# Responses to Major Comments on Technical Support Document

# Public Health Goal
# For
# Carbon Tetrachloride
# In Drinking Water

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# INTRODUCTION

The following are 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 carbon tetrachloride as discussed at the PHG workshop held on November 5, 1999. Some commenters provided comments on both the first and second drafts. 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.org. OEHHA may also be contacted at:

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# RESPONSES TO MAJOR COMMENTS RECEIVED

## Comments by the U.S. Environmental Protection Agency Office of Water

Comment 1: *Comment that each of the animal cancer studies reviewed, including Edwards et al., 1942, Della Porta et al., 1961, and mouse and rat studies by NCI (1976 a,b), were deficient in some respect, and that the choice of any one study might not be appropriate. The U.S. EPA calculated the geometric mean from these studies to determine the oral slope factor for carbon tetrachloride.*

Response 1: Commenter is correct regarding the lack of a flawless study upon which to base our risk calculation. The California Department of Health Services (DHS) chose not to adopt U.S. EPA's approach of using the geometric mean of the above studies, although little quantitative difference results from the two approaches. DHS eliminated from consideration the studies by Della Porta *et al.* (1961) (hamster) and the National Cancer Institute (NCI) (1976a,b) (rat). The NCI rat data do not indicate a statistically significant association between dose and tumor response for either sex at either of the doses tested, yielding a negative carcinogenic result. The hamster bioassay was very small, with only one dose level tested. The vehicle controls were not conducted concurrently. Additionally, there was a suspicion that the hamster colony may have been infected with a liver disease (DHS, 1987). The California Department of Health Services eliminated the NCI mouse study because the high tumor incidence in both dose groups prevented an accurate assessment of dose versus response (DHS, 1988b).

The calculation of a health protective PHG concentration for carbon tetrachloride, based on its carcinogenicity, uses the study selected by DHS. In 1988, DHS determined that the appropriate study upon which to derive the *de minimis* drinking water concentration was that of Edwards *et al.* (1942), although the reference was indirect (DHS, 1988a). Also in 1988, DHS recommended the potency value of 0.18 $(mg/kg\text{-}day)^{-1}$, from the analysis of Edwards *et al.* (1942) data performed by the California Public Health Foundation (CPHF) (1988), to establish a risk-specific intake level for carbon tetrachloride ingestion exposure for Proposition 65 (DHS, 1988b). In a review of the carcinogenic potency for the Standards and Criteria Workgroup, the Reproductive and Cancer Hazard Assessment Section of DHS concurred that the potency value of 0.18 $(mg/kg\text{-}day)^{-1}$, derived by CPHF (1988) from the analysis of Edwards *et al.* (1942), was the appropriate potency value for the ingestion route of exposure (RCHAS, 1991). In our reanalysis of the data for the PHG evaluation, we concurred with this determination. Calculation of a PHG from this potency results in the same value of 0.1 ppb (rounded to 1 significant figure) for a $10^{-6}$ risk level as would result from use of the U.S. EPA geometric mean potency value.

Comment 2: *Suggestion that 2 L/day be used for water exposure.*

Response 2: The 4 L/day value was used in accordance with OEHHA methods for volatile chemicals. The default is 2 L/d for non-volatile chemicals; however, the higher value accounts for additional equivalent exposure to volatile chemicals from various uses of drinking water such as bathing (Bogen and McKone, 1988). Accounting for inhalation of volatile chemicals from household uses of water is also recommended in the U.S. EPA's Exposure Factors Handbook (U.S. EPA, 1997)

Comment 3: *Suggestion for the noncancer health-protective concentration calculation. A conversion factor of 5/7 should be applied to account for the 5 days/week dosing regimen used by Bruckner et al., (1986).*

Response 3: We accept the suggestion. This correction factor changes the noncancer health-protective concentration for carbon tetrachloride from 7 ppb to 5 ppb. The change has been made to the final document.

## Comments by the U.S. EPA National Center for Environmental Assessment

Comment 1: *Suggestion to include mention of gastrointestinal, respiratory and nervous system effects in acute, human section.*

Response 1: Added gastrointestinal effects such as nausea and vomiting to the first paragraph in acute, human section. Added mention of pulmonary edema to third paragraph.

Comment 2: "Carcinogenicity in humans: The material included in this section is inadequate. Quite a few references are missing. Instead of presenting the Cal EPA's conclusions, the conclusions drawn by the authors of the paper are presented. The studies that are included give very little information for a reader to understand on what basis the conclusions were drawn. For example, the reference to Lynge *et al*. (1997) gives the conclusions drawn by the authors of the article. The description of the paper does not give the sample sizes, follow-up period, findings etc., basic study details necessary for the readers to understand whether the conclusions drawn by the authors were sound or not. The same is true about the other studies that are included in this section." *The commenter also suggested several epidemiological studies.*

Response 2: Commenter is correct about Lynge *et al.* (1997) offering conclusions with little substantiation. The paper, in fact, did not give "…the sample sizes, follow-up period, findings etc., basic study details necessary for the readers to understand whether the conclusions drawn by the authors were sound," and accordingly, the Lynge citation was removed. We added three additional summaries of epidemiological studies, Heineman *et al.* (1994) which related human brain cancer to occupational exposure, Wilcosky *et al.* (1984) which reported a relationship of carbon tetrachloride exposure to lymphatic leukemia, and Cantor *et al.* (1995) which suggested associations between carbon tetrachloride exposure and female breast cancer.

Comment 3: *Commenter stated that the draft reported what other authors concluded too often, without detailing Cal/EPA's position. For example, the commenter writes,* "…the draft states that the U.S. EPA (1984) reported that the studies performed by Pendergrast *et al*. (1967) are criticized due to small sample size…."

Response 3: We believe that citing the conclusions of other authors is acceptable, appropriate and strengthens the PHG document. However, if we strongly disagree with the conclusions, we would normally state so.

Comment 4: "Subchronic NOAEL: The description of the Bruckner *et al*. (1986) study is confusing. The rationale for choosing the NOAEL based on this study is still not clear. The paragraph on page ten needs to be rewritten."

Response 4: Rationale for selection of the Bruckner study as the noncancer no-observed-adverse-effect-level (NOAEL) source was expanded in both the subchronic, animal section and the dose-response assessment portions of the draft. The paragraph was additionally modified to mention that the NOAEL is

changed by 5/7 to account for dosing schedule and that U.S. EPA used this NOAEL in its RfD calculation.

Comment 5: *Along with several excellent minor suggestions, the commenter asked for additional information for the Bove et al. (1995) study.*

Response 5: We added a new Table 4 which lists birth outcomes, odds ratios and confidence intervals for the pertinent information from the study.

## Comments by University of Southern California

Comment 1: "The reviewer questions the use of only the Edwards data of l942 to derive the cancer slope factor and the regulatory concentrations of carbon tetrachloride to be used for carcinogenesis based on only this one study. The reviewer prefers the approach of the U.S. EPA in which the cancer slope factors from the studies in mice, hamsters, and rats were used, and a geometric mean was derived from all these studies for the cancer slope factor. The reviewer suggests that the authors revisit this issue. Since carbon tetrachloride is a multispecies, both sex carcinogen, it would seem most appropriate to use the cancer slope factors from mice, rats, and hamsters to take advantage of this in determining the PHG."

Response 1: As described in our response to the U.S. EPA's Office of Water comment 1, the two approaches provide similar potency values and an identical PHG (rounded to 1 significant figure), so we have decided to retain the previous California approach.

Comment 2: "1. SUMMARY: Page 1, para. 1, the second line should read, "...of 0.1 ug/L (or 1 ppb)."

Response 2: This is incorrect; 0.1 μg/L is 0.1 ppb, as stated.

Comment 3: "On page 1, para. 1, lines 5-6: The authors should state directly that there was no evidence for a threshold for carcinogenesis with this compound, so that a linear, no threshold model was used in calculating cancer slope factors. In addition, can an error bar (uncertainty) be associated with the calculated PHG for carbon tetrachloride based on cancer?"

Response 3: A discussion of cancer modeling parameters does not appear appropriate in the summary. A no-threshold assumption for cancer risk assessment is the default, rather than the other way around, as appears to be implied by this comment. The estimated cancer potency used in the risk assessment is the upper 95% confidence limit. No lower confidence limit is calculated, so error bars are not applicable.

Comment 4: "Page 1, para. 3: A few sentences describing the reasoning why the California OEHHA PHG of 2000 is proposed to be 0.1 ug/L, whereas the California DHS PHG is 0.5 ug/L as of l998 and the U. S. EPA MCL of l998 is 5 ug/L, would be helpful here."

Response 4: These explanations are provided in the Section titled "Other Regulatory Standards." It does not seem necessary to repeat these in the Summary. One important point to note is that 0.5 ug/L is a California MCL, not PHG. An MCL (Maximum Contaminant Level) is a regulatory standard whereas a PGH (Public Health Goal) is non-regulatory in nature. The PHG is to be considered in setting any new MCL in the future.

Comment 5: *Introduction should mention the well-known hepatotoxicity and hepatocarcinogenicity of carbon tetrachloride to introduce the document properly.*

Response 5: Good suggestion, a few brief sentences added to introduction.

Comment 6: "Production and Uses: This section is in general adequately written. The authors might provide the reasons for why production of carbon tetrachloride, its use as a feedstock in production of chlorofluorocarbons, and agricultural use of carbon tetrachloride have stopped in California. Is this due to its toxicity, for economic reasons, why?"

Response 6: It can be assumed that the 1986 ban on agricultural use of carbon tetrachloride was related to its toxicity, but we have no specific information on that. Phaseout of chlorofluorocarbons removed the market for carbon tetrachloride as a chemical precursor. This decreased demand for carbon tetrachloride presumably eliminated the need for production in California, but we have no specific information on the market issues, and see no particular reason to discuss this in the PHG document.

Comment 7: "The authors should consider describing the specific types of cytochrome P450's (if they are known) that metabolize carbon tetrachloride."

Response 7: A sentence has been added to the metabolism section describing the major human enzyme responsible for carbon tetrachloride bioactivation at lower, "environmentally relevant" levels to be cytochrome P450-2E1 (Zangar *et al.*, 2000).

Comment 8: "Genetic Toxicity: Page 11, para. 1 under this section, line 2: A sentence is missing here, for transition. This para. should read, "...to form trichloromethyl radical. This reactive intermediate should bind to DNA. Adduct identification, however, is ....."

Response 8: Sentence added as suggested.

Comment 9: "Page 11, para. 2 under this section: The authors should insert that it is notoriously difficult to test volatile compounds in the Ames bacterial mutagenesis assays. Further, their statement that "Almost all bacterial mutagenicity tests have been negative" is not sufficiently clear. They should note that some assays are positive, and indicate that it may be difficult to get the type of S-9 used (whether induced by MCA or Arochlor 1254 or by carbon tetrachloride itself) right in such studies."

Response 9: These comments would be incidental to the information presented and would require specific citations which we do not have. It appears to us that the reporting of the data should be sufficient to the use of these studies in the context of the PHG document.

Comment 10: "Page 11: The authors should construct a short summary table of all of these results, to help the reader. This section overall is a fair assessment of the data on the genotoxicity of carbon tetrachloride. It is well-written and comprehensive, but also laudably concise.

Response 11: A summary table would be an option here, but is not wholly necessary. We elect to leave as written to maintain the concise nature which was otherwise lauded.

Comment 12: "Developmental and Reproductive Toxicity: Pages 12 and 13: The reviewer suggests a summary table for these results to help the reader assimilate the data quickly. Overall, this section is written in a clear manner, and the citation of studies from the literature appears to be comprehensive and indicates that carbon tetrachloride causes embryotoxicity and fetotoxicity."

Response 12: A summary table is not clearly indicated here, since these endpoints are not germane to either the noncancer or the cancer endpoints. We have elected not to include such a table.

Comment 13: *The section on animal immunotoxicity needs a summary sentence.*

Response 13: A summary sentence has been added.

Comment 14: "Carcinogenicity: …that the rat studies showed tumor production in at least four strains, and in both sexes, is indicative that carbon tetrachloride is a very effective carcinogen in animals, and this point should be more strongly emphasized in the text on page 15, paragraph 4, line 3. Please stress that most of these studies used subcutaneous injection, only one study used gavage. More relevant routes of exposure to the human situation would be inhalation and in the drinking water. This point should be made more clearly."

Response 14: Routes of exposure for rats were given in both text and Table 3. Further emphasis does not appear to be indicated, because we believe that the mode of action of this chemical in causing liver cancer is largely independent of route of administration. Acute exposures in animal studies and in humans have shown severe liver effects by multiple routes of exposure.

Comment 15: The hamster carcinogenicity data should also be summarized in a table similar to that constructed for the rats (Table 3).

Response 15: A table was used to summarize and compare rat data from several studies. A table does not appear to be needed for the hamster carcinogenicity data because there was only one study and the data is therefore much simpler.

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