

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

**Public Health Goal
For
1,1,2,2-Tetrachloroethane
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 proposed public health goal (PHG) technical support document for 1,1,2,2-tetrachloroethane, based on the pre-release review draft. Changes have already been made in response to these comments, and have been incorporated into the draft 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. OEHHA may also be contacted at:

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RESPONSES TO MAJOR COMMENTS RECEIVED

Comments from University of California, Davis

Comment 1. “Overall, I found the TCA draft document to be complete in its coverage of the available literature. Much of the material presented in the PHG document is an update to the material provided in the ATSDR toxicology profile on TCA, particularly the information on recent releases of TCA in various media. However, I found the material in the PHG document to be an improvement on the ATSDR document in its handling of environmental occurrence and human exposure.”

Response 1: Thank you. Comment noted.

Comment 2. “There are some slight discrepancies between the citations used in the ATSDR document and the PHG document. For example, the PHG document cites a study by Morgan et al. (1972) having authors Morgan, Black and Belcher. The same article is cited in the ATSDR document as Morgan and Belcher (1972) without Black as an author.”

Response 2: The citation in the PHG document is correct for Morgan, Black and Belcher (1972). To ensure that all citations in PHG document are accurate, each citation was checked and compared directly with those in the ATSDR document. While slight changes were made, overall the PHG document citations contain more complete information than those in the ATSDR document.

Comment 3. *The commenter suggested that some language in the PHG document was taken verbatim from ATSDR.* “Specifically, the paragraph at the bottom of page 10 is essentially verbatim from the ATSDR TCA document on page 50.” *It was suggested that the document be checked* “to remove the implication that this document is...a cut and paste job.”

Response 3. The cited paragraph was reviewed and two sentences were found to be similar to ATSDR. While ATSDR was cited as the source of the information presented, these two sentences have been rewritten. The rest of the PHG document was also checked to ensure that the language is our own, except where a direct quote is indicated.

Comment 4. *The commenter disagrees with the selection of Schmidt et al. (1972) as the basis for the non-carcinogenic PHG calculation. His conclusion is that the study provides equivocal results and that it is unclear* “what the significance of increased ACTH levels is, and...if the differences in fat content of the liver are statistically significant.” *He notes, however that* “because the PHG is based on the 1978 NCI cancer study, it [the Schmidt study] is not critical to the development of the PHG.”

Response 4. OEHHA chose the Schmidt *et al.* (1972) study because it shows significant decreases in body weights at day 110 and significant increases (34 percent) in fat content of the liver at day 265 in test animals. Body weights were no longer significantly different by the end of the study; however, these significant decreases in body weight, albeit transient, reflect an important indication of toxicity that should be incorporated into the risk assessment of this chemical. That, coupled with the significant increases in liver fat content, indicates adverse effects in this study. However, as the commenter stated, the 1978 NCI cancer study is the basis for the PHG, so the selection of the Schmidt study is not critical to the development of the PHG value.

Comment 5. “I have a question about the use of 4 L_{eqs}/day as the tap water exposure rate. In other PHG draft documents, e.g., dichloromethane, the number is 3.8 L_{eqs}/day based on calculations by Bogen *et al.* (1992).”

Response 5. OEHHA chose to use the default value of 4 L_{eqs}/day for this volatile organic solvent for the combined drinking water, inhalation and dermal exposures. While a combined pathway calculation with the CalTOX program could be performed, in our experience the resulting value would be similar. There are no data on which to derive a more accurate value. The Bogen *et al.* (1992) research study involved specific calculations for dichloromethane exposure, not applicable to 1,1,2,2-TCA.

Comment 6. “Despite the use of uncertainty factors in the analysis, there is essentially no discussion of the uncertainties involved in the analysis used to establish the PHG.”
“Many readers may feel that by incorporating the uncertainty factors into the analysis that the uncertainty associated with all of the analysis is adequately addressed.”

Response 6. We agree that much more could be said about the underlying uncertainty and variability in the extrapolations made in the noncancer risk assessment. Similarly, there is great uncertainty in the extrapolation to low cancer risk levels, based on carcinogenicity mechanism considerations as well as such factors as cellular repair mechanisms with low amounts of macromolecular damage. Because of our attempt to be relatively brief in these documents, we would direct the reader to more comprehensive discussions of these factors in the broader risk assessment literature.

Comment 7. *The commenter noted that the proposed PHG value is the lowest of any value found in the Other Regulatory Standards section except for the “cryptic standard of 0-2.5 ppb for New York”.*

Response 7. The OEHHA PHG value for TCA represents the most current evaluation of the scientific literature, with our conclusions as to appropriate use of risk assessment methodologies. The citation for New York State is as described in the referenced source, the ATSDR document.

Comments from University of California, Los Angeles

Comment 1. “In general, the document is a well written and fairly comprehensive treatment of this topic. The review of relevant literature on 1,1,2,2-TCA chemistry, toxicity, kinetics, etc. appears to be reasonable and accurate.”

Response 1: Comment noted.

Comment 2. “The statement ‘...1,1,2,2-TCA is expected to exist mostly in the vapor phase of air.’ may be a bit misleading to the naive reader. This compound is a liquid at room temperature and pressure with a boiling point of 145° C. Although it is volatile, its ability to exist "mostly" in the vapor phase will be a function of conditions. For example, in an industrial or laboratory setting, 1,1,2,2-TCA will likely exist primarily as a liquid.”

Response 2. The language in the PGH document has been revised to incorporate this comment.

Comment 3. “It is not clear to this reviewer why the experimentally derived evaporation half-life will be significantly different from that expected in ‘natural waters’. This needs some explanation.”

Response 3. The laboratory experiment was conducted using a 250 ml beaker of room temperature water containing 1,1,2,2-TCA that was stirred continuously at 200 rpm. This experiment was not an attempt to elucidate the half-life of 1,1,2,2-TCA in natural waters, and the text of the PHG document has been modified to clarify this.

Comment 4. “Since 1,1,2,2-TCA is not a pharmacological agent, but rather a compound of industrial importance and of toxicological concern, it may be best to use the term ‘Toxicokinetics’ instead of ‘Pharmacokinetics’ for the section heading.”

Response 4. Semantically, the observation is correct. However, the titles of each section follow a standardized PHG format to ensure uniformity and ease of use for a wide variety of compounds. Further, in the scientific community the term “pharmacokinetics” is understood to be applicable to compounds other than pharmaceuticals. Nonetheless, toxicokinetics is the more accurate term.

Comment 5. *The commenter noted that there are a few typographical errors.*

Response 5. Corrections have been made to the PHG document in response to this comment.

Comment 6. “I would have thought there would be a greater emphasis on the mechanistic work regarding enzymatic (P450) bioactivation since it may be important in identifying

polymorphisms in the susceptibility to 1,1,2,2-TCA toxicity...however, is more of an academic concern as these issues do not significantly compromise the conclusions of this report.”

Response 6. Comment noted.

Comment 7. *The commenter noted that the use of the 1978 NCI study is “somewhat problematic” because the technical grade of 1,1,2,2-TCA was only 90% pure, but goes on to say, “The remaining 10% impurities may significantly contribute to the overall observed toxicology. However, in light of the fact that an equivalent study using highly pure 1,1,2,2-TCA is unavailable, the authors of the report are justified in using this study.”*

Response 7. Comment noted. As an aside, it appears that at the time NCI conducted their study, 90 percent was considered technical grade. Methods to improve the purity of 1,1,2,2-TCA have advanced; however, even today technical grade 1,1,2,2-TCA contains 3 percent impurities.

Comment 8. *For the non-cancer PHG, the commenter stated that use of an inhalation study to derive an oral exposure lowest observed adverse effect level (LOAEL) is “problematic.” He continued by stating, “the toxicokinetics from an inhalation exposure and an oral administration are going to be very different. That is, the bioavailabilities of most substances by these two routes of exposure are known to be distinct and different. Since this report concerns drinking water exposure to 1,1,2,2-TCA, the use of an LOAEL value based on an inhalation study is problematic.”*

Response 8. For the selection of the non-cancer LOAEL, OEHHA chose the most sensitive endpoint at the lowest dose from the available scientific literature. While this was an inhalation study, the expected net absorption/retention of about 50 percent was accounted for in the calculation. Uncertainty due to the route-to-route extrapolation should be adequately accounted for within the total UF of 1000, although this factor is not specifically addressed. The current California MCL for 1,1,2,2-TCA of 1 ppb is based on the Schmidt (1972) inhalation study in question, so the precedence for this has long been established. Therefore, OEHHA believes the selection of the non-cancer LOAEL to be appropriate.

Comment 9. *The commenter stated that OEHHA might want to consider recalculating our estimated daily dose value differently to see how the PHG value would change. He noted that OEHHA calculated a daily dose over the entire study period, which included an observation period when animals were not being dosed. The commenter suggested that OEHHA calculate the daily dose based on the exposure phase only, but also noted that doing so would “only slightly alter the eventual outcome/conclusions of this report” and that “this issue is probably not a major factor.”*

Response 9. It is current OEHHA practice to calculate average dose expressed as the entire study duration for cancer studies. OEHHA concurs with the commenter that the ultimate calculation would be changed only slightly.

Comment 10. *The commenter noted that the public-health protective levels for both non-cancer and cancer endpoints were “very conservatively derived.” Nonetheless, “given the paucity of data, and that it is line with drinking water standards in other states, the value of 0.1 ppb derived in this report appears reasonable, albeit very conservative.”*

Response 10. In deriving the proposed PHG values for 1,1,2,2-TCA, OEHHA utilized what we considered to be the most appropriate toxicological endpoints and current risk assessment practices. The proposed value of 0.1 ppb may appear conservative, but it is where the science led us.

Comments from U.S. EPA, Office of Science and Technology/Office of Water

Comment 1. *The reviewer questioned the selection of an inhalation study reported by Schmidt et al. (1972) as the basis for the calculation of a non-cancer end-point. The reviewer suggested two oral studies reported by NCI (1978) and Gohlke et al. (1977) that could be used for this purpose.*

Response 1. Among the three studies, data reported by Schmidt *et al.* (1972) give the lowest estimated LOAEL of 1.1 mg/kg-day. LOAELs derived from NCI (1978) and Gohlke *et al.* (1977) are 31 mg/kg-day and 3.2 mg/kg-day, respectively. OEHHA selected the dataset that generates the lowest LOAEL to ensure that the estimated result is health protective. As the adverse health effects reported by Schmidt *et al.* (1972) are systemic effects, the route of exposure should not have a major impact on the results.

Comment 2. *The reviewer questioned the use of 80 percent as the relative source contribution in estimation of a safe drinking water level for the non-cancer end-point. The review commented that 1,1,2,2-TCA is very volatile and would not stay long in the water. Furthermore, the chemical has been detected in sampled air and food. A lower relative source contribution is recommended.*

Response 2. Limited air and food sampling data show that levels of 1,1,2,2-TCA in air and food are in the ppb or sub-ppb range. Due to sampling and reporting limitations, it is not clear how pervasive is the contamination and how representative are the data. Due to the lack of quality information, the default assumption of 80 percent is judged to represent a fair estimate of the relative source contribution. It is also important to note that the PHG of 1,1,2,2-TCA is based on the estimated cancer risk of the chemical. Relative source contribution is not used in the estimation of cancer risk.

REFERENCES

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Schmidt P, Binnewies S, Gohlke R, Rothe R (1972). [Subacute action of low concentrations of chlorinated ethanes on rats with and without additional ethanol treatment. I. Biochemical and toxicometric aspects, especially results in subacute and chronic toxicity studies with 1,1,2,2-tetrachloroethane.] Zur subakuten Wirkung geringer Konzentrationen chlorierter Athane ohne und mit zusätzlicher Athanolbelastung auf Ratten. I. Biochemische und toxikometrische Aspekte, insbesondere Befunde bei subakuter und chronischer Einwirkung von 1.1.2.2-Tetrachlorathan. Int Arch Arbeitsmed 30:283-298. (German)