Date: 01.04.2018

External peer review of the proposed "Public Health Goals for Health Effects of Water Contaminants: Cis-1,2-Dichloroethylene and Trans-1,2-Dichloroethylene."

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Overall Evaluation Summary:

Originally the proposed Public Health Goals (PHGs) for cis-1,2-dichloroethylene and trans-1,2-dichloroethylene were published in 2006 as mandated "under the California Safe Drinking Water Act of 1996 (Health and Safety Code section 116365), the Office of Environmental Health Hazard Assessment (OEHHA) develops PHGs for drinking water contaminants in California based exclusively on public health considerations. OEHHA periodically reviews PHGs and revises them as necessary based on the availability of new scientific data. This document presents an update for cis- and trans-1,2-dichloroethylene for which PHGs were published in 2006. PHGs published by OEHHA are for use by the State Water Resources Control Board (SWRCB) in establishing primary drinking water standards (State Maximum Contaminant Levels, or MCLs). Whereas PHGs are based solely on scientific and public health considerations without regard to economic considerations, MCLs adopted by SWRCB consider economic factors and technological feasibility. State law requires that MCLs be set at a level that is as close as feasible to the corresponding PHG, placing emphasis on the protection of public health. PHGs established by OEHHA are not regulatory and represent only non-mandatory goals. Under federal law, MCLs established by SWRCB must be at least as stringent as the corresponding federal MCL if one exists. In July 2014, responsibility for the state's drinking water regulatory program was transferred to SWRCB from the California Department of Public Health (taken directly from the review document's preface page iii)". These documents and the analyses contained therein provide estimates of the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime.

Overall the document is well written with adequate details and appendices to explain newer methodology and guide line which have been used to arrive at the proposed PHGs of 13 and 50 ppb for cis-1,2-dichloroethylene(cis-1,2-DCE) and trans-1,2-dichloroethylene (trans-1,2-DCE), respectively. No new studies are published dealing with toxicity of these chemicals in general and chronic toxicity including carcinogenicity in particular since the last PHG values were set in 2006. Since then both cis-1,2-DCE and trans-1,2-DCE were detected in recent years in California public water supply wells in the range of 0.097 - 40 ppb for cis-1,2-DCE and 1.8 – 33 ppb for trans-1,2-DCE. Cis-1,2-DCE is not produced in United States. Therefore, its genesis could be contributed to anaerobic degradation of polychloroethylenes, namely perchloroethylene (PCE) and trichloroethylene (TCE) due to their relatively extensive use in industry. Trans-1,2-DCE is currently used in industry and could be a source of water contaminant, however, its formation through anaerobic degradation of PCE and TCE is also possible while such possibilities cannot be substantiated.

Useful appendices are also included detailing the use of software for specific calculation details, current guidelines and practices.

Conclusion 1: Proposed PHG for Cis-1,2-Dichloroethylene

The original PHGs values were set in 2006 as 100 ppb for cis-1,2-DCE based upon the observation of McCauley et al., 1990 (as presented in 1995) of increased kidney weight in a 90 days study. The same study is used to derive current proposed PHG of 13 ppb by using benchmark dose modeling software (BMDS), updated drinking water consumption, dermal/inhalation estimates from house hold tap water and updated revised intra-species variability factor. These advancements in risk assessments have led to a proposed updated PHG of 13 ppb for cis-1,2-DCE, a reduction from 100 ppb which was originally set in 2006.

The carcinogenic potential of cis-1,2-DCE cannot be evaluated due to lack of information. However, these compounds are not listed in a recent EPA proposition 65 program either as a carcinogen or reproductive toxicants (EPA, 2015).

PHG DERIVATION:

The study by McCauley et al. (1990 as presented in McCauley et al., 1995) used by OEHHA in 2006 is again used for derivation of current updated PHG of cis-1,2-DCE utilizing increased liver and kidney weights without related histological findings. Benchmark dose software (BMDS, version 2.6, USEPA) is used to calculate the point of departure (POD). Continuous models were run with default parameters and a bench mark response (BMR) of one standard deviation (SD) from control mean; a methodology used for compounds where data lack to a level of significant biological response. Using Hill model $BMDL_{1sd}$ was calculated as 376 mg/kg-day for changes in rats' kidney relative weight used as POD because the lowest BMDL value derived from the model fits the data well and is the most sensitive end point. Acceptable daily dose (ADD) calculations of 0.00125 mg/kg-day are described in proper details. Since cis-1,2-DCE is a volatile compound, its exposure will also occur via inhalation/dermal routes as estimated by CalTox 4.0 modeling. A RSC of 0.8 was rightfully used to calculate the public protective concentration of cis-1,2-DCE as 13 ppb.

Based upon increased relative kidney weight in male rats from 90 days oral gavage study using various sophisticated risk assessment tools and updated guidelines and practices led to proposed PHG as 13 ppb for cis-1,2-DCE as proposed by OEHHA.

RISK CHARACTERIZATION:

The calculated proposed PHG of 13 ppb is based upon noncarcinogenic effect of cis-1,2-DCE causing an increased kidney weight. Its highest level of 22 ppb has been found in California public water system and can be rightfully attributed to incomplete anaerobic degradation of TCE and PCE to cis-1,2-DCE as it is not commercially available in the United States. No chronic, developmental or reproductive toxicity studies are otherwise reported for cis-1,2-DCE.

The cis-1,2-DCE research has not been actively pursued since the original PHG was set in 2006. The proposed PHG has rightfully incorporated updated risk assessment and sophisticated methodology by utilizing current state-of-the-art of BMD modeling for estimation of POD, updated age-specific water intake rates, dermal and inhalation exposure modeling and updated intra-species variability factor.

OTHER STANDARD CRITERIA:

No Comments or Suggestions. Reported values in the document are given below**:**

- US EPA's MCL and MCLG for cis-1,2-DCE is 70 ppb. Current California's MCL is 6 ppb.
- US EPA 2010 review calculated chronic oral RfD as 0.002 mg/kg-day derived from $BMDL_{10}$ of 5.1 mg/kg-day based upon adverse effects on kidneys (McCauley et al., 1995) and uncertainty factor of 3,000 (USEPA, 2010b).

Conclusion 2: Proposed PHG for Trans-1,2-Dichloroethylene

For trans-1,2-DCE, since no new findings are described since 2006, the proposed PHG is derived by using immunotoxicity end points (Shopp et al., 1985) resulting in changing the critical study for risk characterization due to more sensitive end points and using a well-validated and predictive test. Other improvement to derive PHG for trans-1,2-DCE included more sophisticated estimation of POD through BMD modeling, updated age-specific drinking water intake rates, modeling to estimate dermal and inhalation exposures and an updated intra-species variability factors.

The PHG set for trans-1,2-DCE of 60 ppb in 2006 was based upon increases in liver weight and increases in alkaline phosphatase in a 90 days drinking water study (Barnes et al., 1985). The updated revised proposed value is reduced to 50 ppb using the immunological findings of Shopp et al. (1985) and the assertion that such end points are predictive of overall immunotoxicity (Landics, 2007; Loveless et al., 2007; Luster et al. 1993). Updated drinking water intake rates, dermal/inhalation exposure estimates by household tap water and updated intra-species variability concept were also applied in the present assessment.

No new toxicological study for trans-1,2-DCE involving animals or humans is published since 2006 PHG. However, a series of epidemiological studies are published (Ruckart, et al., 2013, 2014, 2015) reporting water contamination at Base Camp Lejeune, North Carolina. Predominant contaminants were TCE, PCE and benzene followed by vinyl chloride and trans-1,2-DCE. The vinyl chloride and trans-1,2-DCE levels may also be reflective of biodegradation of TCE and PCE rather than as primary contaminants. A distinction between these two possibilities cannot be made which is inconsequential as this would not change the exposure levels.

A case control study was conducted to determine if children born to mothers who consumed contaminated drinking water at Camp Lejeune during pregnancy increases the chance of childhood hematopoietic cancers, neural tube defects or oral cleft. Odd ratio calculated for various exposure were greater than one indicating high confidence interval. No evidence was noted related to trans-1,2-DCE exposure and health outcomes examined (Ruckart et al., 2013).

A second cross sectional study (Ruckart et al., 2014) was addressed at Camp Lejeune's for contaminated water intake in relation to premature birth, small gestational age, term low birth weight and reduced mean birth weight. In utero exposure to TCE was associated with small gestational weight, low birth weight and reduced birth weight; PCE to pre term birth and benzene to low term birth weight. Trans-1,2-DCE was not implicated in any correlations.

The third study (Ruckart, 2015) of contaminated water exposure at Camp Lejeune related to male breast cancers. Cumulative odd ratios and confidence interval related to chlorinated ethylenes, PCE, trans-1,2-DCE, and vinyl chloride were 1.2 (95/CI, 0.16-5.89), 1.5 (95/CI, 0.30-6.11) and 1.19(95/CI, 0.16-5.89), respectively. Adjusted odd ratios for high cumulative exposure ratios for TCE, benzene and the cumulative chlorinated ethylenes were not elevated. Authors suggest that high cumulative exposure to PCE, trans-1,2-DCE and vinyl chloride indicate possible association to male breast cancer.

However, odd ratios (OR) for PCE and vinyl chloride exposure based upon two cases and the OR for trans-1,2-DCE exposure based on three cases in the cumulative group, resulted in large confidence intervals.

The carcinogenic potential of trans-1,2-DCE cannot be evaluated due to lack of information. However, trans-1,2-DCE not listed in a recent EPA proposition 65 program either as a carcinogen or reproductive toxicants (EPA, 2015).

PHG DERIVATION:

The PHG value for trans-1,2-DCE is proposed to be 50 ppb based upon the existing study by Shopp et al. (1985). The chemical as such is not extensively investigated for chronic toxicity with limited the studies related to reproductive and developmental toxicity. Genotoxicity and mutagenicity studies are generally negative while carcinogenicity evaluation is lacking for trans -1,2-DCE. New toxicity studies for trans-1,2-DCE do not exist since the original PHG was set in 2006. Reevaluation of existing studies leads to immunotoxicity as the critical end point for risk characterization (Shopp et al., 1985). The use of current available advanced risk assessment methodology such as estimation of POD by BMD modeling, updated age-specific water intake rates, modeling to estimate dermal and inhalation exposure and updated intra-species variability has been appropriately used which resulted in the proposed PHG of 50 ppb for trans-1,2-DCE.

RISK CHARACTERIZATION:

The proposed PHG of 50 ppb is calculated on the basis of adverse effects on the immune system. A very low level of trans-1,2-DCE (4.8 ppb) has been reported in California public water system. No chronic toxicity studies and limited developmental and reproductive toxicity studies are reported.
Although no new toxicity studies for trans-1,2-DCE were conducted since the 2006 PHGs publication, an existing immunotoxicity study by Shopp et al. (1985) provided immunotoxic critical endpoint and has been utilized to study risk characterization. To improve risk assessment, current updated risk assessment methodology is used to provide more relevant estimation of POD by utilizing BMD modeling, updated age-specific drinking water intake rates, modeling better estimates for dermal and inhalation exposures and an updated intra-species variability factor leading to the proposed PHG.

OTHER STANDARD CRITERIA:

No Comments or Suggestions. Reported values in the document are given below**:**

- US EPA's MCL and MCLG for trans-1,2-DCE are both 100 ppb. The current California MCL is 10 ppb.
- US EPA 2010 review calculated chronic oral RfD as 0.02 mg/kg-day derived from $BMDL_{1sd}$ of 65 mg/kg-day based upon adverse effects on immune system (Shoppe et al., 1985) and uncertainty factor of 3,000 (USEPA, 2010b).
- In June 2015, US EPA updated its Human Health Ambient Water Quality Criteria for trans-1,2-DCE based on the 2010 RfD to100 ppb (U.S. EPA 2015).

Appendices:

APPENDIX I. BMD Modeling:

Adequate details are provided for utilizing BMD modeling for cis-and trans-1,2-dichloroethylene.

APPENDIX II. CalTOX Modeling:
Adequate details are provided to explain how this software is utilized for calculating the levels of cis- and trans-1,2-DCE for an adult exposure.

APPENDIX III. Default uncertainty factors for PHG Derivation:
Various parameters are described and parameters used in present PHG evaluations are marked.

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