



September 26, 2016

Submitted Via E-Mail

Michelle Ramirez
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency
P.O. Box 4010, MS-12B
Sacramento, CA 95812-4010
Attention: 2016 Chloroform Reconsideration
Email: P65Public.comments@oehha.ca.gov

Re: Availability of Hazard Identification Materials to Support Reconsideration of Listing—Chloroform

Dear Ms. Ramirez:

The American Chemistry Council¹ (ACC) appreciates this opportunity to provide comments to the California Environmental Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA) on the reconsideration by the Developmental and Reproductive Toxicant Identification Committee (DARTIC) of chloroform as a chemical listed as a reproductive toxicant under Proposition 65, and the availability of Hazard Identification Materials (HIM) to support the reconsideration.² The ACC Chlorine Chemistry Division represents the major producers and users of chlorine in North America and works to promote the sustainability of chlorine chemistry processes, products and applications. ACC supports the thorough review and assessment of chloroform utilizing the most up to date scientific knowledge, methods and practices to underlie OEHHA's decision making.

At its October 27, 2016 meeting, the DARTIC will be tasked with determining whether the available scientific evidence supports a conclusion that chloroform has been "clearly shown, through scientifically valid testing according to generally accepted principles to cause reproductive toxicity."³ The DARTIC's review must include evaluating the sufficiency of the available scientific literature for chloroform using a weight of evidence approach to determine if it meets

¹ ACC represents the leading companies engaged in the business of chemistry. ACC members apply the science of chemistry to make innovative products and services that make people's lives better, healthier and safer. ACC is committed to improved environmental, health and safety performance through Responsible Care®, common sense advocacy designed to address major public policy issues, and health and environmental research and product testing. The business of chemistry is a \$797 billion enterprise and a key element of the nation's economy. It is the largest exporting sector in the U.S., accounting for 14 percent of U.S. exports. Chemistry companies are among the largest investors in research and development, investing \$93 billion in 2015.

² OEHHA. 2016. Evidence of Developmental and Reproductive Toxicity of Chloroform. August 12, 2016. Weblink: <http://oehha.ca.gov/media/downloads/cnr/chloroformhid081216.pdf>.

³ Cal. Health & Safety Code § 25249.8.



the criteria for listing under Proposition 65.⁴ The available evidence does not support a conclusion that chloroform causes reproductive toxicity.

- **Previous Reviews by Government Agencies Show Lack of Consistent Evidence for Chloroform and Reproductive Toxicity**

In 2001, the U. S. Environmental Protection Agency (EPA) conducted a review of chloroform, including reproductive and development toxicity.⁵ EPA's assessment found that chloroform had been evaluated in a number of chronic and reproductive/developmental studies and, although some effects had been observed, those effects were generally secondary to maternal toxicity. In 2004, the World Health Organization (WHO) conducted a review of the available chloroform science and noted no impacts on fertility and reproduction in rodents.⁶ While some impacts on development were observed, the results were inconsistent and usually resulted when maternally toxic doses were given.

Similarly, in 2004 and 2005, the DARTIC reviewed the available scientific evidence for reproductive toxicity (including developmental toxicity, female reproductive toxicity, and male reproductive toxicity) and chloroform was not moved forward by the DARTIC for listing. Chloroform was later listed in 2009 under the Labor Code mechanism due to a 2009 ACGIH threshold limit value (TLV) that was based on a developmental endpoint.⁷ However, in 2012, the Occupational Safety and Health Administration (OSHA) amended the federal Hazard Communication Standard and no longer incorporates TLVs as a definitive source for establishing that a chemical is hazardous. Therefore, the Labor Code listing of chloroform became invalid.

- **The Evidence is Inconsistent and Does Not Clearly Show Chloroform Causes Reproductive Toxicity**

The HIM includes a discussion and summary of the available human and animal data for chloroform and reproductive endpoints. The materials include studies collected for consideration during the 2004 and 2005 DARTIC reviews and any materials published through 2015. As the DARTIC reviews the available information, it must evaluate the sufficiency of the available data using a weight of evidence approach. A robust weight of evidence assessment should evaluate the quality and consistency of the findings among studies as well as the relevance of animal findings in conjunction with the absence of

⁴ OEHHA. 1993. (Nov. 1993) CRITERIA FOR RECOMMENDING CHEMICALS FOR LISTING AS "KNOWN TO THE STATE TO CAUSE REPRODUCTIVE TOXICITY". Weblink: <http://oehha.ca.gov/media/downloads/proposition-65/proposition-65/dartcriterianov1993.pdf>.

⁵ EPA. 2001. Toxicological Review of Chloroform. In Support of Summary Information on the Integrated Risk Information System (IRSI). Weblink: https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0025tr.pdf.

⁶ WHO. 2004. Concise International Chemical Assessment Document 58. Chloroform. Weblink: <http://www.who.int/ipcs/publications/cicad/en/cicad58.pdf?ua=1>.

⁷ Cal. Health and Safety Code § 25249.8(a).



sufficient human data. As discussed below, based on the data summarized in the HIM, chloroform has not been clearly shown to cause reproductive toxicity.

- **Female reproductive toxicity**

Spontaneous Abortions – Three epidemiology studies (Savitz et al., 2005; Waller et al., 1998; Wennborg et al., 2000) demonstrate a lack of consistency for increased risk of spontaneous abortions as a result of exposure to chloroform and/or trihalomethanes (THMs). For example, the Wennborg et al. study reported only a weak association with increased risk from chloroform exposure. Additionally, a 2006⁸ study by Savitz and colleagues found that pregnancy loss was not associated with high personal THM exposure (note: Savitz et al., 2006 is a peer-reviewed article with a subset of findings published in Savitz et al., 2005). Additionally, the animal data are also inconsistent. For example, Infante-Rivard (2004) did not yield statistically significant results even when the authors were asked by the DARTIC to utilize a less conservative cut-off point.

Still Birth – Epidemiologic data are not consistent for increased risk of still births with chloroform concentrations in water. One recent study found no increased risk (Iszatt et al., 2014); two studies found increased risks, but they were not statistically significant (Dodds et al., 2004; King et al., 2000); and one study (Toledano et al., 2005) found a small, but statistically significant, increased risk.

Fertility – Data are lacking and inconsistent for impacts to fertility. The available human study observed no impacts (Dahl et al., 1999), one mouse inhalation study observed reduced fertility (Murray et al., 1979), and one mouse study observed increased fertility (Chapin et al., 1977/NTP 1988).

Menstrual Cycle Function – The available human data do not indicate impacts to menstrual cycle length (Windham et al., 2003).

- **Male reproductive toxicity**

Sperm Quality – Human and animal data are mixed when evaluating impacts to sperm quality. Some studies found a decrease in sperm quality (Land et al., 1981; Zeng et al., 2013, 2014), whereas others found no association with decreased sperm quality (Chapin et al., 1977/NTP 1988; EPA, 1980; Heywood et al., 1979; Iszatt et al., 2013).

⁸ Savitz, D. A., Singer, P. C., Herring, A. H., Hartmann, K. E., Weinberg, H. S., & Makarushka, C. 2006. Exposure to drinking water disinfection by-products and pregnancy loss. *American Journal of Epidemiology*, 164(11), 1043-1051.



○ **Developmental toxicity**

Gestational Stage and Size Ratio – The available data lack consistency associated with changes to gestational size. Ten human studies (Costet et al., 2012; Danileviciute et al., 2012; Grazuleviciene et al., 2011; Hinckley et al., 2005; Hoffman et al., 2008; Levallois et al., 2012; Porter et al., 2005; Rivera-Nuñez and Wright, 2013; Savitz et al., 2005; Villanueva et al., 2011) found no risk of small for gestational age (SGA), whereas three human studies found increased risk of SGA (Kramer et al., 1992; Summerhayes et al., 2012; Wright et al., 2004).

Gestation Length – There are no demonstrated effects of chloroform on length of gestation in experimental studies in animals. The available human preterm birth studies illustrate no adverse health effect as five studies found no association with gestational length (Costet et al., 2012; Hinckley et al., 2005; Kramer et al., 1992; Rivera-Nuñez and Wright, 2013; Villanueva et al., 2011) and three studies showed a protective effect on gestation length (Lewis et al., 2007; Savitz et al., 2005; Wright et al., 2004).

Summary

The available scientific literature does not support the conclusion that chloroform is a reproductive toxicant. Therefore, the DARTIC should direct OEHHA to remove chloroform from the Proposition 65 list because the weight of the evidence does not merit its retention. ACC appreciates consideration of these comments by the DARTIC members as well as OEHHA staff. If you have any questions, please feel free to contact me by phone at 202-249-6709 or via email at judith_nordgren@americanchemistry.com.

Respectfully,



Judith Nordgren
Managing Director Chlorine Chemistry Division

