



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

FEB 26 2016

Ms. Faye Graul
Executive Director
Halogenated Solvents Industry Alliance, Inc.
1530 Wilson Boulevard
Suite 690
Arlington, VA 22209

Dear Ms. Graul:

This letter is in response to your Information Quality Guidelines (IQG) Request for Reconsideration (RFR) dated June 17, 2015 (RFR 13401A) submitted to the Environmental Protection Agency (EPA) by the Halogenated Solvents Industry Alliance, Inc. (HSIA) pursuant to EPA's *Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by the Environmental Protection Agency* (EPA IQG). Your RFR requests that EPA reconsider its response, dated March 19, 2015, to your Request for Correction¹ (RFC 14001) regarding the *Toxicological Review of Trichloroethylene in Support of Summary Information on the Integrated Risk Information System (IRIS)* (Toxicological Review of TCE).²

Consistent with the EPA IQG, EPA convened an executive panel to determine EPA's response to this RFR. The executive panel consisted of the EPA Economics Advisor (the Associate Administrator of the Office of Policy), the Associate Administrator for the Office of Water, and me, the EPA Chief Information Officer. The panel reviewed your original RFC, EPA's response³, and the RFR and have concluded that EPA's RFC response was appropriate and the information presented in the Toxicological Review of TCE meets our EPA IQG standards of objectivity and utility. Some of the considerations that led to this conclusion are summarized below.

IRIS Toxicological Reviews evaluate complex toxicity databases and integrate multiple types of evidence to provide high-quality, science-based hazard and dose-response information that is used in risk assessment. IRIS assessments are not regulations, but they provide a critical part of

¹ <http://www2.epa.gov/quality/request-correction-iris-assessment-trichloroethylene>

² <http://www2.epa.gov/iris/supporting-documents-trichloroethylene>

³ <http://www2.epa.gov/sites/production/files/2015-09/documents/14001-response.pdf>

the foundation for decision-making across EPA. The IRIS Toxicological Review for TCE describes the derivation of the Reference Dose and Reference Concentration (a.k.a. reference values), which are estimates of continuous exposures to the human population (including sensitive subgroups) that are likely to be without appreciable risk of deleterious effects during a lifetime. HSIA's RFR and RFC focus on the appropriateness of the use of one study [Johnson et al. (2003)⁴] that contributed to the development of the reference values for TCE. The conclusions of the Toxicological Review of TCE regarding developmental toxicity were based on the review and evaluation of dozens of studies, including 21 studies focused on cardiac developmental toxicity, and integrated all the available human, animal, and mechanistic information. The quantitative values for the TCE reference values were also based on multiple studies. The Reference Dose was based on toxicity information from studies on developmental Immunotoxicity and decreased thymus weights, as well as the heart malformation toxicity information from Johnson et al. (2003). In addition to the Johnson et al. (2003) study, the Reference Concentration was based on another principal study on decreased thymus weight and a supporting study on kidney toxicity. The Toxicological Review for TCE states that using multiple studies to derive reference values leads to more robust values that are less sensitive to limitations of individual studies and that the various reference concentrations are similar for multiple effects at low dose.

EPA takes very seriously its responsibility for ensuring the accuracy and reliability of information prior to publication. In this instance, the Toxicological Review of TCE underwent scientific review consistent with the IRIS assessment development process⁵, which includes reviews both within EPA and across federal agencies as well as independent external peer review. The IRIS assessment development process also allows for the public to provide comments on draft assessments prior to and during external peer review.

The independent external peer review of the draft Toxicological Review of TCE was conducted through EPA's Science Advisory Board (SAB). The SAB has a public process⁶ for selecting members and forming panels,⁷ which involves public nomination and review of panelists' credentials and is consistent with the Federal Advisory Committee Act (5 U.S.C. App. C) and related regulations. The draft Toxicological Review of TCE was reviewed by an SAB panel selected through this process for their knowledge and expertise related to TCE and its potential health effects.⁸ The charge to the SAB panel specifically asked them to consider the Johnson et al. (2003) study and its use in deriving the Reference Dose and Reference Concentration for

⁴ Johnson PD, SJ Goldberg, MZ Mays, and BV Dawson. Threshold of Trichloroethylene Contamination in Maternal Drinking Waters Affecting Fetal Heart Development in the Rat, *Environmental Health Perspectives* 111:289-292 (March 2003).

⁵ <http://www2.epa.gov/iris/basic-information-about-integrated-risk-information-system#process>

⁶ <http://yosemite.epa.gov/sab/sabproduct.nsf/WebSABSO/PublicInvolvement?OpenDocument>

⁷ <http://yosemite.epa.gov/sab/sabproduct.nsf/WebBOARD/CommitteesandMembership?OpenDocument>

⁸ <http://yosemite.epa.gov/sab/sabproduct.nsf/c91996cd39a82f648525742400690127/773dc7e8c5c1332d852574f200699a89!OpenDocument&TableRow=2.1#2>.

TCE. The final SAB panel was comprised of 21 scientists, which included professors and research scientists from 15 universities and 5 other scientific research organizations. The panel held 4 public meetings, each of which included an opportunity for public comment, over a period of 5 months. The chartered SAB also held a public meeting to review the panel's draft peer review report. The SAB at that time consisted of 48 scientists with expertise in a broad range of scientific disciplines, including toxicology and risk assessment.

EPA's response to HSIA's RFC found that most of the comments were either identical or similar to those submitted to EPA during the public comment period and/or peer review. HSIA and its consultants provided multiple sets of comments during the peer review of the draft Toxicological Review of TCE.⁹ HSIA also provided multiple sets of written and verbal comments on the draft Toxicological Review of TCE at a "Listening Session" hosted by EPA.¹⁰ In all, HSIA submitted and/or presented at least nineteen sets of comments on the draft Toxicological Review of TCE. The comments were reviewed and considered by EPA and the external peer reviewers as a part of the IRIS assessment development process.

HSIA's RFR requests EPA to reconsider the Agency's conclusions stated in its response to HSIA's RFC. HSIA's rationale focuses on an update of TCE developmental toxicity conducted by EPA, the use of concurrent control animals in the Johnson et al., (2003) study, the objectivity of one of the members of the SAB panel who reviewed the draft Toxicological Review of TCE in 2010, and other peer reviews mentioning Johnson et al. (2003). Each of these issues is discussed below.

EPA Update on TCE Developmental Toxicity Studies

HSIA's RFR states that the use of Johnson et al. (2003) is "scientifically unacceptable" and asserts that an update conducted by EPA (TCE Developmental Cardiac Toxicity Assessment Update¹¹) supports HSIA's perspective. HSIA's RFR cites text in the update summarizing that a team of EPA scientists characterized their level of confidence in the Johnson et al. (2003) study for the purposes of dose-response evaluation as "low" or "low-to-medium."

HSIA is correct that the TCE Developmental Cardiac Toxicity Assessment Update concluded that confidence in the dose-response derived from the Johnson study was "low" or "low-to-medium." That conclusion is consistent with EPA's statements that there are limitations in the data. However, the majority of the team concluded that the database adequately supported a determination of "Sufficient Experimental Animal Evidence" and "Limited Human Data" regarding TCE developmental cardiac toxicity and that the point of departure derived for the

⁹ See submissions for meetings on 9/13/2010, 6/24/2010, 5/10/2010, and 4/20/2010:

<http://yosemite.epa.gov/sab/sabproduct.nsf/c91996cd39a82f648525742400690127/773dc7e8c5c1332d852574f200699a89!OpenDocument&TableRow=2.2#2>.

¹⁰ See public comments in docket EPA-HQ-ORD-2009-0791 at <http://www.regulations.gov/>

¹¹ <http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPPT-2012-0723-0045>

2011 TCE assessments remained a reasonable choice. The update document concluded that “The majority of the team agreed that the results of the present analysis are consistent with the dose-response conclusions of the 2011 IRIS assessment.”

Concurrent Controls

The RFR states that the Johnson et al. (2003) laboratory test animals lacked concurrent control groups. This perspective is contradicted by errata published by Dr. Johnson in 2014¹² noting that “...all of the animal exposure experiments were run with concurrent controls.” In addition, EPA’s TCE Developmental Cardiac Toxicity Assessment Update confirmed that concurrent controls were conducted with each treatment group in Johnson et al. (2003).

SAB Review

The SAB review of the draft Toxicological Review of TCE recommends the use of fetal cardiac defects for developing reference values and specifically finds the Johnson et al. (2003) study adequate for this purpose.¹³ The SAB reached this conclusion after receiving comments from HSIA on the same topics raised in the RFC and RFR, as well as considering all the other available evidence. HSIA’s RFR “recommends that the [TCE reference values] be based on an endpoint other than cardiac malformations,” which is directly contrary to the SAB’s conclusions and recommendations, such that to accept HSIA’s RFC/RFR would require EPA to reject SAB’s advice. HSIA supports their proposed dismissal of the SAB recommendation by asserting that the SAB review of the IRIS TCE assessment was flawed because a member of the panel, Dr. Ornella Selmin, had a conflict of interest. HSIA stated “Dr. Selmin is a lead or co-author on a number of papers reporting these results, and has co-authored papers with Dr. Paula Johnson...” Although Dr. Selmin was not a co-author on the Johnson et al. (2003) study, she and Dr. Johnson are professors at the University of Arizona and have co-authored other papers together along with other scientists. The RFR states: “... Dr. Selmin would be drawn to defend the work done by her co-workers; a dispassionate, objective interpretation might not result.” HSIA states that they raise this concern with Dr. Selmin’s objectivity in the RFR because “[t]he EPA Denial [of the RFC] relies heavily on the external peer review of the draft TCE IRIS Assessment by the EPA Science Advisory Board...”

HSIA’s concern with Dr. Selmin’s participation in the SAB review is not new. HSIA had previously submitted¹⁴ text identical to that in the RFR to EPA in 2010, late in the SAB peer review process, shortly after the SAB panel released its draft report¹⁵ for review by the public and the chartered SAB. The draft SAB panel report recommended the use of the Johnson et al.

¹² Environ Health Perspect. 2014 Apr; 122(4): A94

¹³ EPA’s response to the RFC provides relevant quotes and citations.

¹⁴ [http://yosemite.epa.gov/sab/sabproduct.nsf/A9D745E402CF6DB3852577F800729C51/\\$File/Comments+from+Fa+ye+Graul.pdf](http://yosemite.epa.gov/sab/sabproduct.nsf/A9D745E402CF6DB3852577F800729C51/$File/Comments+from+Fa+ye+Graul.pdf)

¹⁵ [http://yosemite.epa.gov/sab/sabproduct.nsf/ea5d9a9b55cc319285256cbd005a472e/e2effa0dd69ad4d3852577e4006af0a5/\\$FILE/TCE%2011-23-10%20v3%20report.pdf](http://yosemite.epa.gov/sab/sabproduct.nsf/ea5d9a9b55cc319285256cbd005a472e/e2effa0dd69ad4d3852577e4006af0a5/$FILE/TCE%2011-23-10%20v3%20report.pdf)

(2003) study for use in the derivation of risk values. It was only after the SAB panel presented its draft advice that HSIA expressed concern with Dr. Selmin's participation. EPA had previously requested comments from the public on the potential SAB panelists at the time Dr. Selmin, and the other scientists, were nominated; however, there is no record that HSIA expressed concerns regarding Dr. Selmin's affiliations at that time.

Following their nomination, Dr. Selmin, along with the other SAB panelists, were vetted for conflicts of interest and appearances of a lack of impartiality. SAB panelists and members provided detailed background information, including financial statements, and were evaluated under applicable statutes, ethics regulations, and EPA's peer review guidance. The SAB Staff Office also asks potential panel members about circumstances that might affect their ability to provide impartial advice on the matter to come before the panel, any current or previous involvement with the review document(s) under consideration, previous service on advisory panels/committees that have addressed the topic under consideration, and any public statements made by them on the issue under consideration. At each meeting, the panelists were also publicly reminded that they were subject to federal ethics regulations and conflict-of-interest laws.

Dr. Selmin was not a co-author of the Johnson et al. (2003) study. She was determined to be eligible to participate on the panel based on her scientific expertise and was not found to have a conflict of interest. The fact that she had previously worked with Dr. Johnson on research projects did not preclude her from offering her scientific opinions on the merit of other research conducted by Dr. Johnson and other researchers. At the time of the review, Dr. Selmin had published extensively on TCE's developmental toxicity mechanisms and effects (including at least five peer-reviewed papers without Dr. Johnson). It should also be noted that while Dr. Selmin was one of 21 panelists that provided comments on the draft Toxicological Review of TCE, the work of the panel was subsequently reviewed for transparency, completeness and accuracy by the chartered SAB prior to its transmittal to the EPA.

Other Peer Reviews Mentioning Johnson et al. (2003)

HSIA argued in its RFC and RFR that other peer review panels convened for other purposes than reviewing the draft Toxicological Review of TCE were not supportive of the use of the Johnson et al. (2003) study. The peer reviews mentioned by HSIA include the 2014 Office of Pollution Prevention and Toxics (OPPT) review of a draft risk assessment of certain TCE uses. The OPPT draft TCE risk assessment peer review was a contractor-organized independent external review panel with nine scientists¹⁶. Contractor-organized panel reports generally express the individual opinions of the peer reviewers and in this instance only one of the peer reviewers made any comments regarding the Johnson et al. (2003) study. The HSIA RFR can leave the impression that these comments should be attributed to the panel as a whole, whereas the comments are those of only one panelist and are not consensus panel comments. Although it was not mentioned

¹⁶ <http://www.scgcorp.com/tcl2013/>

in the response to the RFC, EPA previously addressed this peer reviewer's comments upon finalizing the TCE risk assessment in 2014¹⁷:

“Developmental effects, including fetal cardiac defects, may occur following maternal exposure to TCE. Chick embryo and oral developmental studies, including those reported by the Johnson et al. studies (see list of references below), have reported cardiac malformations after exposure to TCE. The incidence of congenital cardiac malformation has been replicated in several studies from the same laboratory group and has been shown to be TCE-related. Moreover, studies with TCE metabolites have also induced cardiac defects in developmental oral toxicity studies. A recent erratum (Johnson, 2014) and subsequent evaluation of the developmental toxicity data reaffirmed that the Johnson et al. studies are adequate to use in hazard identification and dose-response assessment (Appendix N). As explained in the TCE IRIS assessment, while the Johnson et al. studies have limitations, there is insufficient reason to dismiss their findings, especially when the findings are analyzed in combination with human, animal and mechanistic evidence. A summary of the weight of evidence supporting TCE-related fetal cardiac defects is provided in section 2.6.2.3.6 and Appendix N of the final TCE OPPT risk assessment. The comprehensive WOE evaluation of the developmental toxicity data, including fetal cardiac teratogenesis, is discussed in the TCE IRIS assessment and expanded in this assessment (Appendix N). Thus, EPA/OPPT has incorporated the Johnson et al. studies in the final risk assessment (see Tables 2-18, 2-31 to 2-35; sections 2.7.2 and 2.7.3.2)”

In the RFR, HSIA also mentions another peer review conducted for the 1,1-dichloroethylene (1,1-DCE) IRIS Toxicological Review that had also been raised in the RFC. The RFR states

“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 “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....”

HSIA states that the 1,1-DCE IRIS Toxicological Review was peer reviewed by the SAB, which is incorrect. The 1,1-DCE IRIS Toxicological Review peer review was conducted by a contractor organized panel of five scientists in 2001, approximately two years prior to the publication of Johnson et al. (2003). In addition, the underlying databases used in the 1,1-DCE and TCE assessments were, as noted in EPA’s response to the HSIA RFC, distinctly different. The draft Toxicological Review of TCE included data and analyses that had been published following the 1,1-DCE assessment peer review. The additional information in the draft Toxicological Review of TCE included lower-dose rodent toxicity data that expanded the dose-response

¹⁷ http://www.epa.gov/oppt/existingchemicals/pubs/TCE_response_to_comments_FINAL_062414.pdf

characterization, individual fetal malformation data that allowed independent EPA statistical analysis of the incidences of cardiac malformations, evidence of heart defects in rodent studies on primary metabolites of TCE, associative evidence from epidemiological studies, a 2006 NRC report on TCE that emphasized that the heart defects in avian studies were relevant to the discussion since the processes of early cardiac development is conserved across species, and several mechanistic studies on how TCE could cause the cardiac defects. The SAB panel concluded that supporting mechanistic information further justified the conclusion of cardiac malformations associated with TCE exposure and the use of the Johnson et al. (2003) study.

After considering the information that you provided in your RFR the executive panel concluded that EPA's RFC response was appropriate and the information presented in the Toxicological Review of TCE is consistent with EPA's IQG standards of objectivity and utility. If you have any questions about this response, please contact Monica D. Jones, Director, Quality Staff, at (202) 564-1641.

Sincerely,



Ann Dunkin
Chief Information Officer

cc: Joel Beauvais, Acting Deputy Assistant Administrator, Office of Water
Thomas A. Burke, PhD, MPH, Deputy Assistant Administrator, Office of Research and
Development and EPA Science Advisor
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