Responses to Major Comments on Technical Support Document

Public Health Goal
For
1,1,1-Trichloroethane
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 1,1,1-trichlorethane, 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 that are direct quotations appear within quotation marks and 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, please visit the OEHHA website at www.oehha.ca.gov. OEHHA may also be contacted at:

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RESPONSES TO MAJOR COMMENTS RECEIVED

Comments from National Center for Environmental Assessment, U.S. EPA

Comment 1: "Three toxicity studies have been conducted by the National Toxicology Program (NTP) that are not included in the PHG support document. All three studies involve oral administration of 1,1,1-trichloroethane and would appear to be relevant to the characterization of the oral toxicity of the chemical."

Response 1: These three studies are now cited in the report. This is an especially useful suggestion.

Comment 2: "The subchronic gerbil study by Rosengren et al. (1985) was selected as the basis for the proposed PHG value. Rosengren et al. reported significantly increased concentrations of glial fibrillary acidic protein (GFAP) in the sensorimotor cerebral cortex following exposure to 1,1,1-trichloroethane. EPA scientists have reviewed this study and identified certain issues that should be recognized in evaluating the relevance of these findings to humans. These observations and issues include the following:" [*Alphabetical paragraph identifiers added*]

> [*A*] *Discussion of glial hypertrophy and associated changes, including the increase in the glial cytoskeletal protein, GFAP*
>
> [*B*] *Criticism of GFAP quantitation and dose-response in the data of Rosengren et al., including graphic analysis of the data* "Thus, these changes would not be considered a result of treatment. Overall, the data do not provide compelling evidence for a dose-related effect on any of the parameters measured."
>
> [*C*] *Variability in GFAP quantification with dissection, and questions of it as a reliable marker in the study of Rosengren et al.*
>
> [*D*] *Points out lack of replication and questions biological plausibility of an effect of this chemical on the sensorimotor cortex.*
>
> [*E*] "The possibility remains that the Rosengren et al. findings may reflect treatment-related neuronal alterations. Nevertheless, limitations in the study and uncertainty about the toxicological relevance of the findings to humans should be acknowledged."

Response 2: [*A*] This excellent discussion was condensed and added to the Risk Characterization portion of the PHG document.

[*B*] and [*C*] We do not have the benefit of reviewing the commenter's graphic analysis. Other scientific analyses (including those of ATSDR, WHO, and the University of California peer reviewers of this PHG document) have reviewed Rosengren *et al.* (1985) and have not reached conclusions similar to those of the commenter.

[*D*] We share U.S. EPA's concern and we are also not aware of attempts to replicate the findings of Rosengren *et al.* Nevertheless, it is not unusual to find a critical study on a chemical for which a replication study has not been attempted or is lacking in some other fashion. Identifying the "best available" research often involves using a study with identified weaknesses.

[*E*] We completely agree with the commenter about the limitations in the study and uncertainty about the toxicological relevance of the findings, and have acknowledged these in the Risk Characterization section of the PHG document.

We appreciate the U.S. EPA's thorough analysis of Rosengren *et al.*, (1985), and we understand that U.S. EPA did not use the results from this paper to establish its MCL. The ATSDR (1995) cited Rosengren *et al.* (1985) as a basis for its intermediate inhalation MRL. From their Toxicological Profile document, "Choice of a neurological end point for derivation of the MRL is supported by numerous studies in humans and animals showing neurological effects to be the critical end point for 1,1,1-trichloroethane." Additionally, OEHHA adopted its chronic Reference Exposure Level for Methyl Chloroform using Rosengren *et al.*, (1985) as its critical study (OEHHA, 2005). As shown later in this document, two researchers from the University of California at Davis have also independently reviewed the 1,1,1-trichlorethane PHG draft. Neither reviewer expressed issues with the selection of Rosengren *et al.*, (1985), and one specifically described the choice as follows: "The NOAEL derived from the Rosengren *et al.*, (1985) inhalation study is the most appropriate currently available for determining the PHG."

Adding confidence to the draft PHG value derived from the Rosengren *et al.*, (1985) study is the NTP (1996) citation recently added to the PHG document. With a NOAEL of 66.8 mg/kg-d, and no change in other parameters in the noncancer PHG calculation, the health-protective value which would be derived from the NTP study is 0.94 ppm, essentially the same value as was produced via employment of the Rosengren *et al.*, (1985) study. The Rosengren *et al.* work remains the critical study as it represents a higher NOAEL, a longer dosing period, and a 4-month interval between the last dosage and evaluation of effects.

Comment 3: "On page 10, the PHG support document includes the following statement regarding the formation of astroglial fibers: "Astroglia fibers form following damage to astrocytes and are characterized by the presence of the unique protein GFA (Bogen and Hall 1989)." Two assertions in this statement…are incorrect.…"

Response 3. The sentence has been rephrased to correct the problems.

Comment 4: "The toxicity database for 1,1,1-trichloroethane in experimental animal systems is extensive, and in particular the inhalation toxicity literature. In general, the draft technical support document focuses on a relatively few selected studies, without providing an indication of the extent of the available literature or the route of exposure associated with given effects." *The commenter also suggests inclusion of additional*

inhalation information focusing on neurotoxicological effects, particularly in the neurotoxicology section.

Response 4: We agree with the commenter that additional emphasis on neurological effects should be added, but do not wish to dwell too much on inhalation studies, since our focus is on oral exposures for drinking water risk assessment. We have slightly expanded the neurotoxicity section, citing a few more of the animal studies.

Comment 5: *The U.S. EPA commenter suggested some further re-organization within the document. Among the recommendations were to move the study by Herd et al. (1974) to the section on acute toxicity and Pendergrast et al. (1967) to subchronic toxicity.*

Response 5: These are good suggestions, and the text has been changed accordingly.

Comment 6: *The commenter advises that there are several papers (mentioned in the comments) that contradict the Wang et al. (1996) assertion that 1,1,1-trichlorethane does not induce CYT P450 (cited on page 7 of the PHG document).*

Response 6: We have acknowledged these results and added references to the commenter-cited papers whose authors conclude that 1,1,1-trichlorethane intoxication does induce P450 enzymes.

Comment 6: "Toxicological Effects in Humans, Acute and Short Term Toxicity" (pp. 15-16): In the first sentence of this section, the statement appears that "The main tissues affected by large amounts of ingested 1,1,1-TCA are the gastrointestinal tract, nervous system (from behavioral observations and psychomotor testing), and liver." A similar statement appears in the "Dose-Response Assessment" section (p. 20). The basis for this statement should be verified. The only oral study in humans included in the technical support document (and identified by the EPA as part of the IRIS reassessment) is the case report by Stewart and Andrews (1966), in which gastrointestinal symptoms following an accidental exposure are reported. Effects on other organ systems have been associated with inhalation exposure; however, based on the literature reviewed as part of the IRIS reassessment, such effects are not associated with oral exposure."

Response 6: We concur with the comment, and have revised the text accordingly.

Comments from UC reviewer 1 (University of California, Davis)

Comment 1: "Accuracy of the information presented: The draft PHG for 1,1,1-Trichloroethane in Drinking Water accurately summarizes and evaluates the available scientific information on the chemistry, environmental occurrence and mammalian toxicity of this chemical. A search using SciFinder Scholar (CAPLUS, MEDLINE) did not yield any additional publications or relevant information on the toxicity of this compound. "

Response 1: No response needed.

Comment 2: "Appropriateness of approach: The approach taken to determine the PHG is largely appropriate. The NOEAL derived from the Rosengren et al. (1985) inhalation study is the most appropriate currently available data for the determination of a health-protective value for 1,1,1-TCE. "

Response 2: No response needed. We acknowledge that this comment supports the approach used in the PHG document .

Comment 3: "Data evaluation and interpretation: The available data has been evaluated and interpreted carefully and thoroughly. I agree with the authors on their conclusions regarding the toxicological effects and their data selection for determining the PHG."

Response 3: No response needed. Comment helps address concern from previous commenter.

Comment 4: *Chapter Toxicology: Toxicological Effects in Animals. Commenter recommends consideration of changing subject heading to* "Toxicological Effects in Mammals", *since that is what was reviewed.*

Response 4: We prefer not to change the standard format of our template so that we may maintain consistency among the documents.

Comment 5: "Table 3: The numbers do not add up. Was there a loss of 10.75% (rats) and 1% (mice) of the labeled 1,1,1-TCE? If so, it should be noted that "recovery" was 89.25% (rats) and 99% (mice). The % Metabolized is obviously the sum of CO_2, Excreta and Carcass, but it should be noted as well."

Response 5: Commenter is correct, and a percent recovery column is added to the table.

Comment 6: "Page 16, Dermal exposure: If available, the doses that caused skin irritation and other dermal effects should be stated."

Response 6: Minor correction added to text to reflect that the pure compound, when tested on human skin, caused minor erythema and fine scaling.

Comment 7: *Regarding appropriateness of risk assessment methodology used, commenter recommends including an additional uncertainty factor of at least 3 for incompleteness of the database.*

Response 7: We agree that the ideal database would be larger; however, we feel that with the addition of the oral NTP (2000) study, which provides a near identical NOAEL and calculated health-protective value, that the additional weight of evidence from these

similar results via a different route of exposure (oral) adds sufficient confidence to our calculation that an additional uncertainty factor of 3 is not needed.

Comments from UC reviewer 2 (Center for Health and the Environment, University of California, Davis)

Comment 1: "The new proposal indicates a new level should be set at 1.0 mg/L which is 5-fold higher than the current level. The rationale to raising the safety standard is based largely on the results of non-cancer inhalation studies using the rodent animal model. Specifically, 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 response required.

Comments from UC reviewer 3 (University of California, Davis)

Comment 1: *Accuracy of information.* "The information provided is accurate although not complete as described above. There has been a considerable amount of research published on 1,1,1-trichloroethane and a complete review of the literature would expand the size of the PHG document considerably."

Response 1: Although the preparation of PHG documents involves a thorough evaluation of the pertinent literature, these documents do not include such exhaustive literature reviews as might be found in the ATSDR Toxicological Profile documents, as the latter are developed for a greater variety of applications and include a larger range of exposure pathways, media and sources.

Comment 2: *Appropriateness of the data se*t. "The data set used to set the PHG is appropriate."

Response 2: This comment is included because it reinforces the response to comment 1.

Comment 3: *The commenter describes serious reservations about the calculations to establish the Liters/day value used in the equation for the determination of the PHG.*

Response 3: The commenter makes a persuasive point regarding potential flaws in the calculation of equivalent total exposure to drinking water. We agree that this was a needlessly complex calculation. However, this and other methods do result in an equivalent value of about 4 L/day for total combined-route exposures to small volatile halogenated hydrocarbons in drinking water, to account for showering and other household uses of drinking water. We have decided merely to accept the 4 L/day value and cite one of the methods by which such values are calculated (the CalTox program), rather than show the chain of calculations. A value of 4 L/day provides a useful health-

protective estimate, and has been used in several other PHGs for chemicals with similar properties.

Comment 4: *Description of uncertainty*. "There is no description of uncertainties for the calculation of the PHG. There is a discussion of the uncertainties associated with the study in the Risk Characterization portion of the document. However, this discussion is very limited and does not adequately characterize the uncertainties in the analysis."

Response 4: The commenter is correct that while OEHHA discusses potential data quality uncertainties and potential confounding and conflicting information in our PHG documents, we do not affix a level of uncertainty to our calculations of the final health-protective concentration value. These types of values do not lend themselves to reliable uncertainty estimates.

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