UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
NATONAL CENTER FOR ENVIRONMENTAL RESEARCH
WASHINGTON, D.C. 20460

OFFICE OF
RESEARCH AND DEVELOPMENT

Ms. Faye Graul
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Dear Ms. Graul:

This letter is in response to your November 5, 2013, Request for Correction[1] (RFC) and subsequent letters[2] sent on behalf of the Halogenated Solvents Industry Alliance, Inc. (HSIA) regarding the *Toxicological Review of Trichloroethylene in Support of Summary Information on the Integrated Risk Information System (IRIS)* (Toxicological Review of TCE).[3] In your RFC, you state that "HSIA seeks the correction of information" in the Toxicological Review of TCE and take issue with a study used to support some of the conclusions of the Toxicological Review of TCE. Specifically, your RFC states that "EPA's exclusive reliance on a single inappropriate and unreproducible study, as well as an RfC/RfD [Reference Concentration/Reference Dose] based on that study, constitutes erroneous information, the dissemination of which contravenes the IQA [Information Quality Act] criteria…." The study you identify as being "inappropriate and unreproducible" is 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 (Johnson *et al.*, 2003).

Your RFC states that the Johnson *et al.*, 2003 study does not meet IQA criteria for objectivity, utility, or reproducibility. After reviewing your RFC and subsequent letters, the U.S. Environmental Protection Agency (EPA) disagrees with a number of your assertions on a factual basis and believes that your information quality concerns were addressed through the IRIS assessment development process, which was used to develop and review the Toxicological Review of TCE.

The assertions and comments made in your RFC are not new. These same assertions were made in public comments prior to peer review of the 2009 external review draft of the Toxicological Review of TCE. The issues raised in your RFC were carefully considered by EPA and the EPA Science Advisory Board (SAB) in the development of the final Toxicological Review of TCE. The Agency's IRIS Program uses a transparent, open, and public process[4] for developing assessments. This process includes

[1] http://epa.gov/quality/informationguidelines/documents/14001.pdf
[2] http://epa.gov/quality/informationguidelines/documents/14001-rel.pdf
http://epa.gov/quality/informationguidelines/documents/14001-rel2.pdf
[3] http://www.epa.gov/iris/toxreviews/0199tr/0199tr.pdf
[4] http://www.epa.gov/iris/process.htm

multiple review steps,[5] provides opportunities for the public to make verbal comments and submit written comments, and includes a public external peer review. In 2009, EPA released the draft Toxicological Review of TCE for public comment and independent, external peer review through the SAB.[6] During the public comment period and the peer review, the HSIA made verbal presentations and submitted written comments to EPA and the SAB, including comments on the validity of Johnson *et al.*, 2003. On December 10, 2010, you submitted written comments[7] on behalf of the HSIA that made identical arguments critical of Johnson *et al.*, 2003 to those raised in your RFC. You stated:

> "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. In the earlier published study, there was no difference in the percentage of cardiac abnormalities in rats dosed during both pre-mating and pregnancy…. …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, and the earlier studies were rejected as the basis for minimal risk levels (MRLs) by the Agency for Toxic Substances and Disease Registry (ATSDR). 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…."[8]

The IRIS assessment development process states that public comments submitted on draft IRIS products are reviewed by EPA and provided to peer reviewers for their consideration. Consistent with the IRIS process, the written comments you submitted in 2010 on behalf of HSIA were reviewed by EPA and provided to both the SAB panel established to conduct the peer review of the draft Toxicological Review of TCE as well as the chartered SAB committee that conducts a quality review of the SAB panel's draft report.

In addition, the SAB's website[9] shows that HSIA made presentations to the SAB panel at each of the five TCE meetings and made fourteen presentations in all. Although most of HSIA's concerns and

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[5] In addition to the review steps identified in the IRIS process, all critical studies used in IRIS assessments are peer reviewed. The Johnson *et al.*, 2003 study underwent a review for scientific quality consistent with *Environmental Health Perspectives* review policies: http://ehp.niehs.nih.gov/instructions-to-authors/#submit

[6] http://yosemite.epa.gov/sab/sabproduct.nsf/02ad90b136fc21ef85256eba00436459/773dc7e8c5c1332d852574f200699a89!OpenDocument&Highlight=0,tce

[7] See p. 6-7: http://yosemite.epa.gov/sab/sabproduct.nsf/A9D745E402CF6DB3852577F800729C51/$File/Comments+from+Faye+Graul.pdf

[8] http://yosemite.epa.gov/sab/sabproduct.nsf/A9D745E402CF6DB3852577F800729C51/$File/Comments+from+Faye+Graul.pdf

[9] http://yosemite.epa.gov/sab/sabproduct.nsf/c91996cd39a82f64852574240069012 7/773dc7e8c5c1332d852574f200699a89!OpenDocument&TableRow=2.2#2.

comments addressed other issues, some focused on fetal cardiac effect studies. To help ensure that the SAB panel was aware of issues evaluated in the draft Toxicological Review of TCE, including those related to fetal cardiac effect data, the general concerns were presented by EPA in two slide presentations to the panel.[10, 11] The slide presentations noted "limitations" in the available fetal cardiac data and HSIA's concerns about the studies. The draft Toxicological Review of TCE noted the cardiac dissection methods used in the developmental toxicity studies and the varying results recorded across studies.[12] The charge to the SAB panel[13] specifically asked them to consider the Johnson *et al.*, 2003 study and its use in deriving the Reference Dose and Reference Concentration for trichloroethylene. The SAB panel's draft report was reviewed and approved by the chartered SAB committee.

The SAB panel's conclusions are documented in a report available on the SAB's website.[14] In its report, the SAB panel supported EPA's approach to deriving the Reference Dose and Reference Concentration based on multiple studies and EPA's inclusion of fetal heart defects as a critical endpoint. The SAB panel found that the Johnson *et al.*, 2003 study was adequate for deriving the Reference Dose and Reference Concentration in conjunction with other studies:

> "The Panel found that the draft document adequately synthesizes the available scientific information to support a conclusion that TCE poses a potential human health hazard for non-cancer toxicity, including effects on the central nervous system, the kidney, the liver, the immune system, the male reproductive system, and the developing fetus.
>
> "The Panel supported the selection of an RfC [Reference Concentration] and an RfD [Reference Dose] based on multiple candidate reference values that fell within a narrow range rather than reliance on a single most sensitive critical endpoint. … The Panel recommends that EPA derive RfD/RfC values based on immunological endpoints and cardiac malformations."[15]

The SAB panel also found:

> "The Panel concluded that the choices of Keil *et al.* (2009) [decreased thymus weights and increased anti-dsDNA and anti-ssDNA antibodies], Peden-Adams *et al.* (2006)

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10 http://yosemite.epa.gov/sab/sabproduct.nsf/ECEE2A65B84C9B508525770A005ED12C/$File/USEPA+Draft+Tox+Review+of+TCE-Key+Aspects-1.pdf

11 http://yosemite.epa.gov/sab/sabproduct.nsf/C4E2D10DE301736C8525772900760E71/$File/TCE_Preuss+Presentation+to+TCE+Panel+for+My+10-12+2010+Meeting.pdf

12 See pages 4-532 through 4-535 and 4-600 through 4-603: http://yosemite.epa.gov/sab/sabproduct.nsf/c91996cd39a82f648525742400690127/773DC7E8C5C1332D852574F200699A89/$File/IRIS_TOX_REVIEW_TCE_ERD.PDF

13 http://yosemite.epa.gov/sab/sabproduct.nsf/9FD55029FA9326318525770A005F2C7F/$File/TCE+Charge+to+External+Peer+Reviewers-annotated-1.pdf

14 http://yosemite.epa.gov/sab/sabproduct.nsf/02ad90b136fc21ef85256eba00436459/B73D5D39A8F184BD85257817004A1988/$File/EPA-SAB-11-002-unsigned.pdf

15 SAB Review of EPA's Draft Assessment entitled *"Toxicological Review of Trichloroethylene"* (October 2009). See p. ii (http://yosemite.epa.gov/sab/sabproduct.nsf/ea5d9a9b55cc319285256cbd005a472e/e2effa0dd69ad4d3852577e4006af0a5/$FILE/TCE%2011-23-10%20v3%20report.pdf)

> [developmental immunotoxicity], and Johnson *et al.* (2003) [fetal heart malformations] as critical studies and effects were technically/scientifically adequate to support EPA's draft RfC and RfD. The Panel noted that questions related to the use of cardiac malformations from Johnson *et al.* (2003) as a critical endpoint were adequately addressed in the response to Charge Question 3."[16]

Further, the SAB panel identified additional studies that "confirm and reinforce the results obtained in the Johnson *et al.* 2003 study…."[17]

EPA's Information Quality Guidelines (IQGs) recognize the importance of peer review in ensuring and maximizing information quality and reference EPA's Peer Review Policy and *Peer Review Handbook.* EPA's *Peer Review Handbook*[18] states that "[EPA] recognizes peer review as a component of pre-dissemination review that complements and enhances the 'objectivity' and 'utility' of EPA's information products." EPA relies on peer review to enhance scientific work products so that decisions or positions taken by EPA are sound and credibly based on those scientific work products. Consistent with the IQGs and the IRIS assessment development process, the Toxicological Review of TCE relied upon peer reviewed studies.

Furthermore, EPA's draft Toxicological Review of TCE itself underwent independent external peer review by the EPA's SAB. The IRIS assessment development process is publicly described and includes a structured opportunity for public comment associated with peer review. As stated in the IQGs in section 8.5, "When EPA provides opportunities for public participation by seeking comments on information, the public comment process should address concerns about EPA's information." EPA believes that the concerns you raise in your RFC were considered by the EPA and the SAB as a part of the IRIS assessment development process prior to completing the Toxicological Review of TCE.

TCE's fetal cardiac effects were further addressed by a team of EPA scientists in a "TCE Developmental Cardiac Toxicity Assessment Update."[19] This update followed the completion of the Toxicological Review of TCE and was intended to further evaluate and address issues related to TCE and fetal cardiac effects including a systematic evaluation of study quality, detailed description of the study design (*e.g.*, the source of concurrent controls), reexamination of the dose response for cardiac defects, evaluation of the study results in light of studies that did not observe cardiac defects with *in utero* exposures, and concerns that have been raised regarding the interpretation of the epidemiological database for cardiac defects associated with TCE exposures. The update further affirmed the fetal cardiac developmental effect finding of the draft Toxicological Review for TCE:

> "Overall, taking into account the study's design, its strengths and limitations, and uncertainties in the weight of evidence, a majority of the team members agreed that the Johnson *et al.* (2003) study was suitable for use in deriving a point of departure." And "…the team members concluded that the point of departure derived in the 2011 [Toxicological Review for TCE],

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[16] SAB Review of EPA's Draft Assessment entitled *"Toxicological Review of Trichloroethylene"* (October 2009). See p. 40. Link provided above.
[17] SAB Review of EPA's Draft Assessment entitled *"Toxicological Review of Trichloroethylene"* (October 2009). See p. 49. Link provided above.
[18] http://www.epa.gov/peerreview/
[19] http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPPT-2012-0723-0045

which used an approach consistent with standard U.S. EPA dose response practices, remained a reasonable choice."

HSIA's RFC could be interpreted to assert that EPA's Toxicological Review of TCE relies exclusively on a single study to support the derivation of reference values and this is factually incorrect. Rather, in developing the Toxicological Review of TCE, EPA reviewed more than one hundred toxicological studies to evaluate TCE hazards, including dozens of developmental toxicity studies of animals and humans that are documented in Tables 4-33, 4-34, 4-95, 4-96 and 4-98 in the Toxicological Review of TCE. The twenty-one developmental cardiac studies, which reported both positive and negative findings, are documented in Table 4-103 along with a discussion of the variability of results. The Toxicological Review of TCE evaluated and integrated all of the available human, animal and mechanistic information in Section 4.8.3.3.2.

Studies supporting the importance of the observed cardiac malformation were summarized along with studies that found no effect and the Toxicological Review for TCE noted that the animal cardiac data are inconsistent: "However, cardiac malformations were not observed in a number of other studies in laboratory animals in which TCE was administered during the period of cardiac organogenesis and fetal visceral findings were assessed." Similar observations of divergent results across laboratories and species were also reached by California's Office of Environmental Health Hazard Assessment[20] and the National Academies[21] as your RFC noted.

The Toxicological Review of TCE summarized the weight of evidence related to cardiac developmental effects in Section 4.3.3.2.3:

> "Strengths of the evidence are the duplication of the adverse response in several studies from the same laboratory group, detection of treatment-related cardiac defects in both mammalian and avian species (*i.e.*, rat and chicken), general cross-study consistency in the positive association of increased cardiac malformations with test species (*i.e.*, rat), route of administration (*i.e.*, oral), and the methodologies used in cardiac morphological evaluation (*i.e.*, fresh dissection of fetal hearts). Furthermore, when differences in response are observed across studies, they can generally be attributed to obvious methodological differences, and a number of *in ovo* and *in vitro* studies demonstrate a consistent and biologically plausible mode of action for one type of malformation observed. Weaknesses in the evidence include lack of a clear dose-related response in the incidence of cardiac defects, and the broad variety of cardiac defects observed, such that they cannot all be grouped easily by type or etiology."

Consistent with the SAB's recommendations, Section 4.3.3.2.3 concluded that "Taken together, the epidemiological and animal study evidence raise sufficient concern regarding the potential for developmental toxicity (increased incidence of cardiac defects) with *in utero* TCE exposures."

The numerical values of the Reference Dose and Reference Concentration were also based on multiple studies. As described in the Toxicological Review of TCE, EPA used three studies to derive the Reference Dose numerical value and identified two additional studies that support it.[22] EPA used two

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[20] CalEPA Public Health Goal for Trichloroethylene in Drinking Water (July 2009), p 21.
[21] National Academies Press, Assessing the Human Health Risks of Trichloroethylene: Key Scientific Issues (2006), page 211.
[22] See p. 6-30 of http://www.epa.gov/iris/toxreviews/0199tr/Chapter6_0199tr.pdf

studies to derive the Reference Concentration numerical value and identified one additional study that supported it.[23]

In your letters dated July 3 and September 8, 2014, which were submitted subsequent to your RFC, you provide additional information to support your initial claims regarding the Johnson study and the Toxicological Review of TCE. Your July 3rd letter reiterated your claim that the draft Toxicological Review relied upon a single study and stated that a recently published erratum (Johnson *et al, Environ. Health Perspect.* 122: A94 (2014)) "strongly supports" your RFC. You state, alluding to the Johnson study, that a "lack of data availability and clarity" should "disqualify" the use of studies in important agency decisions such as RfC/RfD derivation. In the letter, you also assert that Table 1 in the published erratum provides information showing that concurrent control groups did not exist for the test animals being exposed to TCE. Contrary to your assertions, in our review of the erratum we noted that a concurrent control group is identified for each of the TCE study groups identified. Table 1 shows that during each time period that laboratory animals were being exposed to TCE, there was a temporally overlapping control group of test animals.

As noted above, the SAB recommended the use of Johnson *et al.,* 2003 and other studies that were identified stating "…EPA's TCE hazard assessment has clearly, accurately, logically and objectively represented and synthesized the available scientific evidence to support its conclusions that TCE poses a potential human health hazard…."
Your September 8th letter provides additional information that is intended to support your RFC by providing references to another study, Dawson *et al.*, 1993,[24] that was considered by the IRIS program in evaluating the potential for another chemical, 1,1-dichloroethylene, to cause cardiac defects. As you note, the IRIS Toxicological Review for 1,1-dichloroethylene was completed in 2002. Your letter also repeats a request for statistical information to which EPA previously responded and takes issue with the approach used to quantify the total number of fetuses affected in the TCE Toxicological Review through comparison to the Toxicological Review for 1,1-dichloroethylene.

In reviewing your letter and the referenced materials, we note that EPA also followed the advice of peer reviewers on the draft Toxicological Review for 1,1-dichloroethylene, [25] stating that the observed cardiac changes in the Dawson *et al.*, 1993 study could not be concluded to be caused by 1,1-dichloroethylene. Although the methods and process used in the development of the Toxicological Review of 1,1-dichloroethylene included similar quality review steps to ensure the utility and objectivity of the Toxicological Review, the assessment focused on a different chemical and a different set of studies and as such the previous Toxicological Review is not directly comparable and does not materially change the conclusions reached in the Toxicological Review of TCE.

If you are not satisfied with this response, you may choose to submit a Request for Reconsideration. EPA requests that any such Request for Reconsideration be submitted within 90 days of the date of the agency's response. If you choose to submit a Request for Reconsideration, please send a written request to the EPA Information Quality Guidelines Processing Staff via mail (Information Quality Guidelines Processing Staff, Mail Code 2811A, U.S. EPA, 1200 Pennsylvania Avenue, N.W. Washington, D.C.

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[23] See p. 6-29 of http://www.epa.gov/iris/toxreviews/0199tr/Chapter6_0199tr.pdf
[24] Dawson BV, Johnson PD, Goldberg SJ, Ulreich JB. Cardiac teratogenesis of halogenated hydrocarbon-contaminated drinking water. J Am Coll Cardiol. 21(6):1466-72 (1993).
[25] See p. 55-56 in the Toxicological Review of 1,1-dichloroethylene (CAS No. 75-35-4) June 2002 (EPA/635/R02/002). Available at http://www.epa.gov/iris/toxreviews/0039tr.pdf

20460); or electronic mail, quality@epa.gov. Additional information about how to submit a Request for Reconsideration can be found on the EPA IQG website (www.epa.quality/informationguidelines).

Sincerely,

Lek Kadeli
Acting Assistant Administrator

cc: Renee P. Wynn, Acting Assistant Administrator and Chief Information Officer
Kenneth Olden, Director, National Center for Environmental Assessment
Vincent Cogliano, Interim Director, Integrated Risk Information System Program
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