Public Health Goals

Responses to Comments on Technical Support Document

Public Health Goals for Cis- and Trans-1,2-Dichloroethylene in Drinking Water

July 2018

Pesticide and Environmental Toxicology Branch
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

TABLE OF CONTENTS

INTRODUCTION

The draft technical support document *Public Health Goals for Cis- and Trans-1,2-Dichloroethylene in Drinking Water* was released by the Office of Environmental Health Hazard Assessment (OEHHA) for public comment on August 4, 2017 and a public workshop was held on September 18, 2017. The draft proposed an update to the 2006 public health goals (PHGs) for cis- and trans-1,2-dichloroethylene, and provided the scientific basis for the update. This draft also received formal external scientific peer review pursuant to Health and Safety Code Section 116365(c)(3)(D). The document was revised in response to public comments and the external scientific peer review. The revised draft was released for public comment on June 1, 2018.

OEHHA's responses to comments received are summarized herein. Public and peer review comments are directly quoted (italicized), followed by OEHHA's responses. The full citations of journal publications and reports cited in the comments and responses are given in the PHG document.

The full text of the public and peer review comments is available on OEHHA's website. No comments were received on the June 2018 draft. Public comments on the August 2017 draft were received from Environmental Working Group.

External scientific peer review comments were received from:

Ghulam Ahmad Shakeel Ansari, PhD
Professor
Department of Pathology
The University of Texas Medical Branch

John Barnett, PhD
Professor and Chair
Department of Microbiology, Immunology and Cell Biology
West Virginia University School of Medicine

Virunya Bhat, PhD, DABT
Principal Toxicologist
NSF International

Public comments and OEHHA's responses are an important part of the overall PHG development process under Health and Safety Code Section 57003. They provide for deliberation and in-depth consideration of the underlying scientific issues during PHG development. The PHG document has now been finalized and is available at www.oehha.ca.gov.

For more information about the PHG process or to obtain copies of PHG documents, visit the OEHHA website. OEHHA may also be contacted at:

Office of Environmental Health Hazard Assessment
California Environmental Protection Agency
P.O. Box 4010, MS-12B
Sacramento, CA 95812
Attention: PHG Program

(916) 324-7572

PHG.Program@oehha.ca.gov

RESPONSES TO EXTERNAL SCIENTIFIC PEER REVIEW COMMENTS

G. A. Shakeel Ansari

Comment: *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. … 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.*

Response: OEHHA acknowledges the comment.

John B. Barnett

Cis-1,2-dichloroethylene

Comment: *In reviewing the sum-total of data several limitations were noted. … These deficiencies are 1) lack of any immunotoxicology data, 2) lack of developmental studies in which immunotoxicology was an end point, and 3) lack of studies on the aged, with immunotoxicology endpoints. … Thus, some consideration should be made to include in the ADD calculation, a* 'Database deficiency factor' *for the lack of data described above, i.e., √10, as indicated in Appendix III.*

Response: An uncertainty factor of √10 was included in the ADD calculation for "deficiencies in toxicity data." Furthermore, OEHHA's combined intraspecies uncertainty factor of 30 allows for diversity, including pregnant women, their fetuses, and the elderly (OEHHA, 2008).

Trans-1,2-dichloroethylene

Comment: *I agree that these data* [Barnes et al., 1985] *should not be used for the calculations of the ADD. …it is agreed that the immunotoxicology data is of sufficient quality to be used for the determination of the ADD for trans-DCE.*

Response: OEHHA acknowledges the comment.

Comment: *However, some consideration should be made to include in the ADD calculation, a* 'Database deficiency factor' *for the lack of developmental immunotoxicity data, i.e., √10, as indicated in Appendix III*.

Response: An uncertainty factor of √10 was included in the ADD calculation for "deficiencies in toxicity data."

Virunya Bhat

Cis-1,2-dichloroethylene

Comment: *The BMD modeling for cis-1,2-DCE indicates that p>0.05 was considered acceptable. This is inconsistent with US EPA (2012) guidelines which specify that p>0.1 is acceptable. … Either be consistent with EPA guidelines or specify the rationale for deviating.*

Response: OEHHA's risk assessment guidelines (OEHHA, 2008) consider a goodness-of-fit p-value >0.05 to be acceptable. These guidelines were peer-reviewed and approved by the state' Scientific Review Panel, which consists of independent scientific experts. The p-value >0.05 standard has been applied in various externally peer-reviewed assessments published by OEHHA (OEHHA, 2016a,b) and is consistent with US EPA's 2012 *Benchmark Dose Technical Guidance*, which states, "Note that in some cases most of the available model fits may not appear to be adequate on the basis of goodness-of-fit *p*-values alone, i.e., *p*-values are less than 0.1. Some of these less adequate fits may be satisfactory when other criteria are taken into account (including the nature of the variability of the endpoint, visual fit, and residuals in the most relevant region of the data range); expert judgment is useful in these cases."

Comment: *BMD modeling is also presumed to occur in the range of linear kinetics such that there is a monotonic dose-response. No indication is given as to whether the modeled dose range (0 to 872 mg/kg-day) in the key McCauley et al. study is anticipated to be in the range of linear kinetics. There is evidence that 1,2-DCE displays saturation kinetics and/or inhibits its own metabolism in a dose-dependent manner.*

Response: The BMD approach is a curve-fitting exercise to determine "dose levels corresponding to specific response levels near the low end of the observable range of the data" (US EPA, 2012). OEHHA chose to model the male rat relative kidney weight data from McCauley et al., consistent with US EPA (2010), because the effect was the most sensitive and it was biologically and statistically significant. Furthermore, there was a response at the low end of the dose-response region (i.e., 14% increase in relative kidney weight at the lowest dose) that would typically be considered biologically significant. The modeled dose-response curve had an adequate fit to the data; thus, it does not appear that saturation kinetics altered the ability to fit the data to the BMDS models.

Comment: *Consider expressing the rat $BMDL_{10}$ as a human equivalent dose (HED) according to current US EPA (2011a) guidelines. … If inadequate toxicokinetic data are available, US EPA (2011a) considers the default approach to be allometric scaling (BW ¾ power) rather than using the animal point-of-departure. … If the point-of-departure is expressed as a HED, the interspecies UF would be reduced from 10x to √10 to account for potential remaining interspecies toxicodynamic differences.*

Response: It is current OEHHA policy to use a human equivalent dose (HED) with allometric scaling when calculating the PHG for a cancer endpoint, but not for noncancer endpoints. Adoption of body weight scaling to the ¾ power ($BW^{¾}$) to derive HEDs for noncancer points of departure (PODs) would be a policy and guideline change that would require further consideration within OEHHA as well as public and scientific peer review. In this case, calculation of the PHG using $BW^{¾}$ scaling with a default male Sprague-Dawley rat weight of 0.267 kg (US EPA, 1988) and adult human body weight of 70 kg would result in a health-protective concentration of 10 ppb for cis-1,2-DCE versus 13 ppb.

Comment: *Use of a 30x intraspecies UF represents a departure from the default (10x) factor and should be accompanied by more explicit rationale and preferably, an empirical basis. There is more than one combination of toxicokinetic and toxicodynamic factors specified in Table A6 of Appendix III that could result in 30x and it is unclear which option(s) were selected and what data or rationale were used to support the option(s).*

Response: OEHHA's current default intraspecies uncertainty factor (UF_H) is 30. As detailed in Table A6 of Appendix III, a toxicokinetic subfactor ($UF_{H\text{-}k}$) of 10 is used "to allow for diversity, including infants and children, with no human kinetic data," and a toxicodynamic subfactor ($UF_{H\text{-}d}$) of √10 is used when there is "no reason to suspect additional susceptibility of children." This has been clarified in the revised draft. The departure from the previous combined UF_H of 10 is based on a careful review of the available scientific literature and is outlined in OEHHA's externally peer-reviewed *Technical Support Document for the Derivation of Noncancer Reference Exposure Levels* (OEHHA, 2008).

Comment: *The stated rationale of "to account for sensitive individuals" is nondescript. … The methodology employed…should be specified. Also, with respect to terminology, RfD are intended to account for sensitive "subpopulations" rather than sensitive "individuals".*

Response: The phrase "sensitive individuals" was not in the draft PHG. Table A6 in Appendix III refers to "sensitive subpopulations" (page 30).

Comment: *Further, Appendix III notes that "when scientific evidence is compelling, these defaults are supplanted by alternative factors or modeling results". It is unclear*

and potentially misleading what the word "default" refers to in this statement as well as what the word "Default" in the title of Table A6 refers to, since there appears to be both default approaches as well as alternative factors being described in Table A6. What is the OEHHA definition of "default" and which scenarios in Table A6 are defaults and which are "alternative factors"? In practice or by convention, "default" tends to refer to both a magnitude (i.e., 10x) and an approach (i.e., when there are no data). However, some of the approaches in Table A6 seem to be alternative (non-default) approaches, that do not require a chemical-specific and/or empirical basis and they can be applied in addition to (rather than supplant) default approaches. Thus, the criteria that constitute compelling scientific evidence is unclear, particularly in relation to when an alternative factor is adopted in addition to the default factor as well as when a default is supplanted by an alternative factor. There should also be a clearer distinction between science and policy.

Response: Uncertainty factors (UFs) are used when insufficient data are available to support the use of chemical-specific and species-specific extrapolation factors. In the past, UFs have typically been order-of-magnitude factors to represent adjustments for variability and uncertainty in different areas of extrapolation. However, OEHHA and US EPA have more recently adopted intermediate UFs (e.g., $\sqrt{10}$ or 2) in areas estimated to have less residual uncertainty (OEHHA, 2008). Table A6 summarizes OEHHA's default uncertainty factors, which underwent public and peer review, that can be chosen depending on the availability and nature of the data. For example, when a LOAEL but not a NOAEL is identified in a study, the default UF would be 10 for extrapolating from LOAEL to NOAEL. The same is true for the choices for the intraspecies subfactors. A default toxicokinetic subfactor ($UF_{H\text{-}k}$) of 10 is chosen when there is a lack of human kinetic data to describe the toxicokinetic differences among life stages (e.g., infants, children, adults) in a PBPK exercise. If there are some kinetic data that can partially account for kinetic differences across lifestages, then the default toxicokinetic subfactor would be $\sqrt{10}$. A default toxicodynamic subfactor ($UF_{H\text{-}d}$) of $\sqrt{10}$ is used when the critical study subjects are adult animals or humans and there is no reason to suspect additional susceptibility of children beyond what would be covered by the $UF_{H\text{-}d}$ of $\sqrt{10}$. Thus, a default intraspecies UF of 30 is used in the draft PHGs for cis-/trans-1,2-DCE because the critical studies utilized adult animals, there is no reason to suspect additional susceptibility of children (beyond the factor of $\sqrt{10}$) for the critical endpoints, and there are no kinetic data on humans useful to apply in a kinetic model to account for variability across life stages.

Comment: *The updated Database UF is now 10x (compared to 3x in the original PHG) since "There are no chronic and no developmental and reproductive toxicity studies on cis-1,2-DCE." The lack of a chronic study is already addressed with the 10x Subchronic Extrapolation UF and thus it is unconventional to also account for the lack of a chronic study in the Database UF. Further, since it was noted that no new data were identified, it would be useful to more explicitly specify the methodology and rationale for assigning*

a Database Deficiency UF, particularly since Table A6 in Appendix III does not include an option for full 10x Database Deficiency UF.

Response: A total UF of 3,000 is used in calculating the acceptable daily dose. This consists of a UF of 10 for interspecies extrapolation, 30 for intraspecies variability (10 for toxicokinetics and √10 toxicodynamics), √10 for extrapolation from a subchronic exposure to lifetime exposure, and √10 for deficiencies in toxicity data. As shown in Table A6, a subchronic UF of √10 is applied when the study duration is 8-12% of estimated lifetime, not for lack of a chronic study. There have been instances where chronic studies were available yet a subchronic study was chosen as the critical study because of superior study quality and/or it had a more sensitive endpoint. The database deficiency factor of √10 is used because of significant data gaps, i.e., there are no chronic, developmental, and reproductive toxicity studies on cis-1,2-DCE.

Comment: *The composite UF is comprised of four areas of uncertainty of at least 10x each. The convention to collapse four areas of uncertainty to 3000x (despite mathematically amounting to 10000x at times) is based on four areas of uncertainty (US EPA, 2002). As currently configured, the composite UF is 30,000x, which could be considered too uncertain to derive a RfD with confidence according to US EPA (2002) guidelines. Clarify and/or cite the methodology used to ascribe the total UF.*

Response: While UFs have historically been order-of-magnitude factors, OEHHA and US EPA have used intermediate factors, usually having a value of 3 (the rounded square root of 10) in areas estimated to have less residual uncertainty (OEHHA, 2008). Thus, the UF for each area of uncertainty is not a minimum of 10 but instead ranges from a value of 1 up to a value of 10 (see Table A6). The methodology used in deriving the total UF of 3,000 for cis-1,2-DCE, which takes into account both uncertainty and variability, is described in the response to the previous comment.

Comment: *The new proposed intake rate, while also considering incidental inhalation and dermal exposure, estimated daily water intake to be 0.075 L_{eq}/kg-day (at the 95th%ile), which is 50% more than the previous rate… Recognizing that incidental inhalation or dermal exposure are not represented, the new proposed intake rate of 0.075 L_{eq}/kg-day is also more than twice the lifetime intake rate of 0.034 L/kg-day (at the 90th%ile) suggested by the most recent NHANES exposure data (US EPA, 2011b)… Thus, since CalTOX modelling suggests that incidental inhalation and dermal exposure and other life stages are contributing a significant portion to the estimated daily intake of 0.075 L_{eq}/kg-day, the updated model parameters and/or revised assumptions in the current model should be more transparent given that it is not a widely-recognized standard practice.*

Response: The water intake rate of 0.075 L_{eq}/kg-day represents the amount of tap water one would have to drink to account for the daily exposure to cis-1,2-DCE in tap water through oral, inhalation, and dermal routes, averaged over a lifetime for infants (0

to 2 years), children (2 to 16 years) and adults (16 to 70 years). OEHHA's age-specific water intake rates, described in detail in OEHHA's exposure assessment guidelines (OEHHA, 2012), are derived from a nationwide survey of food and beverage intakes from approximately 20,000 individuals, the US Department of Agriculture's Continuing Survey of Food Intake of Individuals (1994, 1996, 1998 dataset). These data allow age-specific tap water intake rate derivations. OEHHA's exposure guidelines (OEHHA, 2012) also used water intake for infants drinking reconstituted formula, who have higher tap water exposure than breast-fed infants, to derive drinking water intake rates for the age group 0-1 year. These analyses indicate much higher tap water intake per body weight for infants than for older children and adults.

Studies have shown that exposures to some volatile chemicals from routes other than oral ingestion may be as large as or larger than exposure from ingestion alone (McKone, 1987). To estimate inhalation and dermal exposures to chemicals in tap water, OEHHA uses the CalTOX 4.0 multimedia total exposure model developed for the California Department of Toxic Substances Control by the Lawrence Berkeley National Laboratory. Details on model inputs, including exposure pathways and OEHHA-derived 95th percentile exposure parameters for various life stages, are described in Appendix II.

Comment: *When considering the 80% ceiling RSC value, the Exposure Decision Tree (Figure 4-1* [US EPA, 2000]*) indicates that adequate exposure data be available "to describe central tendencies and high-ends for relevant exposure sources/pathways" such that these data would enable "apportion" of the RfD into % contributions from each of the relevant exposure sources (e.g., food, water).*

There is inadequate information to determine whether the porposed 80% RSC factor was derived using current practices or standard methodology or is supported by the available data because the methodology or empirical basis was not indicated.

Response: According to US EPA (2000), "If it can be demonstrated that other sources and routes of exposure are not anticipated for the pollutant in question (based on information about its known/anticipated uses and chemical/physical properties), then EPA would use the 80 percent ceiling." Based on the available data indicating that cis-1,2-DCE is no longer in use and only 16 pounds of 1,2-DCE were released in California in 2015, it is OEHHA's policy to assume that exposure from sources other than tap water are not anticipated. Thus, the ceiling value of 80% is chosen as the RSC.

Comment: *Ideally, this* [risk characterization] *section would be more transparent with respect to the overall level of confidence, strengths and limitations, data gaps and/or remaining uncertainty that would inform future research.*

Response: Additional text was added to the risk characterization section (page 14) to clarify the data gaps in the risk assessment.

Trans-1,2-dichloroethylene

Note: All comments for trans-1,2-DCE, except one, are the same as for cis-1,2-DCE. OEHHA's responses are the same as well, thus only one comment is presented below for trans-1,2-DCE.

Comment: *For trans-1,2-DCE, the BMD/BMDL ratio (77.22/14.5) of 5 suggest a nonoptimal fit, recognizing it is an acceptable fit according to US EPA (2012) guidelines. As a point-of-departure for the RfD, it may be preferable to use the empirical NOAEL of 17 mg/kg-day for this response compared to the $BMDL_{10}$ of 14.5 mg/kg-day, which is a model estimate, recognizing that both values are approximately the same.*

Response: As stated by this peer reviewer, US EPA guidelines recognize a BMD/BMDL ratio of 5 as acceptable. OEHHA agrees. Furthermore, OEHHA's policy is to use BMD modeling to derive PODs, when possible, because it mitigates some of the limitations of the NOAEL/LOAEL approach, including:

- dependence on dose selection and sample size;
- inability to account for uncertainty and variability of experimental results due to the characteristics of the study design;
- the need to use an uncertainty factor when a NOAEL cannot be determined in a study;
- inability to account for the shape of the dose-response curve.

References

OEHHA (2008). Air Toxics Hot Spots Risk Assessment Guidelines: Technical Support Document for the Derivation of Noncancer Reference Exposure Levels. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, CA.

OEHHA (2012). Air Toxics Hot Spots Program Risk Assessment Guidelines: Technical Support Document for Exposure Assessment and Stochastic Analysis. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, CA.

OEHHA (2016a). Public Health Goal for Antimony in Drinking Water. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, CA.

OEHHA (2016b). Public Health Goals for Carbofuran, Diquat, Endrin, Picloram, and Thiobencarb in Drinking Water. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, CA.

US EPA (1988). Recommendations for and documentation of biological values for use in risk assessment. Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Office of Research and Development, United States Environmental Protection Agency, Cincinnati, OH.

US EPA (2000). Methodology for deriving ambient water quality criteria for the protection of human health (2000). EPA-822-B-00-004. Office of Water, Office of Science and Technology, United States Environmental Protection Agency, Washington, DC.

US EPA (2010). Toxicological Review of Cis-1,2-Dichloroethylene and Trans-1,2-Dichloroethylene in Support of Summary Information on the Integrated Risk Information System (IRIS). EPA/635/R-09/006F. National Center for Environmental Assessment, United States Environmental Protection Agency, Washington, DC.

RESPONSES TO PUBLIC COMMENTS, FIRST COMMENT PERIOD

Environmental Working Group

Comment: *EWG applauds the efforts of OEHHA to conduct a thorough literature review and incorporate the most current scientific data for the development of the updated PHGs for cis-/trans-1,2-DCE. We found OEHHA's assessment to be scientifically sound and thorough, with one exception. We suggest that the agency strengthen the draft assessment by reviewing the chemical's synergistic effects, an aspect of toxicology that is crucial to fully understanding a chemical's potential public health impact.*

Response: From the literature, it is unclear whether cis-/trans-1,2-DCE induces toxicity synergistically with each other or with other chemicals, and effects of chemical mixtures are typically difficult to assess when conducting risk assessments on individual chemical species.

OEHHA reviewed a study by Malley et al. (2002), which attempted to address whether the isomers of 1,2-DCE (along with another chemical, perfluorobutylethylene, PFBE) have additive or synergistic effects when administered as a mixture. In this study, male and female Crl:CD Br rats (20/sex/dose) were exposed to 0, 400, 2,000, or 8,000 ppm of a mixture of cis-1,2-DCE (5%), trans-1,2-DCE (70%), and PFBE (25%) via inhalation for 6 hours/day, 5 days/week for 4 weeks. The most sensitive effect reported was a reduced response to a sound stimulus in animals exposed to ≥2,000 ppm of the mixture. This effect was transient, as no adverse neurological effects were observed after the daily exposure period. The authors determined a NOEL of 400 ppm in male and female rats, and suggest that the mixture may have produced synergistic effects

with respect to neurotoxicity. This conclusion was based on a comparison to data regarding the individual components of the mixture from other inhalation studies in rats. However, the database is inadequate to determine synergistic effects between cis- and trans-1,2-DCE and other chemicals.

Reference

Malley LA, Hansen JF, Everds N, Warheit DB (2002). 4-Week inhalation toxicity study with a mixture of dichloroethylene and perfluorobutylethylene in rats. *Inhal Toxicol* 14:773-787.