HSIA
halogenated
solvents
industry
alliance, inc.

June 17, 2015

Information Quality Guidelines Processing Staff
Mail Code 2811A
Environmental Protection Agency
1200 Pennsylvania Ave., NW
Washington, DC 20460

Re: Request for Reconsideration/#14001

Dear Sirs:

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 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 trichloroethylene ("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 in 2014 by Johnson *et al.*[3] Thereafter, on September 8, 2014, HSIA

[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 Johnson *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).

submitted additional information in support of the Request for Correction. This additional information consisted of EPA's own assessment of the predecessor study (which reported some of the TCE data cited) to Johnson *et al.* (2003).[4] In this EPA assessment for a different compound, vinylidene chloride (1,1-dichloroethylene),[5] EPA rejected these data as not biologically significant and concluded that they were *not* suitable to be the basis for an RfC/RfD.

On March 19, 2015, under the signature of Acting Assistant Administrator Lek Kadeli, EPA denied the HSIA Request for Correction ("EPA Denial"). For the reasons discussed below, HSIA disagrees with this EPA decision and requests reconsideration. Specifically, HSIA recommends that the RfC/RfD for TCE be based on an endpoint other than cardiac malformations.

## I. Peer Review

The EPA Denial relies heavily on the external peer review of the draft TCE IRIS Assessment by the EPA Science Advisory Board ("SAB"), noting that HSIA made presentations at five TCE meetings and made 14 presentations in all. HSIA supports independent peer review. In this case, however, there are two serious problems with EPA's reliance on the SAB review as ensuring quality assurance. First, the SAB review was influenced by the inappropriate and improper participation by a scientist with a direct interest in the outcome, indeed, a co-author of some of the research under consideration. Second, the SAB review of the TCE IRIS Assessment was only the second of three external peer reviews of the specific question of whether the Arizona studies reported by Johnson, Dawson and co-authors were of good enough quality to warrant EPA reliance: the other two peer reviews determined quite conclusively that they *were not*.

### A. The SAB Review Was Tainted by the Active Participation of a Conflicted Member

The SAB panel made specific recommendations regarding the studies to be given greatest emphasis in the calculation of the RfD and the RfC. It advised EPA to give priority to three studies for deriving the RfC and RfD, most particularly Johnson *et al.* (2003) (fetal heart malformations in rats). It is the reliance on this and supporting studies from the same laboratory that raises concerns regarding the impartiality and dispassionate judgment of a member of the panel.

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[4] Dawson, BV, Johnson, PD, Goldberg, SJ, *et al.*, Cardiac Teratogenesis of Halogenated Hydrocarbon-Contaminated Drinking Water, J. Am. Coll. Cardiol. 21:1466–1472 (1993).

[5] 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").

The Overview of the SAB Panel Formation Process states: "If a conflict exists between a panel candidate's private financial interests and activities and public responsibilities as a panel member, or even if there is the appearance of partiality, as defined by federal ethics regulations, the SAB Staff will, as a rule, seek to obtain the needed expertise from another individual."[6] Pursuant to the EPA's Peer Review Handbook (3rd Edition), "each advisory committee member or peer reviewer should be evaluated to ensure that an appearance of lack of impartiality does not preclude their participation."[7]

The draft TCE Assessment clearly was prepared under EPA's IRIS program. Consequently, the peer review of the draft assessment is subject to EPA's NCEA Policy and Procedures for Conducting IRIS Peer Reviews.[8] Under these procedures, a recertification of a peer-review panelist may be requested to determine if there were any changes to the information they previously disclosed that could create either an actual conflict of interest or an appearance of bias or lack of impartiality during the period of performance. EPA may be informed about a potential emerging conflict of interest situation, including an appearance of bias or lack of impartiality, by a person or organization external to EPA. HSIA did so inform EPA, by letter dated December 10, 2010 to Honorable Paul T. Anastas, Ph.D., Assistant Administrator, and Vanessa Vu, Ph.D., Director, EPA Science Advisory Board Staff.

Most importantly, the Office of Management and Budget ("OMB") Final Information Quality Bulletin for Peer Review states that "agencies shall adopt or adapt the NAS policy for committee selection with respect to evaluating conflicts of interest" concerning non-federal employees. The National Academy of Sciences ("NAS") Policy on Committee Composition and Balance and Conflicts of Interest for Committees Used in the Development of Reports states that "an individual should not serve as a member of a committee with respect to an activity in which a critical review and evaluation of the individual's own work, or that of his or her immediate employer, is the central purpose of the activity, because that would constitute a conflict of interest, although such an individual may provide relevant information to the program activity."[9]

The conduct at issue here is the active participation of Dr. Ornella Selmin in the discussion of the weight to be given a program of *in vivo* and *in vitro* experiments carried out over two decades at the University of Arizona on the relationship between TCE exposure and

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[6] EPA, Overview of the Panel Formation Process at the Environmental Protection Agency Science Advisory Board. Office of the Administrator, Washington DC (2002) (EPA SAB-EC-02-010), p. 9.

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

[8] EPA, NCEA Policy and Procedures for Conducting IRIS Peer Reviews, Office of Research and Development, Washington, DC (2009).

[9] Office of Management and Budget, Final Information Quality Bulletin for Peer Review, Executive Office of the President, Washington, DC (2004).

cardiac malformations. Dr. Selmin is a lead or co-author on a number of papers reporting these results,[10] and has co-authored papers with Dr. Paula Johnson, lead author of the most important and highly criticized of these studies.

As noted in the Request for Correction, "Johnson and Dawson, with their collaborators, are alone in reporting that TCE is a 'specific' cardiac teratogen,"[11] and Dr. Selmin was directly involved in this research program. At various stages in the SAB panel discussions, Dr. Selmin indicated her support for Johnson *et al.* (2003) and expressed her view that recent mechanistic studies made those findings more robust. For example, on May 11, 2010, during the discussions on Charge Question 3, Dr. Selmin indicated her support for EPA's description of the studies relating to cardiac malformations (and their admitted shortcomings) but then indicated that new studies on mechanism of action make the Johnson *et al.* (2003) findings more robust. This theme was repeated during discussion of Charge Question 8 – derivation of RfC and RfD. During the summary discussions of Charge Question 3, Dr. Selmin proposed that EPA should include recent publications to support conclusions based on Johnson *et al.* (2003): she is co-author of three of those studies.[12]

Just as HSIA had feared, the findings of Johnson *et al.* (2003) were elevated to a primary source for hazard assessment and derivation of the RfC and RfD largely at the insistence of Dr. Selmin. Without impugning Dr. Selmin's scientific integrity, the extent of criticisms of the work of the University of Arizona meant that Dr. Selmin would be drawn to defend the work done by her co-workers; a dispassionate, objective interpretation might not result. The appropriate action would, at the least, have been for Dr Selmin to be recused from any discussion of the interpretation of Johnson *et al.* (2003) and related studies.

Under the NAS conflicts policy cited above that is required to be adopted or adapted by EPA, "an individual should not serve as a member of a committee with respect to an activity in which a critical review and evaluation of the individual's own work, or that of his or her

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

[11] Hardin, B, *et al.*, Repro. Toxicol. 21:117–147 (2006), citing several other studies from the University of Arizona, Tucson.

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

immediate employer, is the central purpose of the activity, because that would constitute a conflict of interest, although such an individual may provide relevant information to the program activity." Dr. Selmin's active participation in the discourse resulted in the SAB panel's recommendation that her laboratory's controversial and unreproducible work be the basis for the RfD/RfC for TCE, and would seem to constitute a clear conflict of interest under this policy.

B. Other Peer Reviews Rejected Reliance on the Arizona Studies

1. Vinylidene Chloride IRIS Assessment

The EPA Denial discounts the first SAB peer review of the University of Arizona studies, in connection with the IRIS assessment of vinylidene chloride (1,1-dichloroethylene or 1,1-DCE), on the basis that "the assessment focused on a different chemical and a different set of studies" and thus is "not directly comparable." This is disingenuous, as can be seen in the SAB panel's advice to EPA at the time:

> **"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?**
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> "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.
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> "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.* [Emphasis added.]
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> "Before the discussion of the deficiencies in the developmental toxicity drinking water studies, no panel member felt that 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."

Obviously, Dawson *et al.* (1993) reported developmental toxicity data for *both* TCE and vinylidene chloride. In fact, a single control group was used for both the TCE and vinylidene chloride treatment groups, although there appears to be some confusion as to the size of that control group (see below). The SAB reviewers' comments are equally relevant to TCE because they address quality issues associated with a key component of Johnson *et al.* (2003) -- the evaluation of the 733-fold difference between the 1,100 and 1.5 ppm TCE exposure groups as earlier reported by Dawson *et al.*(1993).

Some of the SAB reviewers' comments relating to study quality are particularly relevant, for example, the "concerns for the high positive responses on a litter basis in the controls." This comment is intriguing as Dawson *et al.* (1993) do not appear to provide information on the number of control litters. Nonetheless, this issue has been raised before and suggests the existence of a colony quality concern with the animals used in the developmental toxicity studies reported by the University of Arizona researchers. Dawson *et al.* (1993) reported that three percent of fetuses in the control group had cardiac defects. For comparison, the literature includes reports of an historical spontaneously occurring cardiovascular malformation rate in Crl:CD Sprague-Dawley rat fetuses of 0.04 percent. Although the source of the Sprague-Dawley rats used in Dawson *et al.* (1993) is not identified, a fetal malformation rate two orders of magnitude higher than that seen in supplier colonies should be a major concern.

Another concern raised by the SAB reviewers was "the lack of increased response between the two exposures that varied by 900-fold." Over that vinylidene chloride dosage range, the fetal cardiac malformation rate increased from 1.9 percent to 3.6 percent. Over a 733-fold increase in TCE exposure (*i.e.,* 1.5 ppm to 1,100 ppm) the fetal cardiac malformation rate increased from 5.5 percent to 10.4 percent in the same study, raising similar concerns for HSIA. Indeed, it is particularly interesting that the reviewers noted "[q]uality control issues, including lack of analytical confirmation of the concentrations in the drinking water in the TCE studies". In fact, Dawson *et al.* (1993) indicates that the drinking water concentrations of TCE (and vinylidene chloride) were tested by gas chromatography at the time of preparation. In the follow-up paper, Johnson *et al.* (2003) report a 35 percent loss of TCE from drinking water solutions over a 24-hour period. It is not clear from Dawson *et al.* (1993) that TCE losses were even measured for the 1,100 and 1.5 ppm solutions.

2. TSCA Chemicals Work Plan Assessment of TCE

Even more egregiously, the EPA Denial does not even mention the third independent peer review that considered the quality of the Arizona studies – this one clearly in the context of an EPA risk assessment of TCE. The Request for Correction