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]

[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).

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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.