRIS Assessment was also conducted without the benefit of systematic review.

2. Evidence Identification

Searching for and identifying evidence are critical steps in conducting a systematic review and should utilize a standardized search strategy and reporting format. This should include a line-by-line description of the search strategy and statement of the inclusion/exclusion criteria for studies developed in collaboration with an information specialist trained in systematic review methodologies. The NRC encourages the use of at least two reviewers, working independently, to screen and select studies using standardized procedures and forms.

Without benefit of a protocol, there was no information provided in the TCE Update describing either the search strategy used or the inclusion/exclusion criteria. Presumably a selection process was utilized; however, there can be little confidence that it was appropriate given the lack of detail or transparency.

3. Evidence Evaluation

Once studies are identified, relevant data are extracted and summarized using standardized approaches and evaluating human, animal and *in-vitro* data separately. Under the NTP/OHAT approach, this activity is carried out by a two-person team, one performing the data extraction and the other quality assurance. Both the NRC and OHAT recommend the incorporation of risk-of-bias assessments for each outcome of interest on each individual selected reference. More specifically, the NRC recommends that "a risk-of-bias assessment should be conducted on studies that are used . . . as primary data sources for the hazard identification and dose-response assessment." Although there are a number of approaches available for assessing risk-of-bias, there is agreement that both the assessment approach and the results should be fully documented. In addition to evaluation of risk-of-bias, the evidence evaluation step should result in a judgment of the quality of both the individual studies, using an approach such as the Klimisch scoring system (Klimisch *et al.* 1997)[39],

[39] Klimisch, H, *et al*., A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. Reg Tox Pharm 25: 1-5 (1997).

and the overall body of evidence for each effect outcome. This can be accomplished through the use of confidence ratings. Although this process can be somewhat subjective, the advantage of the systematic review process is that it provides a framework to document and justify the decisions made.

It is perhaps in the area of evidence evaluation that the lack of a systematic review approach is most apparent in the TCE Update. Risk-of-bias assessments were not undertaken and the results of individual studies were included with little apparent consideration as to their overall quality. Notably, we have identified above several data quality concerns that should not be present in key studies used to derive MRLs.

4. Evidence Integration for Hazard Identification

There are several approaches available for evidence integration. A qualitative approach, utilizing working groups to achieve consensus on a chemical's toxicity, is used by the International Agency for Research on Cancer (IARC). Several quantitative options are also available, including meta-analysis, probabilistic bias analysis and Bayesian analysis. It is essential that the protocol describe the specific approach to evidence integration that will be used in the evaluation. As part of its review of EPA's IRIS process, the NRC recommended the development of templates for structured narrative justifications of the evidence-integration process and the hazard conclusions reached.

Although the TCE Update does present summary tables of data from individual studies, there was really minimal integration of information from different evidence streams in developing conclusions on TCE hazard. Health effects evaluations conducted following systematic review procedures have the potential to improve communication and transparency about hazard identification conclusions through documentation of the sources of data considered, the methods used to assess quality as well as the scientific judgments made during evidence integration.

D. Conclusion

We urge ATSDR to take these comments into account and to substantially revise the TCE Update before it is released as a final document. In particular, it is important that the MRLs be based on reproducible scientific data and be developed in a transparent manner that follows ATSDR guidance.

Respectfully submitted,

Faye Graul
Executive Director

Enclosures

HSIA
halogenated
solvents
industry
alliance, inc.

November 5, 2013

Information Quality Guidelines Staff
Mail Code 2811R
Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

Re: Request for Correction -- IRIS Assessment for Trichloroethylene

Dear Sir or Madam:

This request for the correction of information ("Request for Correction") is submitted under the Information Quality Act ("IQA")[1] and the implementing guidelines issued, respectively, by the Office of Management and Budget ("OMB")[2] and the Environmental Protection Agency ("EPA"),[3] on behalf of the Halogenated Solvents Industry Alliance, Inc. ("HSIA"). HSIA represents producers of trichloroethylene ("TCE") and other chlorinated solvents. As discussed below, HSIA seeks the correction of information disseminated in an EPA document, "Toxicological Review of Trichloroethylene (CAS No. 79-01-6) in Support of Summary Information on the Integrated Risk Information System (IRIS)."[4]

Information for Correction

The IRIS Assessment contains a reference concentration ("RfC") of 0.0004 ppm (0.4 ppb or 2 $\mu g/m^3$) and a reference dose ("RfD") of 0.0005 mg/kg/day for TCE. These are values that are considered by EPA to be protective for all of the candidate critical effects. EPA's derivation of the RfC/RfD for TCE is based, in part, on Johnson *et al.*, Threshold of Trichloroethylene

[1] Section 515(a) of the Treasury and General Government Appropriations Act for Fiscal Year 2001, P.L. 106-554; 44 U.S.C. § 3516 (notes).

[2] 67 Fed. Reg. 8452 (Feb. 22, 2002) ("OMB Guidelines").

[3] EPA, Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity, of Information Disseminated by the Environmental Protection Agency, EPA/260R-02-008 (October 2002) ("EPA Guidelines").

[4] EPA/635/R-09/011F (September 2011) (hereafter "IRIS Assessment").

1530 Wilson Boulevard, Suite 690 • Arlington, VA 22209
703-875-0683 • Fax 703-875-0675

Contamination in Maternal Drinking Waters Affecting Fetal Heart Development in the Rat, Environmental Health Perspectives 111: 289-92 (March 2003). It is one of the few studies cited in support of both the RfC and the RfD.

HSIA submits that EPA's exclusive reliance on a single inappropriate and unreproducible study, as well as an RfC/RfD based on that study, constitutes erroneous information, the dissemination of which contravenes the IQA. After reviewing the IQA criteria, this Request describes how Johnson *et al.* (2003) fails to meet those criteria.

An important indicator that EPA's RfC/RfD fail to meet the standard of the IQA appears in a recent article by the authors of the IRIS assessment, which states:

> "Interpretation of these data has been controversial because many of the studies are limited by small numbers of cases, insufficient exposure characterization, chemical coexposures, and other methodological deficiencies. In addition, these studies aggregate a broad array of TCE-associated cardiac malformations and have inadequate statistical power to identify any particular kind(s) of defect that may be more susceptible to induction by TCE. . . . The approaches and conclusions of the U.S. EPA's analyses (U.S. EPA 2011d) are consistent with the recommendations of the NRC (2006)."[5]

Reference to the National Research Council report cited reveals a very different understanding of the studies in question, one that is quite inconsistent with those studies being the basis for EPA's RfC/RfD:

> "Although some rodent studies have shown effects (Smith et al. 1989, 1992; Dawson et al. 1993; Epstein et al. 1992), other studies have not (NTP 1985, 1986b; Fisher et al. 2001), suggesting either methodological or strain differences. The committee noted that the *rodent studies showing trichloroethylene-induced cardiac teratogenesis at low doses were performed by investigators from a single institution. Also noted were the unusually flat dose-response curves in the low-dose studies from these investigators. For example, the incidences of heart malformations at trichloroethylene concentrations of 1.5 and 1,100 ppm (almost three orders of magnitude greater) were 8.2% to 9.2% (prepregnancy and during pregnancy) to 10.4% (during pregnancy only) (Dawson et al. 1993). The same pattern occurred*

[5] Chiu, W., *et al.,* Human Health Effects of Trichloroethylene: Key Findings and Scientific Issues, Environ Health Perspect. 121(3): 303–311 (2013).

with dichloroethylene. Thus, the animal data are inconsistent, and the apparent species differences have not been addressed."[6]

EPA's IQA Guidelines -- the "Objectivity" and "Utility" Criteria

EPA's IQA Guidelines "contain EPA's policy and procedural guidance for ensuring and maximizing the quality of information [it] disseminate[s]" as well as specifically describing "new mechanisms to enable affected persons to seek and obtain corrections from EPA regarding disseminated information that they believe does not comply with EPA or OMB guidelines."[7] Accordingly, the Guidelines expressly set out a pathway for seeking correction of information disseminated by EPA that falls short of the "basic standard of quality, including objectivity, utility, and integrity," contained in the EPA Guidelines and those issued by OMB.[8]

Both the "objectivity" and "utility" criteria are implicated by EPA's reliance on Johnson *et al.* as a basis for its TCE RfC/RfD. As does OMB, EPA considers the "objectivity" inquiry for IQA purposes to be "whether the disseminated information is being presented in an accurate, clear, complete, and unbiased manner, and as a matter of substance, is accurate, reliable, and unbiased." The "utility" criterion refers to "the usefulness of the information to the intended users."[9]

For giving content to the concept of ensuring the "objectivity" of "influential scientific risk assessment information," EPA, in developing the Guidelines, adapted the quality principles in the Safe Drinking Water Act Amendments ("SDWA") of 1996 as follows:

> (A) The substance of the information is accurate, reliable and unbiased. This involves the use of:
>
> > (i) the best available science and supporting studies conducted in accordance with sound and objective scientific practices, including, when available, peer reviewed science and supporting studies; and

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[6] National Academies Press, Assessing the Human Health Risks of Trichloroethylene: Key Scientific Issues (2006), at 211 (emphasis added).

[7] EPA Guidelines at 3.

[8] *Id.*

[9] *Id.* at 15; OMB Guidelines § V.2, V.3, 67 Fed. Reg. at 8459.

(ii) data collected by accepted methods or best available methods (if the reliability of the method and the nature of the decision justifies the use of the data).

(B) The presentation of information on human health, safety, or environmental risks, consistent with the purpose of the information, is comprehensive, informative, and understandable.[10]

IQA Guidelines -- "Influential Scientific Information"

EPA recognizes that the "influential scientific, financial, or statistical information" it disseminates "should meet a higher standard of quality."[11] Under the EPA Guidelines, information is considered influential if "the Agency can reasonably determine that dissemination of the information will have or does have a clear and substantial impact (*i.e.*, potential change or effect) on important public policies or private sector decisions."[12] More specifically, information is "influential" if it is "disseminated in support of top Agency action (*i.e.*, rules . . .) [or] issues that . . . are highly controversial."[13]

Here, in at least one instance the RfC/RfD values supported by Johnson *et al.* have been the basis for an EPA rule, an agency action which unequivocally has the force and effect of law. Conditional Exclusions from Solid Waste and Hazardous Waste for Solvent-Contaminated Wipes, 78 Fed. Reg. 46448 (July 31, 2013), is a final rule that modifies EPA's hazardous waste management regulations for solvent-contaminated wipes under the Resource Conservation and Recovery Act. The rule revises the definition of hazardous waste to conditionally exclude solvent-contaminated wipes that are disposed, but provides that solvent-contaminated disposable wipes that are hazardous waste due to the presence of TCE are not eligible for the exclusion and thus are subject to all applicable hazardous waste regulations.

In excluding TCE-contaminated wipes, EPA explained that it relied upon updated reference values from the TCE IRIS assessment, described as a "scientific report[] that provide[s] information on chemical hazards as well as quantitative dose-response information, on EPA's Integrated Risk

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[10] EPA Guidelines at 22.

[11] *Id.* at 19.

[12] *Id.*

[13] *Id.* at 20.

Information System (IRIS)," noting that "the final health assessment for trichloroethylene was posted on IRIS on September 28, 2011 (http://www.epa.gov/iris/subst/0199.htm)."[14] EPA stated:

> "[U]sing the updated reference values for trichloroethylene in our 2012 final risk analysis resulted in an *increase* in projected risks, such that the estimated landfill solvent loadings exceeded the risk-based mass loading limit with the ratio of the ELLR to the RB-MLL calculated at 1.4. These revisions to the risk analysis are summarized in addendums to the 2009 risk analysis document ("Impact of Revised Health Benchmarks on Solvent Wipes Risk-Based Mass Loading Limits (RB-MLLs)," April 2012) and the revised document comparing ELLRs to RB-MLLs ("F001-F005 Solvent-Contaminated Wipes and Laundry Sludge: Comparison of Landfill Loading Calculations and Risk-Based Mass Loading Limits," revised April 2012).
>
> "Therefore, based on the 2012 final risk analysis using the updated reference values, wipes contaminated with trichloroethylene (i.e., wipes contaminated with trichloroethylene solvent itself or in F-listed solvent blends) are ineligible for the conditional exclusion for disposable wipes. That is, the updated results of our 2012 final risk analysis indicate that trichloroethylene may present a substantial hazard to human health, even if disposed in a composite-lined unit."[15]

For the avoidance of doubt, reproduced below is Table 1 of *Impact of Revised Health Benchmarks on Solvent Wipes Risk-Based Mass Loading Limits (RB-MLLs)* (April 2012) from the rulemaking docket:[16]

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[14] 78 Fed. Reg. at 46453.

[15] *Id.* at 46453-46454. EPA further noted that: "Use of the updated reference values ensures that the final rule incorporates the most recent scientific data available and will prevent potential risks from disposal of wipes contaminated with trichloroethylene. The updating of the reference values does not impact our overall assessment methodology, which was externally peer reviewed and published for public comment in a 2009 NODA. The IRIS assessment development process includes an internal Agency review, two opportunities for science consultation and discussion with other federal agencies, a public hearing, public review and comment, and an independent external peer review, all of which is part of the official public record. In addition to this rigorous review process, trichloroethylene was reviewed by the EPA's Science Advisory Board. . . . Because both the risk analysis methodology and the IRIS assessments have been peer and publicly reviewed separately, it is appropriate to use the updated IRIS reference values in evaluating which solvents should be included in the conditional exclusion for solvent-contaminated wipes.

[16] EPA-HQ-RCRA-2003-0004-___, Table 1.

Table 1. Comparison of Benchmarks applied in 2009 Analysis to Revised Benchmarks[a]

Constituent	CASRN	Source	RfD (mg/kg-d)		RfC (mg/m^3)		CSFo (per mg/kg-d)		URF (per µg/m^3)	
			Value	Ref	Value	Ref	Value	Ref	Value	Ref
Tetrachloro - ethylene	127-18-4	2009 Value	1.0E-02	IRIS	3.0E-01	ATSDR	5.4E-01	CalEPA[b]	5.9E-06 7.1E-7[b]	CalEPA[b]
		Current IRIS Value	6.0E-03	IRIS(r)	4.0E-02	IRIS(r)	2.1E-03	IRIS(r)	2.6E-07	IRIS(r)
Trichloro - ethylene	79-01-6	2009 Value	none	NA	6.0E-01	CalEPA	1.3E-02	CalEPA	2.0E-06	CalEPA
		Current IRIS Value	*5.0E-04*	IRIS(r)	*2.0E-03*	IRIS(r)	4.6E-02	IRIS(r)	4.1E-06	IRIS(r)

[a] IRIS(r): Final revised IRIS values. (September 2011, February 2012)

U.S. EPA (Environmental Protection Agency). 2011. Integrated Risk Information System (IRIS) for Trichloroethylene (CASRN 79-01-6). Washington, DC: National Center for Environmental Assessment, Office of Research and Development. http://www.epa.gov/iris/subst/0199.htm.

U.S. EPA (Environmental Protection Agency). 2012. Integrated Risk Information System (IRIS) for Tetrachloroethylene (Perchloroethylene) (CASRN 127-18-4). Washington, DC: National Center for Environmental Assessment, Office of Research and Development. http://www.epa.gov/iris/subst/0106.htm.

The italicized values are the RfC/RfDs (*i.e.*, the noncancer values) for TCE based on Johnson *et al.* The second document from the docket, *F001-F005 Solvent-Contaminated Wipes and Laundry Sludge: Comparison of Landfill Loading Calculations and Risk-Based Mass Loading Limits* (April 2012), makes clear that "[f]or trichloroethylene, the noncancer risks drove the exceedance" of the ratio of the Estimated Landfill Loadings Rates to the Risk-Based Mass Loading Limit and hence the ineligibility of TCE-contaminated wipes for the exclusion.[17]

[17] EPA-HQ-RCRA-2003-0004-___, at p. 4. Put another way, "[i]n some cases, the noncancer risks yielded lower RB-MLLs such that the noncancer risks became the limiting factor, e.g., as noted previously for trichloroethylene." *Id.*, at p.5.

Moreover, the IRIS Assessment clearly involves "controversial scientific . . . issues," a specific class of "influential information" that "should adhere to a rigorous standard of quality."[18] Within EPA, there is a significant ongoing dispute as to whether and how the RfC/RfD derived from Johnson *et al.* should be the basis for a short-term TCE exposure limit at Superfund sites.[19] Thus, the proper interpretation and use of this study in risk assessment is a question of the highest priority to EPA's Superfund program.

IQA Guidelines -- "Reproducibility" Criterion for "Influential Scientific Information"

For influential scientific information EPA requires a "higher degree of transparency about data and methods" to "facilitate the reproducibility of such information by qualified third parties." The Guidelines further state: "For disseminated influential original and supporting data, EPA intends to ensure reproducibility according to commonly accepted scientific, financial, or statistical standards" and "It is important that analytic results for influential information have a higher degree of transparency regarding . . . the statistical procedures employed."[20] "Reproducibility" means that the information is capable of being substantially reproduced, *i.e.*, "that independent analysis of the original or supporting data using identical methods would generate similar analytic results."[21]

Johnson *et al.* (2003) Does Not Meet Objectivity, Utility, or Reproducibilty Criteria

Given the recognized deficiencies of Johnson *et al.* (2003), it should not be the basis for the RfC/RfD. At least two GLP-compliant studies conducted under EPA guidelines to support pesticide registration (40 CFR § 870.3700) and OECD guidelines (414) have been unable to reproduce the effect seen by Johnson *et al.*, as described below.

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[18] *See* EPA Guidelines at 20.

[19] *See, e.g.*, DOD Uses New TSCA Assessment to Criticize Trichloroethylene IRIS Value, Inside EPA (June 3, 2013); Exposure Uncertainties May Hamper EPA Effort To Assess TCE's Risks, Inside EPA (April 25, 2013); Amidst Review, EPA Scientists Defend Finding on TCE's Heart-Defect Risks, Inside EPA (February 15, 2013); Massachusetts Adds to Scrutiny of EPA TCE Risk Assessment's Adequacy, Inside EPA (February 11, 2013); New Jersey Short-Term TCE Limits Add to Growing Array of Approaches, Inside EPA (February 6, 2013); Regions Split Over Short-Term TCE Limit, Highlighting Need for EPA Guide, Region X TCE Guidance, Inside EPA (January 2, 2013).

[20] EPA Guidelines at 20-21.

[21] OMB Guidelines, 67 Fed. Reg. at 8460.

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.[22] 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,[23] and the Arizona studies were also expressly rejected as the basis for minimal risk levels (MRLs) by the Agency for Toxic Substances & Disease Registry (ATSDR).[24] 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.[25] No increase in cardiac malformations was observed in a guideline, GLP-quality study,[26] despite high inhalation doses and techniques capable of detecting most of the malformation types reported by Johnson *et al.*

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[22] Dawson, B, *et al.*, Cardiac teratogenesis of halogenated hydrocarbon-contaminated drinking water, J. Am. Coll. Cardiol. 21: 1466-72 (1993).

[23] 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: 117-47 (2006).

[24] 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." Toxicological Profile for Trichloroethylene Update (September 1997), at 88. More recently, however, following publication by EPA in 2011 of its TCE IRIS Assessment, ATSDR issued an Addendum that bases both chronic and intermediate-duration MRLs on the EPA RfD/RfC values (0.0005 mg/kg/day /0.0004 ppm (2 ug/m^3)), which in turn are based in part on Johnson *et al.* Addendum to Toxicological Profile for Trichloroethylene (January 2013).

[25] Fisher, J, *et al.*, Trichloroethylene, trichloroacetic acid, and dichloroacetic acid: do they affect fetal rat heart development? Int. J. Toxicol. 20: 257-67 (2001).

[26] Carney, E, *et al.*, Developmental toxicity studies in Crl:Cd (SD) rats following inhalation exposure to trichloroethylene and perchloroethylene, Birth Defects Research (Part B) 77: 405–412 (2006).

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.[27]

One of the principal criticisms of Johnson *et al.* is that it employed an inappropriate statistical practice:

> "Johnson *et al.* (2003) provided no rationale for designing their study with a concurrent control five times larger than the treatment groups, which leads us to ask whether the control group reported here is, in fact, a composite of controls from multiple, perhaps five, different studies.. The immediate impact of this large control group is that the very cardiac 'abnormalities' at the 1.5 ppm dose that did not differ significantly from controls in 1993 become statistically significant in 2003."[28]

We are hard pressed to find a better summary of Johnson *et al.* than the following statement by the California Office of Environmental Health Hazard Assessment (OEHHA) rejecting the study as deficient:

> "Johnson et al. (2003) reported a dose-related increased incidence of abnormal hearts in offspring of Sprague Dawley rats treated during pregnancy with 0, 2.5 ppb, 250 ppb, 1.5 ppm, and 1,100 ppm TCE in drinking water (0, 0.00045, 0.048, 0.218, and 128.52 mg/kg-day, respectively). The NOAEL for the Johnson study was reported to be 2.5 ppb (0.00045 mg/kg-day) in this short exposure (22 days) study. The percentage of abnormal hearts in the control group was 2.2 percent, and in the treated groups was 0 percent (low dose), 4.5 percent (mid dose 1), 5.0 percent (mid dose 2), and 10.5 percent (high dose). The number of litters with fetuses with abnormal hearts was 16.4 percent, 0 percent, 44 percent, 38 percent, and 67 percent for the control, low, mid 1, mid 2, and high dose, respectively. The reported NOAEL is separated by 100-fold from the next higher dose level. The data for this study were not used to calculate a public-health protective concentration since a meaningful or interpretable dose-response relationship was not observed. *These results are also not consistent with earlier developmental and reproductive toxicological studies done outside this lab in mice, rats, and rabbits: The other studies did not find adverse effects on fertility*

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[27] "Johnson and Dawson, with their collaborators, are alone in reporting that TCE is a 'specific' cardiac teratogen." Hardin, B, *et al.*, Trichloroethylene and cardiac malformations, Environ. Health Perspect. 112: A607-8 (2004).

[28] Hardin, B, *et al.*, Trichloroethylene and cardiac malformations, Environ. Health Perspect. 112: A607-8 (2004).

or embryonic development, aside from those associated with maternal toxicity (Hardin et al., 2004)."[29]

Moreover, reliance upon an irreproducible study result is a significant scientific deficiency in itself. This particular problem, which is at the heart of this Request for Correction, was illustrated most vividly during a recent EPA-empanelled peer review.[30] The comments of the peer reviewers include the following critique of EPA's reliance on Johnson *et al.*:

> "It is not clear why OPPT relied on the results of the Johnson et al. (2003) study to the exclusion of all other inhalation and oral developmental toxicity studies in rodents and rabbits. If in fact the OPPT is reliant upon only the inhalation data, why is it the Carney et al. (2001), the Schwetz et al. (1975), the Hardin et al. (1981), the Beliles et al. (1980) or the Dorfmueller et al. (1979) study was not used? Why is there no discussion of all of the available developmental toxicity inhalation bioassays in the present analysis?
>
> * * * * *
>
> "As submitted, the exposure parameters appear arbitrary (e.g., 0.5 and 1 hr/day) and may have been selected for sake of convenience. The data upon which conclusions put forward by OPPT on risk for developmental toxicity associated with arts and crafts use of TCE are not reliable. Nearly all developmental toxicity studies with TCE in rodents find no sign of teratogenicity (e.g., Beliles et al., 1980) or find only slight developmental delay (Dormueller et al., 1979). Chiu et al. (2013) cite the NRC (2006) report as verification of their risk assessment for TCE developmental toxicity, but actually the NRC (2006) concluded:
>
> > "Additional studies evaluating the lowest-observed-adverse-effect-level and mode of action for TCE-induced developmental effects are needed to determine the most appropriate species for human modeling."

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[29] California EPA Public Health Goal for Trichloroethylene in Drinking Water (July 2009), at 21 (emphasis added).

[30] Peer Review Meeting for EPA's Draft TSCA Work Plan Chemical Risk Assessment for Trichloroethylene: Degreaser and Arts/Crafts Uses (CASRN: 79-01-6) 1,1,2-Trichloethene (July 9 – August 21, 2013).

"In its present assessment, the OPPT ignored the serious deficiencies already identified in conduct of the Johnson et al. (2003) rat drinking water study upon which the BMD01 was based (Kimmel et al., 2009; Watson et al., 2006) [Attachments 1 and 2]. In their weight-of-evidence assessment, Watson et al. (2006) concluded:

> "...application of Hill's causality guidelines to the collective body of data revealed no indication of a causal link between gestational TCE exposure at environmentally relevant concentrations and congenital heart defects."

"Those conclusions were consistent with Hardin et al. (2005). Perhaps most disturbing of all in US EPA's reliance upon Johnson et al. (2003) as the key study (which for the basis for their lowest non-cancer TCE hazard index and margin of exposure) is the observation by Hardin and associates (2004):

> "Conventional developmental and reproductive toxicology assays in mice, rats and rabbits consistently fail to find adverse effects of TCE on fertility or embryonic development aside from embryo- or fetotoxicity associated with maternal toxicity. Johnson and Dawson, with their collaborators, are alone in reporting that TCE is a "specific" cardiac teratogen."

"One of the fundamental tenants in science is the reliability and reproducibility of results of scientific investigations. In this regard, one of the most damning of the TCE developmental toxicity studies in rats is that by Fisher et al. (2005) who stated:

> "The objective of this study was to orally treat pregnant CDR(CD) Sprague-Dawley rats with large bolus doses of either TCE (500 mg/kg), TCA (300 mg/kg) or DCA (300 mg/kg) once per day on days 6 through 15 of gestation to determine the effectiveness of these materials to induce cardiac defects in the fetus. All-trans-retinoic acid (RA) dissolved in soybean oil was used as a positive control."
>
> "The heart malformation incidence for fetuses in the TCE-, TCA- and DCA-treated dams did not differ from control values on a per fetus or per litter basis. The RA treatment group was significantly higher with 33% of the fetuses displaying heart defects."

"Unfortunately, Johnson et al. (2005) failed to report the source or age of their animals, their husbandry or provide comprehensive historical control data for spontaneous cardiovascular malformations in their colony. The Johnson study with 55 control litters compared to 4 affected litters of 9 treated was apparently conducted over a prolonged period of time (perhaps years); it is possible this was due to the time required to dissect and inspect fresh rodent fetuses by a small academic research group. However, rodent background rates for malformations, anomalies and variants show temporal fluctuations (WHO, 1984) and it is not clear whether the changes reported by Johnson et al. (2005) were due to those fluctuations or to other factors. Surveys of spontaneous rates of terata in rats and other laboratory animals are common particularly in pharmaceutical and contract laboratory safety assessment (e.g., Fritz et al., 1978; Grauwiler, 1969; Palmer, 1972; Perraud, 1976). The World Health Organization (1984) advised:

> "Control values should be collected and permanently recorded. They provide qualitative assurance of the nature of spontaneous malformations that occur in control populations. Such records also monitor the ability of the investigator to detect various subtle structural changes that occur in a variety of organ systems."

"Rates of spontaneous congenital defects in rodents can vary with temperature and housing conditions. For example, depending on the laboratory levocardia and cardiac hypertrophy occur in rats at background rates between 0.8-1.25% (Perraud, 1976). Laboratory conditions can also influence study outcome; for instance, maternal hyperthermia (as a result of ambient elevated temperature or infection) can induce congenital defects (including cardiovascular malformations) in rodents and it acts synergistically with other agents (Aoyama et al., 2002; Edwards, 1986; Zinskin and Morrissey, 2011). Thus while the anatomical observations made by Johnson et al. (2003) may be accurate, in the absence of data on maternal well-being (including body weight gain), study details (including investigator blind evaluations), laboratory conditions, positive controls and historical rates of cardiac terata in the colony it is not possible to discern the reason(s) for the unconventional protocol, the odd dose-response and marked differences between the Johnson et al. (2003) results and those of other groups.

"As noted by previous investigators, the rat fetus is "clearly at risk both to parent TCE and its TCA metabolite" given sufficiently high prenatal TCE exposures that can induce neurobehavioral deficits (Fisher et al., 1999; Taylor et al., 1985), but to focus

on cardiac terata limited to studies in one laboratory that have not been reproduced in other (higher dose) studies and apply the BMD01 with additional default toxicodynamic uncertainty factors appears misleading."[31]

This damning indictment of EPA's reliance on this irreproducible study as the basis for the TCE RfC/RfD by its own external peer reviewers provides strong support for prompt action on this Request for Correction.

Respectfully submitted,

Faye Graul

Faye Graul
Executive Director

Enclosures

[31] http://www.scgcorp.com/tcl2013/prcomments.asp, pp. 56-73. Attachments containing more detailed critiques of Johnson *et al.* are enclosed and are also available via this link.

HSIA
halogenated
solvents
industry
alliance, inc.

September 8, 2014

Information Quality Guidelines Staff
Mail Code 2811R
Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

Re: Request for Correction -- IRIS Assessment for Trichloroethylene (TCE)

Dear Sir or Madam:

On November 5, 2013, HSIA submitted a request for the correction of information ("Request for Correction") under the Information Quality Act ("IQA").[1] HSIA sought the correction of the reference concentration ("RfC") of 0.0004 ppm (0.4 ppb or 2 $\mu g/m^3$) and reference dose ("RfD") of 0.0005 mg/kg/day first disseminated in EPA's "Toxicological Review of Trichloroethylene (CAS No. 79-01-6) in Support of Summary Information on the Integrated Risk Information System (IRIS)."[2] EPA's derivation of the RfC/RfD for TCE was based, in part, on Johnson *et al.*, Threshold of Trichloroethylene Contamination in Maternal Drinking Waters Affecting Fetal Heart Development in the Rat, Environ. Health Perspect. 111: 289-92 (March 2003). More recently, on July 3, 2014, HSIA supplemented its Request for Correction in light of an erratum published earlier this year by Johnson *et al.*[3]

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[1] Section 515(a) of the Treasury and General Government Appropriations Act for Fiscal Year 2001, P.L. 106-554; 44 U.S.C. § 3516 (notes).

[2] EPA/635/R-09/011F (September 2011) ("TCE IRIS Assessment").

[3] Johnson *et al.*, Environ Health Perspect 122: A94 (2014): erratum to Environ Health Perspect 113:A18 (2005), which is an erratum for Johson *et al.*, Threshold of Trichloroethylene Contamination in Maternal Drinking Waters Affecting Fetal Heart Development in the Rat. Environ Health Perspect 111:289–292 (2003). The previously published articles covered by the Johnson *et al.*, 2014 erratum are: Dawson BV, Johnson PD, Goldberg SJ, Ulreich JB, Cardiac Teratogenesis of Halogenated Hydrocarbon-contaminated Drinking Water, J Am Coll Cardiol 21(6):1466–1472 (1993); Johnson PD, Dawson BV, Goldberg SJ., Cardiac Teratogenicity of Trichloroethylene Metabolites, J Am Coll Cardiol 32(2):540–545 (1998); Johnson PD, Dawson BV, Goldberg SJ., A Review: Trichloroethylene Metabolites: Potential Cardiac Teratogens. Environ Health Perspect 106 (Suppl 4):995–999 (1998); Johnson PD, Dawson BV, Goldberg SJ, Mays MZ., Trichloroethylene: Johnson *et al.*'s Response [Letter], Environ Health Perspect 112:A608–A609 (2004).

1530 Wilson Boulevard, Suite 690 • Arlington, VA 22209
703-875-0683 • Fax 703-875-0675

This further supplement is being submitted to bring to your attention further information, published by EPA itself, that supports the Request for Correction. This additional information consists of EPA's own assessment of the predecessor study (which reported some of the TCE data cited) to Johnson *et al.* (2003): Dawson, BV, Johnson, PD, Goldberg, SJ, *et al.* Cardiac Teratogenesis of Halogenated Hydrocarbon-Contaminated Drinking Water, J. Am. Coll. Cardiol. 21:1466–1472 (1993). This EPA assessment is for a different compound, vinylidene chloride (1,1-dichloroethylene).[4] Notably, it has never been revised, and it expressly addresses advice directed to EPA from the peer-review panel for that assessment. The excerpts reproduced below make it clear that EPA has rejected these data as not biologically significant and concluded that they are not suitable to be the basis for an RfC/RfD:

> "No demonstrated exposure-response relationship was found in the Dawson *et al.* (1993) study. A 900-fold increase in exposure did not produce a significant increase in response in any measure of effect. The observed cardiac changes are of questionable biological significance, as there were no biologically significant effects reported on growth and survival in the three generation study (Nitschke *et al.*, 1983). No cardiac effects were reported in a prenatal developmental study (Murray et al., 1979); however, in this study exposure to 1,1-DCE did not occur throughout pregnancy. The pharmacokinetics of 1,1-DCE make it biologically implausible that the observed cardiac changes were causally associated with exposure to 1,1-DCE. The exposures used in Dawson *et al.* (1993) were below the level of saturation of CYP2E1 in the rat liver. Essentially all of the 1,1-DCE administered to the dams would have been metabolized in the liver and would have reacted with GSH or macromolecules in the liver. See the discussion and references in section 3. Therefore, it is extremely unlikely that any significant amount of 1,1-DCE or any toxic metabolite would have been present in the fetal compartment. CYP2E1 is not expressed in fetal liver but begins to be expressed shortly after birth (Cresteil, 1998). EPA is not aware of any information on the expression of CYP2E1 in fetal cardiac tissue. Cardiac tissue, however, is not generally considered to be a tissue with significant potential for metabolism of xenobiotics. For these reasons EPA cannot conclude that the observed cardiac changes were caused by exposure to 1,1-DCE."[5]

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[4]Toxicological Review of 1,1-Dichloroethylene (CAS No. 75-35-4) in Support of Summary Information on the Integrated Risk Information System (IRIS) (EPA/635/R02/002) (June 2002) ("Vinylidene Chloride Assessment").

[5] *Id.*, at 23-24.

"General Question 3: For the RfD and the RfC, have the appropriate studies been chosen as "principal"? The principal study should present the critical effect in the clearest dose response relationship. If not, what other study (or studies) should be chosen and why?

"The Panel unanimously agreed that Quast *et al.* (1983, 1986) were the appropriate studies for the RfC and RfD evaluations. The Panel also discussed the Dawson *et al.* (1993) developmental study, which suggested an increased incidence of cardiac malformations in neonatal rats after exposure of dams to 1,1-DCE in drinking water before mating and throughout gestation. This study was discussed both to assert why the Quast *et al.* (1983, 1986) studies were used and why the panel did not recommend use of the Dawson *et al.* (1993) developmental study as the principal study.

"Although their reasons differed, the panelists unanimously believed that the Dawson *et al.* (1993) developmental toxicity study should not be considered as the principal study or considered to represent a potential developmental hazard from 1,1-DCE exposure. The reasons included concerns for the high positive responses on a litter basis in the controls, the lack of increased response between the two exposures that varied by 900-fold, and quality control issues identified in a 1996 Agency for Toxic Substances and Disease Registry review of other developmental toxicity studies with trichloroethylene (TCE) conducted by these investigators. Quality control issues, including lack of analytical confirmation of the concentrations in the drinking water in the TCE studies, were brought to the attention of the Panel by one panelist on the basis of his participation in an earlier review of these studies. Finally, other studies by Fisher *et al.*, 2001 were cited as failing to replicate developmental cardiac changes with TCE.

"Before the discussion of the deficiencies in the developmental toxicity drinking water studies, no panel member felt that the Dawson *et al.* (1993) study should be used as the principal study. Interestingly, the panelists were against using the Dawson *et al.* (1993) study because it does not provide confidence that the effects were exposure-related and associated with DCE exposures, not because the changes were variations in cardiac morphology."[6]

As a final note, the Vinylidene Chloride Assessment states: "The author provided additional data (letter from B. Dawson, University of Auckland, New Zealand, to R. Benson, U.S. EPA, January 24, 2001) to resolve typographical errors in the exposure information for each group and to clarify the number of affected litters and number of fetuses per litter affected." HSIA has requested such statistical information on these studies from EPA and

[6] *Id.*, at 55-56 (Appendix A (Peer-Review Panel Comments)).

been told that no such information exists. We repeat our request with specific reference to the cited letter.

It appears, however, that the cited Dawson letter did not contain information that would allow calculation of actual malformation incidence of fetuses matched to each treated litter. Rather, the EPA calculations presented in the text of the Vinylidene Chloride Assessment are still based on total numbers of affected fetuses either (i) compared to total number of fetuses in affected litters; or (ii) compared to total number of all fetuses from all litters of a treatment (regardless of whether a litter had a malformation or not). EPA admits this is the case:

> "This statistical analysis was based on total occurrence of affected fetuses. Because the exposure was to the dam and not to individual fetuses, a nested statistical analysis is preferred. Such an analysis takes into account the correlation among fetuses within a litter and the possible nesting of effects within litters. This analysis has not been conducted because all the necessary data are not available."[7]

The foregoing quotation is an important EPA admission regarding the key deficiency in the ability to calculate a per litter incidence of malformations, and particularly states why it is important (a per litter incidence accounts for possible nesting effects within litters). This critical admission is not found in the TCE IRIS Assessment that is the subject of this Request for Correction.

We respectfully request EPA's careful consideration of these additional points as it reviews our Request for Correction.

Very truly yours,

Faye Graul /WCN

Faye Graul
Executive Director

[7] *Id.*, at 23.

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).

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