EXHIBIT D

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").

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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:
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> > (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).
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> "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 $\mu g/m^3$)), 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?
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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:
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> > "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."
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> "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.