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July 7, 2020

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Director
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency
1001 I Street
Sacramento, California 95814

Re: Notice of proposed rulemaking, amendment to Section 25705 Specific Regulatory Levels Posing No Significant Risk: dichloroacetic acid, trichloroacetic acid, and dibromoacetic acid

Dr. Zeise:

The American Chemistry Council's Chlorine Chemistry Division (CCD) [1] submits the following comments on the proposed No Significant Risk Levels (NSRLs) for dichloroacetic acid (DCA), trichloroacetic acid (TCA), and dibromoacetic acid (DBA). These comments echo those we submitted on May 1, 2020, on the proposed Public Health Goals (PHGs) for these same three chemicals. CCD is troubled by OEHHA's decision to move ahead with NSRLs before the Office has considered the information submitted in response to the PHG proposal and before the science that is the basis for both the PHGs and NSRLs has been subject to peer review. It is not clear what has prompted this action after these chemicals have been on the Proposition 65 list without NSRLs for up to 24 years.[2] We urge OEHHA to withdraw the current proposals until the science regarding the carcinogenic potential of these substances has been fully considered as part of the PHG process.

The proposed NSRLs for DCA, TCA, and DBA are based on cancer data from mouse studies that are limited, inconsistent, and not supported by the available genotoxicity data. The

[1] The American Chemistry Council (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's Chlorine Chemistry Division represents the major producers and users of chlorine in North America and works to promote and protect the sustainability of chlorine chemistry processes, products, and applications

[2] OEHHA included DCA in a group of "second priority" chemicals for establishment of NSRLs in September 2012, behind 37 first priority chemicals, including DBA. Of the 37 chemicals, NSRLs have been established for only 3. TCA was not listed on Proposition 65 until after the 2012 prioritization.

evidence for each HAA is discussed below. Moreover, the OEHHA proposal does not consider the long history of low-level exposure to these substances, and several other disinfection byproducts (DBPs) considered to be liver carcinogens by the Office,[3] resulting from the chlorination of public drinking water supplies necessary to protect public health from waterborne disease. This history reveals a lack of consistent evidence of an increased incidence of liver cancer resulting from exposure to DBPs in the multiple epidemiology studies that have been conducted.

OEHHA Overstates the Potential Cancer Risk from DCA Exposure

The Draft NSRL for DCA is based on reports of liver tumors in studies conducted in male mice. The evidence in female mice is less consistent, however, and studies in rats suggest lower sensitivity than in mice. Moreover, the mice in the key study selected by OEHHA for the DCA risk assessment (DeAngelo et al., 1999)[4] exhibited a high rate of spontaneous liver tumors and significant mortality and body weight decreases at the two highest doses.[5] Consequently, DeAngelo *et al.* is not an appropriate study for deriving a cancer slope factor (CSF). The OEHHA analysis, in fact, notes limitations for all of the cancer studies considered as candidates for deriving the proposed NSRL. In light of these limitations, it is unclear why OEHHA did not derive the geometric mean of the CSFs for the most relevant studies (i.e., 0.027 per mg/kg per day)—rather than selecting the highest CSF among the male mouse studies.[6]

Moreover, although DCA appears to be weakly genotoxic at higher doses, OEHHA assumes that the liver tumors result from a genotoxic mechanism. As noted by the US Environmental Protection Agency (USEPA), there is little basis for judging whether genotoxic effects—including alterations in the genetic messages for various proto-oncogenes—are important in the carcinogenic response, and if so, whether the dose-response curve for genotoxic effects is linear or nonlinear.[7] USEPA notes, moreover, that:

> The importance of these issues regarding the mechanism and shape of the dose-response curves for genotoxicity and carcinogenicity are highlighted by

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[3] OEHHA's estimates of the carcinogenic potential of chloroform, bromodichloromethane (BDCM), and dibromochloromethane (DBCM) also are based on the incidence of liver tumors in animal studies.

[4] DeAngelo, AB *et al.* Hepatocarcinogenicity in the male B6C3F1 mouse following a lifetime exposure to dichloroacetic acid in the drinking water: dose-response determination and modes of action. *J Toxicol Environ Health A* 58(8):485−507 (1999).

[5] OEHHA. First Public Review Draft; Haloacetic Acids in Drinking Water; Monochloroacetic Acid, Dichloroacetic Acid, Trichloroacetic Acid, Monobromoacetic Acid, Dibromoacetic Acid (January 2020).

[6] OEHHA used the geometric mean approach to develop the PHG for chloroform.

[7] USEPA. Toxicological Review of Dichloroacetic Acid (CAS No. 79-43-6). In support of support information on the Integrated Risk Information System (IRIS). EPA 635/R-03/007 Washington, DC (August 2003).

> comparing the concentrations of DCA in water that are carcinogenic in animals (0.05 to 5 grams per liter) with those that are commonly observed in chlorinated drinking water (10 to 100 micrograms per liter) . . . Thus, concentration values are about 4-5 orders of magnitude lower in drinking water than were used in experimental studies in animals. This difference is further magnified by the lower water intake per unit body weight of humans (approximately 0.03 L/kg-day) compared to rodents (about 0.1-0.2 L/kg-day).[8]

TCA Is Not a Genotoxic Carcinogen

As the OEHHA analysis notes, while there is consistent evidence of liver tumors in male mice exposed to TCA, the evidence for tumors is less consistent in female mice and tumors have not been reported in rat studies. As is the case for DCA, the key study selected by OEHHA (DeAngelo et al., 2008)[9] reported a high incidence of tumors in the control group which diminishes the significance of the findings in the dose groups. Although OEHHA considered and rejected two other studies with male mice, it is unclear why the study by Pereira (1996)[10] was excluded. That study reported liver tumors in female mice exposed to TCA for up to 576 days (82 weeks). Benchmark dose (BMD) modeling of the results of the Pereira study produces a 95% lower confidence limit on the BMD for a 10% response ($BMDL_{10}$) of 4.67 mg/kg per day compared to a $BMDL_{10}$ of 1.50 mg/kg per day for the study by DeAngelo *et al.*[11]

Peroxisome proliferation also has been demonstrated in a number of short- and long-term TCA exposure studies in both rats and mice. In light of the very limited evidence for the genotoxicity of TCA, it is likely that the mouse liver tumors result from a non-genotoxic mechanism defined by an exposure threshold in laboratory animals that is of questionable relevance to humans.

The NSRL for DBA Should Not Be Based on Carcinogenicity

The cancer evidence for DBA is limited to a National Toxicology Program (NTP) drinking water study reporting liver tumors in male and female mice and an increase in lung tumors in

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8 Ibid, at 71.

9 DeAngelo AB *et al.* The induction of hepatocellular neoplasia by trichloroacetic acid administered in the drinking water of the male B6C3F1 mouse. *J Toxicol Environ Health A* 71(16):1056−1068 (2008).

10 Pereira MA. Carcinogenic activity of dichloroacetic acid and trichloroacetic acid in the liver of female B6C3F1 mice. *Fundam Appl Toxicol* 31(2):192−199 (1996).

11 USEPA. Toxicological Review of Trichloroacetic Acid (CAS No. 76-03-9). In support of summary information on the Integrated Risk Information System (IRIS). EPA/635/R-09/003F (September 2011).

male mice.[12] Liver and lung tumors were not observed in rats in the NTP study.[13] The control groups for both the male and female mice exhibited a high rate of spontaneous liver tumors, however, and the incidence of lung tumors was increased in the control group of the male mice. In addition, the lung tumors did not show a clear dose-response in the male mice - tumors were significantly increased at a mid-dose of 500 mg/L, but not at the highest dose of 1000 mg/L.

Given the limited cancer data available for DBA, and the conflicting results reported in mice and rats, the mouse cancer data should not be used as the basis for the NSRL. Moreover, any estimate of cancer risk should not include the lung tumors in male mice as a result of the high spontaneous incidence in the control animals and the lack of a clear dose-response in the male mice.

As outlined above, the proposal to establish NSRLs for DCA, TCA, and DBA is both flawed and premature. CCD urges OEHHA to withdraw the current proposal until stakeholder comments on the Office's assessment as part of the PHG process are fully considered and the PHG assessment is subject to peer review. Please contact me at 202-249-6709 or at judith_nordgren@amerincanchemistry.com if you have questions about the above information.

Sincerely,

Judith Nordgren
Managing Director
Chlorine Chemistry Division

[12] NTP. Toxicology and Carcinogenesis Studies of Dibromoacetic Acid (CAS No. 631-64-1) in F344/N Rats and B6C3F1 Mice (Drinking Water Studies). Research Triangle Park, NC (2007).

[13] Increases in malignant mesothelioma in male rats and mononuclear cell leukemia in female rats were reported at the highest dose.