

**Responses to Major Comments on  
Technical Support Document**

**Public Health Goal**

**For**

**Cis- and Trans-1,2-Dichloroethylene**

**In Drinking Water**

**Prepared by**

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## **INTRODUCTION**

The following are the combined responses to major comments received by the Office of Environmental Health Hazard Assessment (OEHHA) on the public health goal (PHG) technical support document for cis- and trans-1,2-dichloroethylene, based on the pre-release review draft. Changes have already been made in response to these comments, and have been incorporated into the final PHG posted on the OEHHA website. For the sake of brevity, we have selected the more important or representative comments for responses. Comments appear in quotation marks where they are directly quoted from the submission; paraphrased comments are in italics.

These comments and responses are provided in the spirit of the open dialogue among scientists that is part of the process under Health and Safety Code Section 57003. For further information about the PHG process or to obtain copies of PHG documents, visit the OEHHA Web site at [www.oehha.ca.gov](http://www.oehha.ca.gov). OEHHA may also be contacted at:

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## RESPONSES TO MAJOR COMMENTS RECEIVED

### Comments from Reviewer 1 (University of California, Davis)

Comment 1: “This reviewer finds the document to be accurate and complete in terms of appropriate citations, interpretation of published work and conclusions drawn from the results contained in those reports.”

Response 1: No changes needed.

Comment 2: *For cis-1,2-DCE, hepatotoxicity is the most likely adverse effect; however, there is sufficient evidence to indicate a concern for nephrotoxicity and for gender and possibly age-related differences.*

Response 2: Careful consideration was given to the fact that male animals in the study of McCauley *et al.* (1990) had increased relative kidney weights at all dose levels. These increases, while significant, were deemed by the study authors to be “interesting” but lacking the clinical chemistry and histopathology to support a definitive finding. Originally, we agreed with the study authors and based the proposed PHG for cis-1,2-DCE on the more robust data on adverse liver effects seen in both sexes in a dose-response manner at the second-lowest dose level. However, several commenters requested that OEHHHA reconsider the kidney data, and we have done so. We agree that the most sensitive significant endpoint is the effect on relative kidney weight in male rats, and we have changed the PHG document to reflect this.

This change does not alter the ultimate proposed PHG value even though the kidney effects are observed at a lower dose level. This proposed value is identical to the one previously proposed because both are based on extrapolation from the lowest dose tested and both incorporate the maximum uncertainty factor of 3,000.

Comment 3: “The physical properties of the 1,2-DCEs are well-characterized and their pharmacokinetics and pharmacodynamics well-defined....”

Response 3: No changes needed.

Comment 4: *The proposed PHG values for cis- and trans-1,2-DCE are “justified by the data presented” and “are based on the most logical and appropriate interpretations of risk factors based on the existing data.”*

Response 4: No changes needed.

Comment 5: “Additional information on transdermal exposures should be sought.”

Response 5: In October 2005, an additional literature search was conducted to ensure the proposed PHGs are based on the most comprehensive, up-to-date data available. At the

time of the literature search, no additional data was available on the transdermal absorption, distribution, metabolism or excretion of these compounds.

Comment 6: “This reviewer agrees [with] the proposed lowering of the safety standard, as proposed, with a single caveat. The lack of epidemiological evidence to indicate that the current or future safety levels are adequate, do not provide proof of safety. ... With unknowns such as species-specificity, gender differences and time-dependent carcinogenicity, it is not unwise to exercise the greater rather than the lesser caution in calculating safety levels for humans.”

Response 6: We concur, and as such we utilized the full complement of uncertainty factors for both chemicals to account for the pharmacodynamic and pharmacokinetic variability between and across species, for the spectrum of unknowns associated with longer exposure durations and for the unknowns associated with database deficiencies, including the lack of a two-generation developmental toxicology study and a long-term carcinogenicity study.

#### **Comments from Reviewer 2 (University of California, Davis)**

Comment 1: “The draft PHG for Cis- and Trans-1,2-Dichloroethylene in Drinking Water accurately summarizes and evaluates all available information on the chemistry, environmental occurrence and mammalian toxicity of this chemical.”

Response 1: No changes are needed.

Comment 2: “The available data has been evaluated and interpreted carefully and thoroughly, however I do not entirely agree with OEHHA’s interpretation of the stud[y] by McCauley et al. (1990)... I do not agree with dismissing the effects of cis-1,2-DCE on the kidneys of female rats. An increasing trend is quite obvious, and it closely follows the data obtained for male rats, which are statistically significant. I suggest including the significant effect level for an increase of relative kidney weight in male rats and use an LOAEL of 32 mg/kg-day.”

Response 2: A re-evaluation of the male and female kidney data indicate that female rats had substantial increases in kidney weights at and above the second highest tested dose. Though the statistical analysis concluded that the effects were not significant, relative kidney weights in females were increased between 19 and 23 percent over controls. These increases mirror those seen in males as the commenter noted, although the effects in males were seen at the lowest dose tested. We concur with the commenter and have changed the PHG document to reflect these observations regarding female kidney weights, and based the proposed PHG on the increased relative kidney weights seen in males at all dose levels.

Although effects were observed on this endpoint at a lower dose than the changes in liver weight, this change does not alter the proposed PHG value because both calculations extrapolated from the lowest dose with the maximum uncertainty factor.

Comment 3: *And for Barnes et al. (1985), there could have been a ceiling effect (maximum effect level), and therefore “I do not agree with the conclusion that the elevated serum glucose levels in exposed mice are meaningless, and would need to see more evidence to support the dismissal of this data set. After all, both control groups have lower levels than all exposure groups, replication is good and the results of the statistical analysis quite convincing. Overall, the effects seen in this study suggest that the LOAEL used for trans-1,2-TCE PHG calculations should be 17 mg/kg-day.”*

Response 3: The PHG document has been expanded to include a more thorough discussion about the rationale for not selecting serum glucose levels as the toxic endpoint. We have retained the 17 mg/kg-day level as the NOAEL, based on hepatotoxic effects in test animals. If the changes in glucose were utilized as the basis for the risk assessment, this level would be considered the LOAEL. As with the calculation for cis-1,2-DCE, the proposed PHG for trans-1,2-DCE incorporates the maximum uncertainty factor allowed according to our risk assessment principles and U.S. EPA guidance. Therefore, even if we had retained the serum glucose endpoint, the revised PHG for trans-1,2-DCE would be identical to the one proposed, based on extrapolation from the 17 mg/kg-day dose and an uncertainty factor of 3,000.

Comment 4: “Given the fact that the compound is readily absorbed via skin and lungs, the use of an equivalent drinking water exposure of 4 /L<sub>eq</sub> is...quite appropriate.”

Response 4: No changes are needed.

Comment 5: “Application of the maximum uncertainty factor of 3,000...is justified. A justification for using a factor of 3 for incompleteness of the database rather than an uncertainty factor of 10 should be provided.”

Response 5: The PHG document has been expanded to address the rationale behind using an uncertainty factor of 3 and not 10 for the incompleteness of the database. The primary reason is that current risk assessment principles and guidelines set 3,000 as the maximum uncertainty to be incorporated into risk assessment calculations. OEHHA can increase this to 10,000 when the data indicate there is an overarching concern that warrants an additional factor, such as a potential for carcinogenic effects but inadequate data to derive a cancer potency factor. The data on these compounds do not indicate that this level of concern, so we have maintained an uncertainty factor of 3,000 for both chemicals.

### **Comments from Reviewer 3 (University of California, Davis)**

Comment 1: “The information provided in both is both complete and accurate.”

Response 1: No changes required.

Comment 2: “The two data sets selected for setting the NOAELS for both compounds are appropriate due to the reasons stated in the document. However, because the function of alkaline phosphatase is not generally known by the public, an explanation of its significance should be included.”

Response 2: We agree. The PHG document has been amended to include a more descriptive explanation of the significance of the function of alkaline phosphatase as an indicator of cellular injury and suggestive of adverse effects on such organs as the liver.

Comment 3: “The use of the 4 L<sub>eq</sub>/day as the value to account for all exposure pathways is not supported by any documentation, not even reference to previous PHG documents. My review of other PHG draft documents calls into question the methodology used in that calculation...it should seem somewhat suspicious that every compound evaluated is convertible to 4 L<sub>eq</sub>/day....”

Response 3: The value of 2 L/day for water consumption is a traditional default value for an adult, nominally representing all uses of water, including that added to food and used for coffee or tea. Inhalation and dermal absorption of volatile organic chemicals released from water used in the household may result in additional human exposure. Thus, for some small, volatile chemicals such as cis- and trans-1,2-dichloroethylene, it is prudent to add an exposure equivalent to drinking two L/day to account for these possible exposures incurred during such household activities as bathing, showering and cooking. This total exposure of four L<sub>eq</sub>/day roughly accounts for exposures to a toxicant due to both drinking and other household activities that result in additional exposures. The PHG document has been expanded to include this explanation.

Comment 4: “The use of an uncertainty factor of 3000 is questionable. Database uncertainty is a judgment call, and it seems like there is a significant database to make a decision. There seems to be sufficient number of good studies on which to base the decision for the NOAEL. I would not use a UF of 3 to account for database uncertainty.”

Response 4: We have concluded that the database is insufficient. There are no studies evaluating the effects of life-time exposures, nor are there any that address the carcinogenicity, reproductive, or teratological effects. Lack of data on any one of these areas can warrant the application of an extra uncertainty factor. All uncertainties combined have resulted in our decision to use the maximum uncertainty factor of 3,000 for both compounds.

Comment 5: *What is the underlying rationale for setting the RSC at 0.6?*

Response 5: It is anticipated that the primary source of exposure to cis- and trans-1,2-DCE will be from water. However, these compounds can be found as pollutants in the air as well as in soils as discussed in the Environmental Occurrence and Human Exposure section of the PHG document, which rules out using the maximum “default” RSC of 0.8. Therefore the RSC was set at 0.6 to account for these other sources of potential exposure while giving greater weight to the anticipated greater exposure from tap water. It should not be inferred that this represents a quantitative estimation of exposure from the respective sources. This OEHHA practice differs from the U.S. EPA practice of assigning a default RSC of 0.2 to all chemicals with insufficient data (assigning 20 percent of allowed exposures to the drinking water route), even if no other exposure sources are known or expected.

Comment 6: “I can find no other information that is relevant to the calculation of the Public Health Goal for cis- and trans-1,2-dichloroethylene.

Response 6: No changes required.

Comment 6: “There is a discussion of the uncertainties associated with the studies used to establish the NOAELs in the Risk Characterization portion of the document. However, this is little more than a restatement of the rationale for the selection of the studies presented in the Dose-Response Assessment section on page 20. There are numerous articles published on the various types of uncertainty associated with any model (e.g., parameter uncertainty, model uncertainty), these PHG documents should establish a set of uncertainties that must be addressed and follow through in each document.”

Response 6: Each proposed PHG adheres to specific criteria for uncertainties, and we attempt to apply these consistently and uniformly across the program. However, a certain amount of professional judgment is always allowed, based on such considerations as structure-activity relationships and lack of needed studies. Because the literature on uncertainty assessment is so voluminous, we do not think it is appropriate to reiterate the justification for the use of the default uncertainty factors in each PHG document.

### **Comments from the U.S. Environmental Protection Agency Office of Research and Development, National Center for Environmental Assessment**

Comment 1: *The commenter requested that additional information be included in the PHG document to more fully describe the toxic effects found in the acute study conducted by McCauley et al. (1990).*

Response 1: The PHG document has been amended to include additional information about this study. The addition includes a more extensive description of the organs evaluated and the tissue injuries reported, the magnitude of change reported for organ weights and BUN levels, and whether OEHHA interprets these changes as an adverse

effect. Additionally, a description has been included on the significance of changes in BUN levels and how they are an indicator of liver injury.

Comment 2: “A discussion of all serum chemistry results (in addition to the decreased BUN levels) would be useful in assessing the potential hepatotoxicity of cis-1,2-DCE in McCauley’s studies.”

Response 2: This discussion has been added to the PHG document.

Comment 3: *The commenter suggested that OEHHA examine our decision about relative kidney weights in light of new mechanistic data on DCEs by Hanioka et al. (1998). The commenter has also provided a graph of relative kidney weights and relative liver weights and contends that both are illustrative of a dose-response relationship.*

Response 3: We have added the study by Hanioka *et al.* (1998) to the PHG document and thank the commenter for this additional insight. OEHHA has re-evaluated the relative kidney weight data and concurs with this and other commenters that the adverse effect on kidneys seen in males should be chosen as the most sensitive endpoint and serve as the basis for the cis-1,2-DCE public health goal. The PHG document has been changed accordingly.

Comment 4: *Referring to page 13, last sentence of first paragraph, “It is unclear if the serum chemistry parameters and results from McCauley et al. (1990) can be used to support the Barnes et al. study (1985) on trans-1,2-DCE.”*

Response 4: Given the similarity between these two compounds, it does not seem unreasonable to infer similar toxic effects. However, because this statement was questioned, it has been removed.

Comment 5: “[T]here are not clear differences in the value of increased relative kidney and liver weights. Although there are differences in variability and therefore statistical significance in individual comparisons, the trends and dose response relationships between relative kidney and liver weight are similar. Pathology was negative for both kidney and liver, so there are no overt signs of toxicity. Since BUN levels are impacted by both liver and kidney function, changes in BUN cannot be used to discriminate. It should be noted that studies showing decreased BUN, did not report changes in liver enzymes. The weight of evidence is at best equivocal as discussed.”

Response 5: OEHHA interprets this comment to mean that given the lack of underlying pathology on both kidney and liver for cis-1,2-DCE and the similarity of dose-response trends, the kidney data should be given equal weight to the liver data. OEHHA has reevaluated the kidney data and has chosen it as the most sensitive endpoint, and cites the liver effects as providing support to the interpretations of adverse effects of this chemical in the study.

Comment 6: *The commenter stated that the presentation of the derivation of a PHG for cis-1,2-DCE based on adverse kidney effects seemed inappropriate if that endpoint was not going to be used for the ultimate PHG.*

Response 6: We have commonly provided calculations based on various endpoints, and chosen one for the proposed PHG, inviting comments on that choice. The current version is based on the kidney effects.

Comment 7: *The commenter indicated that there are some unpublished short term and in vitro studies cited in the NTP database that may be of value to the PHG.*

Response 7: We are grateful for the information. However, we have been unable to secure these unpublished works. It is hoped that these studies will be made available by the next review cycle for these chemicals so they can be included in that review.

## **REFERENCES**

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U.S. EPA (2002). A review of the reference dose and reference concentration processes. Final Report. Prepared by the Risk Assessment Forum for U.S. EPA, Washington, D.C. EPA/630/-02/002F, December 2002.