

**Response to Comments Pertaining to the Request for Relevant Information on Trichloroethylene (TCE), a Chemical Being Considered for Listing by the Authoritative Bodies Mechanism as Causing Reproductive Toxicity under Proposition 65**

**Office of Environmental Health Hazard Assessment  
California Environmental Protection Agency  
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On March 15, 2013, the Office of Environmental Health Hazard Assessment (OEHHA) issued a Request for Relevant Information on trichloroethylene (TCE) under Proposition 65<sup>1</sup> as a chemical known to the State to cause reproductive toxicity (male reproductive and developmental endpoints). The action was based on consideration of TCE for listing under the authoritative bodies mechanism<sup>2</sup> described in the Proposition 65 implementing regulations and the U.S. Environmental Protection Agency's (U.S. EPA) identification of TCE as causing reproductive toxicity. This document responds to comments received in response to the Request for Relevant Information.

The U.S. EPA concluded that TCE causes reproductive toxicity in the 2011 Integrated Risk Information System (IRIS) document<sup>3</sup> and the Toxicological Review of TCE in support of the IRIS entry<sup>4</sup>.

After careful review of the two sets of comments received in response to the Request for Relevant Information, OEHHA has determined that the conclusions in the 2011 U.S. EPA Toxicological Review document meet the formal identification criteria in the Proposition 65 regulations. The U.S. EPA document states that TCE causes male reproductive and developmental toxicity in laboratory animals.

With regard to male reproductive toxicity, U. S. EPA stated that for TCE:

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<sup>1</sup> The Safe Drinking Water and Toxic Enforcement Act of 1986 (codified at Health and Safety Code section 25249.5 *et seq.*) hereinafter referred to as Proposition 65 or the Act.

<sup>2</sup> Title 27, Cal. Code of Regulations, section 25306. All further references are to Title 27, California Code of Regulations unless indicated otherwise.

<sup>3</sup> Available online at <http://www.epa.gov/iris/subst/0060.htm>.

<sup>4</sup> U.S. EPA (U.S. Environmental Protection Agency) (2011) Toxicological Review of Trichloroethylene (CAS No. 79-01-6); in support of Summary Information on the Integrated Risk Information System (IRIS) EPA/635/R-09/011F U.S. EPA, Washington D.C., September 2011. Available online at: <http://www.epa.gov/iris/toxreviews/0199tr/0199tr.pdf>.

- “Together, the human and laboratory animal data support the conclusion that TCE exposure poses a potential hazard to the male reproductive system” (Major Conclusions in the Characterization of Hazard and Dose Response, page 6-9).
- “[T]here is strong and compelling evidence for adverse effects of TCE exposure on male reproductive system and function” (Discussion/Synthesis of Noncancer Reproductive Toxicity Findings, page 4-487).

Regarding developmental toxicity, the U.S. EPA Toxicological Review states that:

- “[B]ased on weakly suggestive epidemiologic data and fairly consistent laboratory animal data, it can be concluded that TCE exposure poses a potential hazard for prenatal losses and decreased growth or birth weight of offspring.” (Major Conclusions in the Characterization of Hazard and Dose Response, page 6-10)
- “[B]ased on weakly suggestive, but overall consistent, epidemiologic data, in combination with evidence from experimental animal and mechanistic studies, it can be concluded that TCE exposure poses a potential hazard for congenital malformations, including cardiac defects, in offspring” (Major Conclusions in the Characterization of Hazard and Dose Response, page 6-11).

The studies cited by U.S. EPA in support of these conclusions were reviewed by OEHHA against the sufficiency of evidence criteria in regulation (Section 25306(g)(2)). Information reviewed for each of the cited studies included parameters related to biological plausibility in humans, including adequacy of experimental design, pattern of dosing, route of administration, numbers of test animals, choice of species, choice of dosage levels, and maternal toxicity. On the basis of the studies, effects and species identified above, OEHHA concluded that the sufficiency-of-evidence criteria in the regulation were met.

Comments were submitted on the Request for Relevant Information on TCE, by two individuals on behalf of the two organizations:

<b>Name</b>	<b>Date</b>	<b>Affiliation</b>
Faye Graul	May 9, 2013	Halogenated Solvents Industry Alliance, Inc. (HSIA)
Richard C. Coffin	May 14, 2013	Barg Coffin Lewis and Trapp, LLP with comments by Exponent on behalf of Schlumberger Technology Corporation (STC)

OEHHA reviewed the two submissions in the context of the regulatory criteria for listing chemicals under the authoritative bodies mechanism in Section 25306.

Comments received are grouped by topic, and the responses directly follow each summarized comment.

## 1. Formal Identification

### Comment:

The commenters stated that TCE has not been “formally identified” by the U.S. EPA in its 2011 Toxicological Review or otherwise as a male reproductive or developmental toxin [toxicant], citing the following statements in the U.S. EPA Toxicological Review document:

- a) Male Reproductive Toxicology: “In spite of the preponderance of studies demonstrating effects on sperm parameters, there is an absence of overwhelming evidence in the database of adverse effects of TCE on overall fertility in the rodent studies.” (page 4-490) [cited by HSIA]
- b) Developmental Toxicology: “In summary, an overall review of the weight of evidence in humans and experimental animals is suggestive of the potential for developmental toxicity with TCE exposure.” (page 4-556) [cited by HSIA and STC]

HSIA concluded that “such conclusions do not rise to the level of a ‘formal identification’ by an authoritative body for the purposes of Proposition 65. *See the American Chemistry Council v Office of Environmental Health Hazard Assessment et al., Sacramento County No. 34-2013-00140720 (April 19, 2013)*”.

### Response:

The statements from the U.S. EPA Toxicological Review of TCE quoted by HSIA do not represent the conclusions that constitute formal identification as causing reproductive toxicity by the authoritative body for purposes of Proposition 65.

- a) As noted above, in the section of the document titled “Major Conclusions in the Characterization of Hazard and Dose Response”, U.S. EPA stated that “Together, the human and laboratory animal data support the *conclusion that TCE exposure poses a potential hazard to the male reproductive system*” (emphasis added).

- b) Similarly for developmental toxicity, in the section of the document titled “Major Conclusions in the Characterization of Hazard and Dose Response”, U.S. EPA stated that “based on weakly suggestive epidemiologic data and fairly consistent laboratory animal data, *it can be concluded that TCE exposure poses a potential hazard for prenatal losses and decreased growth or birth weight of offspring*” and that “based on weakly suggestive, but overall consistent, epidemiologic data, in combination with evidence from experimental animal and mechanistic studies, *it can be concluded that TCE exposure poses a potential hazard for congenital malformations, including cardiac defects, in offspring*” (emphasis added).
- c) The statement by the Court in *American Chemistry Council v Office of Environmental Health Hazard Assessment et al.*, *Sacramento County* case order is not citable as a legal precedent, is referring to a preliminary order in the case, is not on point and is not relevant to the issues being raised here. The statement regarding the chemical bisphenol A was limited to the document being discussed in that case. The Court contrasted that document with another document in which it was determined that a formal identification had been made. As noted above, in the documents that discuss TCE, U.S. EPA has made clear, definitive statements that TCE can cause male reproductive and developmental toxicity, and has explicitly identified these statements as the Agency’s major conclusions.

Thus, TCE “is the subject of a report which is published by the authoritative body and ...concludes that the chemical causes...reproductive toxicity”<sup>5</sup>, and so has been formally identified by U.S. EPA in the Toxicological Review as causing reproductive toxicity.

Comment:

STC states that:

“The IRIS toxicity summary does not constitute a consensus opinion within the EPA on the weight-of-evidence for a causal association between TCE and male reproductive toxicity or developmental toxicity and therefore, does not constitute a formal identification of TCE as a male reproductive or developmental toxicant...”

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<sup>5</sup> Title 27, Cal. Code of Regulations, section 25306 (d)(1).

Response:

There is no requirement in Proposition 65 or its implementing regulations<sup>6</sup> that the authoritative body state that the document relied on is a consensus opinion on the weight-of-evidence for a causal association between a chemical and reproductive toxicity. However, the U.S. EPA Toxicological Review of Trichloroethylene states that “[t]his document has been reviewed in accordance with U.S. Environmental Protection Agency policy and approved for publication.” The document is a report published by an authoritative body, which concludes that the chemical causes reproductive toxicity and specifically and accurately identifies the chemical. The document also meets several of the formal-identification criteria specified in Section 25306(2)(a-f), in that it has been made subject to public review and comment prior to its issuance, published by the authoritative body in a publication, such as, but not limited to, the federal register and set forth in an official document utilized by the authoritative body for regulatory purposes. Thus, the regulatory criteria establishing that the chemical is “formally identified” by an authoritative body have been met.

## **2. Sufficiency of Evidence**

Comment:

STC concluded that the weight-of-evidence of a causal association between TCE and male reproductive effects reported in the U.S. EPA IRIS Toxicological Review does not support a conclusion that the association is causal. STC discussed methodological limitations in the epidemiologic studies reviewed by the U.S. EPA, and asserted that:

“The epidemiological data are very limited and insufficient to show that TCE causes male reproductive toxicity in humans.” (page 3)

“Overall, scant epidemiological data are available on the potential association between TCE exposure and male reproductive effects...Thus, the weight-of-evidence does not support a conclusion that TCE is associated with, much less causes, male reproductive effects.” (page 4)

STC discussed the influence of group size and systemic toxicity on the assessment of adverse male reproductive effects in animal studies and asserted that:

“Overall the toxicity studies with optimal study designs that include sufficient numbers of animals and multiple dose groups indicate that male reproductive toxicity is secondary to systemic toxicity...Given the weight-of-evidence for

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<sup>6</sup> Title 27, Cal. Code of Regulations, section 25306(d).

systemic toxicity being associated with both sperm effects and reproductive organ toxicity in rodents, TCE cannot be shown to directly induce male reproductive toxicity.” (page 5)

Response:

The authoritative bodies listing mechanism for Proposition 65 as well as longstanding case law does not allow OEHHA to substitute its judgment for that of an authoritative body regarding the weight-of-evidence that a chemical causes reproductive toxicity<sup>7</sup>.

Regarding epidemiologic studies of male reproductive toxicity of TCE, the commenters identify no factual errors by U.S. EPA in making its judgment. Indeed, the overall interpretations of the strength of the data in humans by U.S. EPA (“the available epidemiological data and case reports that associate TCE with adverse effects on male reproductive function are limited in size and provide little quantitative dose data”) and the commenters (“the weight-of-evidence does not support a conclusion that TCE is associated with, much less causes, male reproductive effects) are similar. However, U.S. EPA based its conclusion that TCE exposure poses a potential hazard to the male reproductive system on consideration of the epidemiologic and experimental animal data taken together, rather than independently as the commenters have done. Indeed, in evaluating the evidence in animals, U.S. EPA stated “[i]n animal studies,...there is strong and compelling evidence for adverse effects of TCE exposure on male reproductive system and function.” (page 4-487)

With regard to experimental animal studies, the commenters’ conclusion that “male reproductive toxicity is secondary to systemic toxicity” is in direct conflict with the judgment of the authoritative body. After review of exactly the same data, U.S. EPA stated that:

“[the] conclusion [that the observed reproductive toxicity was a secondary effect of generalized systemic toxicity] *is not supported* by the overall toxicological profile of TCE, which provides significant evidence indicating that TCE is a [male] reproductive toxicant.” (page 4-490) (emphasis added)

As with the epidemiologic studies of male reproductive toxicity of TCE, the commenters identify no factual errors by U.S. EPA in making its judgment about the relationship between systemic and male reproductive toxicity. OEHHA cannot substitute its

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<sup>7</sup> Final Statement of Reasons. Title 27 California Code of Regulations, section 25306 - Chemicals Formally identified by Authoritative Bodies. Available at [http://www.oehha.ca.gov/prop65/law/pdf\\_zip/12306FSRFeb1990.pdf](http://www.oehha.ca.gov/prop65/law/pdf_zip/12306FSRFeb1990.pdf); *Western Crop Protection v Davis* (2000) 80 Cal.App.4<sup>th</sup> 741; *Exxon Mobil Corp. v OEHHA* (2009)169 Cal.App.4<sup>th</sup> 1264

judgment for that of the authoritative body, nor can it substitute the conflicting judgment of the commenters when the authoritative body has considered the same information and no factual error by the authoritative body has been identified.

Comment:

HSIA and STC conclude that the weight-of-evidence for a causal association between TCE and developmental effects reported in the U.S. EPA IRIS Toxicological Review does not support a conclusion that the association is causal. The commenters base this conclusion on discussion of U.S. EPA's conclusions and on specific discussion of the studies pertaining to congenital cardiac defects and developmental immunotoxicity studies.

With respect to congenital cardiac defects (CCD), HSIA and STC both made comments stating all of the studies suggesting TCE plays a causal role in CCD were conducted by the same laboratory (Dawson *et al.*, 1990, Dawson *et al.*, 1993, and Johnson *et al.*, 2003). Issues raised by the commenters regarding use of these studies also include:

- "...no meaningful dose-response relationship..." (page 3, HSIA)
- "...pooled control data from other studies..." (page 3, HSIA)
- "...only research group that reported a positive association between TCE and CCD in experimental rodent studies." (page 8, STC)

HSIA also provided comments by Kimmel, Kimmel and DeSesso to OEHHA that had previously been submitted to U.S. EPA and were critical of the data U.S. EPA used on heart defects as a major endpoint for setting the Reference Dose (RfD) and Reference Concentration (RfC).

In addition, based on discussion of the study by Johnson *et al.* (2003)<sup>8</sup> in the OEHHA Public Health Goal for Trichloroethylene, HSIA stated with regards to that study:

"...it is clear that the evidence of developmental toxicity considered by the authoritative body (EPA) is not sufficient, as a primary study relied upon by EPA has been rejected by OEHHA as deficient" (emphasis in original). (page 2, HSIA)

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<sup>8</sup> Johnson et al., 2003. Threshold of trichloroethylene contamination in maternal drinking waters affecting fetal heart development in the rat. *Environmental Health Perspectives*. 111: 289-92.

Response:

As noted in the response to the preceding comment, the authoritative bodies listing mechanism for Proposition 65 does not allow OEHHA to substitute its judgment for that of an authoritative body regarding the weight-of-evidence that a chemical causes reproductive toxicity.

U.S. EPA specifically considered the limitations of the studies by Dawson *et al.* and Johnson *et al.*, but did not consider those limitations of sufficient concern to dismiss the findings in the studies:

“...while the studies by Dawson et al. (1993) and Johnson et al. (2003, 2005) [sic] have significant limitations, including the lack of clear dose-response relationship for the incidence of any specific cardiac anomaly and the pooling of data collected over an extended period, there is insufficient reason to dismiss their findings. See Section 4.8.3.3.2 for additional discussion of the conclusions with respect to TCE-induced cardiac malformations.” (page 6-11)

The additional discussion in Section 4.8.3.3.2 states:

“The analysis of the incidence data for cardiac defects observed in the Dawson et al. (1993, 1990) and Johnson et al. (2005, 2003) studies has been critiqued (Watson et al., 2006). Issues of concern that have been raised include the statistical analyses of findings on a per-fetus (rather than the more appropriate per-litter) basis (Benson, 2004). Johnson et al. was further criticized for the use of nonconcurrent control data in the analysis (Hardin et al., 2004). In response, the study author has further explained procedures used (Johnson et al., 2004) and has provided individual litter incidence data to the EPA for independent statistical analysis (P. Johnson, personal communication, 2008) (see Section 5.1.2.8). In sum, while the studies by Dawson et al. (1993, 1990) and Johnson et al. (2005, 2003), have significant limitations, there is insufficient reason to dismiss their findings.” (page 4-561)

As noted both in the introduction to this document and in response to comments on formal identification, U.S. EPA stated in the “Major Conclusions in the Characterization of Hazard and Dose Response” section of its 2011 Toxicological Review of TCE that “it can be concluded that TCE exposure poses a potential hazard for prenatal losses and decreased growth or birth weight of offspring,” and that “it can be concluded that TCE exposure poses a potential hazard for congenital malformations, including cardiac defects, in offspring” (page 6-11). U.S. EPA has made a scientific judgment about the validity of the related studies of Dawson *et al.* and Johnson *et al.* in hazard

identification, and drawn specific conclusions on that basis. The commenter has disagreed with that judgment, but has not identified any additional relevant data not considered by U.S. EPA.

With regard to the HSIA and STC comments on CCD, U.S. EPA responded to some related concerns over the use of studies conducted by Johnson *et al.* for its Toxicological Review of TCE. These studies by Johnson *et al.* identified CCD as a developmental endpoint that was altered by TCE exposure, and were among the studies that U.S. EPA used to set the RfD. U.S. EPA also considered the comments from Kimmel, Kimmel and DeSesso, as well as from the Agency's Science Advisory Board (SAB). In response, U.S. EPA stated that:

“In accordance with the SAB review, EPA acknowledges the limitations of the available data, but maintains its conclusion that TCE poses a human health hazard for developmental cardiac effects.” (page I-9)

Similarly, U.S. EPA responded that:

“In accordance with SAB recommendations (see Section I.8.2.8), EPA has selected the immune effects from Keil *et al.* (2009) and the cardiac malformations from Johnson *et al.* (2003) as the principal studies supporting the RfC, and the immune effects from Keil *et al.* (2009) and Peden-Adams *et al.* (2008) and the cardiac malformations from Johnson *et al.* (2003) as the principal studies supporting the RfD.” (page I-25)

U.S. EPA also stated in its “Response to Major Interagency Scientific Comments on the Interagency Science Discussion Draft IRIS Toxicological Review of Trichloroethylene<sup>9</sup>”:

“Regarding the dose-response, the SAB noted that the non-monotonic dose-response reported in Johnson *et al.* was consistent with other subsequent studies. The information on the incidence of cardiac malformations provided to U.S. EPA by Dr. Johnson via personal communication was for the same study findings that were previously published in the peer reviewed literature, and thus are considered by U.S. EPA to be peer reviewed.” (page 1)

Thus, the concerns raised by the commenters have been considered and rejected by both U.S. EPA and the Agency's Science Advisory Board.

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<sup>9</sup> EPA's Response & Interagency Science Discussion Comments. September 2011. Available online at [http://cfpub.epa.gov/ncea/iris\\_drafts/recordisplay.cfm?deid=237625](http://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=237625).

In the 2009 “Public Health Goals [PHGs] for Chemicals in Drinking Water: Trichloroethylene” document<sup>10</sup>, OEHHA did not rely upon the Johnson *et al.* study as the primary study for derivation of the PHG. While the 2009 PHG document discusses limitations of the study for purposes of quantitative dose-response assessment, it does not provide an assessment of the utility of the study in hazard identification.

Comment:

Regarding developmental immunotoxicology studies reviewed in the 2011 U.S. EPA Toxicological Review, STC stated that “...the strength of the epidemiological and toxicological evidence does not support a causal role between TCE and developmental immunological effects that warrant listing TCE as a developmental toxicant by the State of California.” The commenters also note that mice were exposed postnatally in these studies, limiting the ability to determine what effects prenatal TCE exposure may have had on their immune system.

Response:

The proposed addition of TCE to the Proposition 65 list as known to cause reproductive toxicity includes consideration of U.S. EPA’s evidence and conclusions in the 2011 Toxicological Review of TCE relevant to all manifestation of developmental toxicity of TCE. As noted above, U.S. EPA concluded that TCE can cause developmental toxicity manifested as prenatal losses and decreased growth or birth weight of offspring and congenital malformations, including cardiac defects, in offspring. U.S. EPA otherwise identified TCE as causing developmental immunotoxicity by basing the inhalation reference concentration and chronic oral reference dose on critical effects that include developmental immunotoxicity in mice. Given the substantial postnatal exposure in the developmental immunotoxicity studies cited by U.S. EPA, however, OEHHA has determined that this manifestation of developmental toxicity of TCE is not applicable to Proposition 65. Nonetheless, the other developmental effects identified by U.S.EPA are sufficient to meet the criteria in the Proposition 65 regulations.

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<sup>10</sup> Available at [http://www.oehha.ca.gov/water/phg/pdf/TCE\\_phg070909.pdf](http://www.oehha.ca.gov/water/phg/pdf/TCE_phg070909.pdf).