HSIA
halogenated solvents industry alliance, inc.

July 3, 2014

Information Quality Guidelines Staff
Mail Code 2811R
Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

Re: Supplement to Request for Correction -- IRIS Assessment for Trichloroethylene

Dear Sir or Madam:

On November 5, 2013, the Halogenated Solvents Industry Alliance, Inc. ("HSIA") submitted a request for the correction of information ("Request for Correction") under the Information Quality Act ("IQA")[1] and its implementing guidelines. 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)."[2]

Our Request for Correction noted that EPA established a reference concentration ("RfC") of 0.0004 ppm (0.4 ppb or 2 μg/m3) and a reference dose ("RfD") of 0.0005 mg/kg/day for TCE, and that these values 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 Contamination in Maternal Drinking Waters Affecting Fetal Heart Development in the Rat, Environ. Health Perspect. 111: 289-92 (March 2003). HSIA submitted that EPA's exclusive reliance on a single inappropriate and irreproducible study, as well as an RfC/RfD based on that study, constituted erroneous information, the dissemination of which contravenes the IQA.

We are supplementing our Request for Correction because Johnson and coauthors have just published an erratum (Johnson *et al.*, Environ. Health Perspect. 122: A94 (2014)) further correcting an earlier erratum (Johnson *et al.*, Environ. Health Perspect. 113: A18

[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) (hereafter "IRIS Assessment").

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(2005)) regarding the publication cited above. This erratum strongly supports our Request for Correction.

In the 2014 erratum, the authors note that the dates listed for conduct of the "2.5-ppb and 250-ppb trichloroethylene (TCE) groups *and their concurrent controls*" were incorrect (emphasis added) (see Table 1 below, from 2005 erratum). The authors now note the correct study start dates were in 1994, not 1995, although exact start dates could "no longer be confirmed." The 2014 author erratum now explicitly states that "all of the animal exposure experiments were run *with concurrent controls*" (emphasis added).

Examination of the data in Table 1, even as corrected in the 2014 erratum, indicates that the claim of concurrent controls is incorrect. The times described for evaluation of control data presented as "concurrent" to the 1,100 and 1.5 ppm TCE treatments (assuming the individual data lines in the Table represent control data on the left for corresponding TCE treatment groups on the right) still are dramatically different from each other. For example, the start times listed for the 1,100 ppm TCE treatment are 29 Jun 1989-12 Mar 1990, while the "concurrent" controls include evaluation times up to 10 Oct 1992, over 2-1/2 years *later.* Similarly, all of the dates for the apparent controls for the 1.5 ppm TCE treatment are listed as starting two to almost three years later. In fact, with the possible exception of an unidentified number of controls listed as starting between 14 Jun 1989 and 10 Oct 1992, the exposure dates of all other controls listed in Table 1 are listed as occurring at least two to four years later than either of the 1,100 ppm and 1.5 ppm TCE treatments (note that the 2014 erratum corrects the exposure dates for "concurrent controls" for the 2.5 ppb and 250 ppb treatments to "unconfirmed" times in 1994, not 1995 as shown in Table 1). The description of having conducted "concurrent controls" as noted in the 2014 author erratum is inconsistent with the accepted technical definition of "concurrent control" as control that occurs *while an activity is in progress* (*i.e,* controls parallel in time that of treatments).

The 2005 erratum states that control values of cardiac malformations were "statistically consistent across and throughout all treatment groups" (data not provided). However, an examination of the data in Table 1 indicates a potential of substantial variability in the average number of fetuses per mother within the various control groups as well as relative to TCE treatments, a factor that could be an untested confounder to cardiac malformation outcomes. The average number of fetuses per mother, calculated from the date in Table 1, is 9, 11.9, 10.3, 12, and 12.2 for the respective control groups, and 11.7, 13.9, 12.0 and 12.2 for the four respective TCE treatments. In addition to this intergroup variability and apparent lack of concurrent controls, it also appears that other confounders were present within the pooled control group population used in Johnson *et al.* (2003) as the basis for their conclusion that TCE induced cardiac malformations. In the initial developmental toxicity reporting exposures to 1.5 and 1,100 ppm TCE, both controls and treatment groups were described as exposed to "normal tap water" (Dawson *et al.*, 1993), while in the subsequent Johnson *et al.* (2003) study, adding the 2.5 ppb and 250 ppb groups, the control animals were described as exposed to "distilled water." Another potential confounder across these studies is that the Dawson *et al.* (1993) study also included TCE treatments with pre-gestation treatments of approximately two months, implying that the age

of the animals at the time of fetal evaluations, and the length of concurrent control pretreatments, likewise was varied across experiments. The data provided in the errata do not allow any assessment of these potential confounders.

Importantly, the data presented by Johnson *et al.* (2003), and subsequently clarified in the two errata, do not allow calculation of the incidence of cardiac malformations per litter that is time-matched to concurrent controls (the standard practice for evaluation of developmental toxicity studies). Accepting the author claims in the 2014 erratum that exposure times cannot be confirmed for substantial amounts of either control or treatment data, it also can be presumed that it is now impossible to reconstruct a calculation of per litter incidence of cardiac malformations that is appropriately matched to concurrent controls. Thus, the data reported in Johnson *et al.* (2003), and as amended in two subsequent errata, do not allow for data analysis generally accepted as key to interpreting adverse outcomes of developmental toxicity study findings. The lack of data availability and clarity sufficient to construct key analyses associated with a key study should disqualify the use of that study in important agency decisions such as RfC/RfD derivation.

From Johnson (2005, erratum):

Table 1. Control versus TCE treatment groups and dates of exposure.

Control		TCE		
Fetuses/mothers[a]	Dates	Dose	Fetuses/mothers	Dates
135/15	14 Jun 1989–10 Oct 1992	1,100 ppm	105/9	29 Jun 1989–12 Mar 1990
155/13	11 Dec 1992–20 Oct 1993[a]	1.5 ppm	181/13	29 Dec 1989–26 Dec 1990
62/6	15 Apr 1994–23 May 1994[a]			
120/10	6 Jul 1994–7 Jul 1995	2.5 ppb	144/12	6 Jun 1995–13 Jun 1995
134/11	18 Jul 1995–6 Oct 1995	250 ppb	110/9	5 Jul 1995–21 Jul 1995

[a]The total number of control rat fetuses/mothers was 606/55. [b]Other studies that coincided with these control groups were carried out during December 1989–June 1995 (e.g., metabolites that were reported in other articles (Johnson et al. 1998a, 1998b).

Combined with the points in our Request for Correction, including the detailed critique of EPA's reliance on Johnson *et al.* (2003) by EPA's own outside peer reviewers, we submit that continued use of this study to set RfC/RfD values would indicate that there is no data quality limit on EPA's decision-making.

Very truly yours,

Faye Graul /WCN

Faye Graul
Executive Director