Responses to Major Comments on Technical Support Document

Public Health Goal
For
TETRACHLOROETHYLENE
In Drinking Water

Prepared by

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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 tetrachloroethylene as discussed at the PHG workshop held on November 5, 1999, or as revised following the workshop. 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.ca.gov. OEHHA may also be contacted at:

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RESPONSES TO MAJOR COMMENTS RECEIVED ON THE PUBLIC HEALTH GOAL FOR TETRACHLOROETHYLENE

United States Environmental Protection Agency, National Center for Environmental Assessment

Comment 1. "The unique features of this assessment, as compared to other recent assessments (State of New York, 1997; ATSDR, 1997; Canada, 1993) are the use of the pharmacokinetic models described on pages 10 to 18 to estimate the metabolized dose in both animals and humans and the use of the CalTOX exposure model described on pages 47 and 48 to include inhalation and dermal exposure from drinking water sources as separate routes of exposure attributable to the presence of perchloroethylene in tap water. Since not enough information was given about these models, we are unable to endorse them and the conclusions drawn from them, although the piecing together of the various models into a coherent assessment seems logical."

Response 1. We agree that this complicated risk assessment would require some additional details and collaboration to reproduce. The CalTOX model has been previously described and used for various assessments; it is available free of charge on the Web site of the Human and Ecological Risk Division of the California Department of Toxic Substances Control (www.cwo/~herd1/ctox_dwn.htm) for those who might desire a better understanding of the methods.

Comment 2. "The section on environmental occurrence would be a better place to describe the CalTOX exposure model than having it buried on page 47 and 48. It is a significant part of the document and fits logically in this section."

Response 2. The addition of the CalTOX exposure model to the environmental occurrence section would not be appropriate. In this section, sources of potential exposure to tetrachloroethylene (PCE) are described. The CalTOX exposure model was used in the document to assess the exposure to PCE and does not describe a source of exposure.

Comment 3. "There is an apparent inconsistency between the text on page 6 describing Table 3 and the footnote a of Table 3 on page 7. The text says that inhalation exposures while bathing have been considered in Table 3, whereas the footnote says that inhalation while bathing has been ignored."

Response 3. The corresponding text has been revised to remove the inconsistency.

Comment 4. "The study length correction as given [in Table 4] was applied as a divisor, while a cursory reading of the footnote suggests it was a multiplier."

Response 4. The correction for study length is obtained by first dividing the lifetime of animals by study duration and taking the result to the 3rd power. This value is used as a multiplier in the correction for study length. Footnote (b) in Table 4 was revised to more accurately reflect the calculation performed.

Comment 5. "In reading the description of the calculations leading to Table 7, page 39, an unanswered question arises: namely, does the assessment account for the fraction of the inhaled dose in animals that is not absorbed? Although this question is not relevant to Table 7 because that table deals with administered dose, the reader would be helped by an indication here about where in the document that issue is dealt with. We could not find such a discussion."

Response 5. Every effort was made to incorporate all aspects of potential exposure. Although a specific section for the unabsorbed dose was not identified in the document, the topic is indirectly touched upon in the Pharmacokinetic Models section. The fraction of the inhaled dose that is not absorbed is excreted from the body. As discussed in the Metabolism and Pharmacokinetics section, 50 percent to 70 percent of the inhaled dose is absorbed. Thus, 50 percent to 30 percent of the inhaled dose is then not absorbed.

Comment 6. A discrepancy was observed in the reported incidence of mononuclear cell leukemia in the low and high dose groups between the values reported in Table 7 and the values reported in NTP Technical Report #311.

Response 6. The data represented in Table 7 are correct.

Comment 7. "One has a hard time seeing how the administered dose metric in Table 8 is converted to the metabolized dose metric in Table 10. The only indication of how this is done is in Table 4 on page 12, where the model of Bogen et al. (1987) is excerpted. But it would be of general interest as well as specific interest in going from Table 8 to Table 10 to see, either through an equation or preferably a graph, the non-linear function of metabolized vs. administered dose that Bogen et al. (1987) used to generate the data quoted in Table 4."

Response 7. Bogen et al. (1987) used a series of equations to convert administered metric dose to metabolized dose. Because of the complexity involved, the reader was directed to the article by Bogen et al. (1987) for a more thorough explanation of the process the researchers used in their conversion. No simple graphic representation was available for this lengthy calculation. We feel that this approach is more appropriate than providing the details on for the purposes of the PHG document.

Comment 8. "For the curious reader, some data on the "improve fit" of the time to tumor model would be of interest. [Page 43, line3] This would include not only the "fit" statistics, but also a graph of the data and the two models."

Response 8. See response to comment # 7.

Comment 9. "The title should refer to NCI (1977) PCE gavage bioassay and the applied dose should be in units of mg/kg-day." [Table 11]

Response 9. Text was revised.

Comment 10. "The sentence starting with "However, it should…" and ending with "…used to run it)." could be a footnote for those who have to reconcile the 1992 OEHHA document with this document. [Page 44, lines 6-13] However, for readers of this document it is a confusing comment because in this document you did not use Bogen's analysis of the tumor incidence."

Response 10. Text was revised in order to clarify this paragraph.

Comment 11. "Although from metabolic considerations inhalation and dermal exposure both bypass the liver and avoid the first pass effect, the obvious difference between the routes is how the perchloroethylene is transferred from air to blood. [Page 46, 1st paragraph] This paragraph needs to say how that transfer was accounted for before one can accept using an inhalation potency for a dermal route of exposure."

Response 11. In this paragraph, we have indicated that there is no direct evidence as to the appropriate potency estimate to be used for dermal exposures. So by default, the inhalation value was used for this route. In terms of differences between these two routes, there are other differences than just the transfer of PCE from air to blood, such as rates of metabolism and other dispositional parameters that could impact the potency estimate. Further discussion on this subject can be found in the calculation of the public health goal (PHG) section of the document.

Comment 12. "Since the CalTOX model considers the variation of input parameters, some indication of the variability of the output parameters in Table 13 could be given and summarized in the Risk Characterization section. This would give some basis for stating the uncertainty of the final water concentration calculated on page 49."

Response 12. Variability in the CalTOX module represents only a small part of the total variability and uncertainty in the analysis. Good variability (sensitivity analysis) tools are not available for the other calculations. Conducting the full variability analysis in CalTOX therefore did not seem very productive.

Comment 13. "This [Table 13] is a bit confusing, because it is not completely clear that the inhalation and dermal doses are all part of the water dose (which as we may recall from earlier in the analysis only makes up around 3%-11% of one's total exposure). The title makes it clear that this table refers to water exposure, but the wording of the column and row headings reintroduce ambiguities. One idea would be to change the column heading for the last column from "% of total dose" to "% of total dose from water."

Response 13. Table was modified to remove ambiguity.

Comment 14. "The calculation of the water concentration corresponding to a cancer risk of 10^{-6} turns out to be on the order of magnitude of 10^{-2} μg/L, but the values for metabolized dose in Table 13 used in this calculation assumed concentrations of 1.0 μg/L (see page 47, bottom), which is on the order of 100 times higher than the result. The question is whether the non-linear relationship between metabolized dose and administered dose should be explicitly considered in this calculation, since this relationship could change considerably over a concentration range of a factor of 100. The only information given in the document on this point is in Table 4, page 12, which shows noticeable non-linearities at (comparatively) very high doses, but says nothing about lower concentrations."

Response 14. As the commenter notes, the calculation assumes a linear relationship at low concentrations. This is expected for any regular mathematical function of this type. Both 1.0 and 0.01 μg/L are in the low, presumed-linear range. The available data showing non-linear factors involves much higher concentrations.

Comment 15. "The risk characterization section fails to discuss the implications of the relative source contribution (RSC) first introduced on page 49. If tap water constitutes only 3% of the total exposure to tetrachloroethylene, the entire document is apparently devoted to only a minor source of exposure. This fact is certainly important in making regulatory decisions, and needs to be mentioned in any credible characterization of the risk of tap water contamination. This is true for both non-cancer risks, where the RSC is an explicit factor, and in cancer risk estimation, where it is not explicitly considered."

Response 15. Tap water should be only a small contributor to exposures to PCE on average, but certain individuals may receive (and have received in the past) much greater exposures by this route. The RSC in this case is calculated at an equivalent drinking water level ten times the PHG value and is based on actual water contamination data. Although RSC is acknowledged as an estimated value in our PHG calculations, it is defensible. The Office of Environmental Health Hazard Assessment (OEHHA) defines the RSC as appropriate for use in non-cancer risk assessments only; this approach explicitly directs that the RSC is not used in cancer calculations.

Other routes of exposure are already addressed by other California regulatory programs, notably the Toxic Air Contaminants regulations which use a similar risk assessment methodology for inhalation exposures to that presented for the PHG program.

Lawrence Livermore National Laboratory, University of California

Comment 1. "[T]here is very little consideration given to the fact that exposure to PCE occupationally as a chemical intermediate occurs in combination with exposure to many other solvents. Environmental exposure to PCE likewise occurs in combination with many other exposures including airborne benzene, PAHs, smog, etc. No consideration is given to chemical interactions and should be to set exposure limits. Most solvents are acted on by similar detoxification/bioactivation processes (CYP2E1, for example) which can lead to potentiation of effects. This should be considered."

Response 1. OEHHA and other regulatory agencies are currently attempting to develop methods for evaluating environmental exposures to a combination of compounds. At present, we can only acknowledge this as one of the uncertainties.

Comment 2. "Non-quantitative statements about dose or effect are frequently made throughout the document that should be quantified." *The document* "could be made more informative by including some quantal indication."

Response 2. Public Health Goals provide estimates of the levels of chemical contaminant in water that would pose no significant risk to individuals, including the most sensitive subpopulations, consuming the water daily, over an entire lifetime. In our extensive review of the best available toxicological data, we focused the quantitative analysis on the critical data that posed the most significant risk to individuals in order to calculate the PHG. As for the remaining data which is adequate for the purpose and it would not be critical for the development of the numerical goal, more descriptive information (non-quantitative statements) was provided not to distract from the critical information were used. The references cited in the document provide more quantitative evaluations of the data, for those who would wish to have a more in-depth study of the subject.

Comment 3. "PCE and some of its metabolites have been used medicinally and its surprising that such information [on molecular mechanisms of PCE toxicity] is lacking. Has this literature been examined to make sure all relevant information on PCE metabolism in humans has been considered?"

Response 3. A discussion of medicinal use or molecular mechanisms of PCE toxicity has not been incorporated into this document because the mechanism or mechanisms of PCE carcinogenicity is/are not well characterized. Such a discussion would be outside the scope of a PHG document at this time, since it cannot currently contribute to setting a PHG.

Comment 4. Very little information is provided on the DNA and protein binding of PCE. Some information is in the literature on this topic but seems ignored under the carcinogenesis sections. This is information that adds to the weight of data supporting a role for PCE in carcinogenesis and other mechanisms of toxicity.

Response 4. The topic of DNA and protein binding was briefly discussed in the sections on metabolism, genotoxicity, and cancer potency estimation. . We agree that this information adds to the weight of data supporting a genotoxic potential for PCE, and it was assumed for the purposes of risk assessment that PCE is acting as a directly genotoxic carcinogen partly on the basis of these data. However, a more extensive discussion of the binding experiments and adduct formation would not be relevant to the derivation of the PHG value, therefore no further discussion on this topic is provided.

Lawrence Berkeley Laboratory, University of California

Comment 1. "[T]here are some instances where the references used are out of date, and more recent information could and should be cited."

Response 1. The indicated references were obtained and reviewed. The appropriate data were incorporated into the document.

Comment 2. "The data evaluation and interpretation are consistent with the state of the art in this field and well described and defended. The OEHHA staff is to commended for making use of many alternate and innovative approaches—metabolized dose as a basis for estimating cancer, time-to-tumor models, linear extrapolation models, multipathway exposure assessments, etc. However, as noted below there is a need for a more formal analysis of the uncertainties in these approaches and some discussion of how sensitive the PHG is to the assumptions and models used."

Response 2. An overall sensitivity analysis would add even more complexity to this already difficult and complicated analysis. Software tools are available for a semi-automated sensitivity analysis only on certain parts of the calculation, such as CalTOX; a consistent approach could not have been extended through the chain of calculations in a reasonable period of time. We acknowledge this as a limitation to the quantitative evaluation and description of our approach, and have noted this in the Risk Characterization section.

Comment 3. "The one area that was left out is a discussion of all potential sources of PCE exposure. There is no mention of exposure to indoor sources of PCE other than tap water and this should be added. There should be some discussion of indoor levels of PCE and indoor exposures. PCE was one of the chemicals considered in the EPA Total Exposure Assessment Methodology (TEAM) studies. The PHG report should provide some perspective on the relative contribution of indoor sources to PCE exposure." *Two references were cited for inclusion.*

Response 3. An additional section titled "Indoor Exposures" was added to the document.

Comment 4. "The report is lacking discussion of uncertainty and variability in the overall characterization of risk. There should be some discussion of uncertainty with dose/response function—in particular how likely is PCE to be a human carcinogen, how reliable and accurate

are the dose response models, and how sensitive is the value of the PHG to models and assumptions selected to characterize the dose/response function? There should also be discussion of the uncertainty and variability of the exposure factors selected—in particular, does the 2 L/day assumption of tap water consumption represent a mean or an extreme value, how representative is 3.54 L/day equivalent inhalation from household water uses, and how much to these assumptions impact the magnitude of the PHG value?"

Response 4. Discussion of uncertainty and variability is included in the PHG document for both the uncertainty with dose/response function and variability of the exposure factors selected.

Comment 5. "Summary. This is actually an Executive Summary and should be referred to as such. The summary discussion should include some discussion of why the PHG value of 0.056 ppb differs so much from the EPA MCL of 5 ppb."

Response 5. A discussion of the reasons for the difference in values for the PHG and the U.S. Environmental Protection Agency (EPA) has been incorporated into the summary. We see no reason to retitle it "Executive Summary" and have left its title unchanged.

Comment 6: "The summary should provide a brief discussion of how feasible it is to make routine measurements of PCE concentrations of 0.06 ppb in water supplies. Is this below the level of detection by most common methods?"

Response 6. The PHG is determined based only on public health considerations, and does not consider detection limits or cost-benefit analyses. These factors are intentionally excluded from discussion in the PHG document.

Comment 7. Introduction. The document has no introduction. Why? Most risk assessment documents provide some type of introduction providing an overview of what is presented in various sections of the report as well as some background on motivations for the study. It would be useful to include that in this document.

Response 7. An introduction was added to the PHG document.

Comment 8. "Table 2 on page 4 and page 47. Are the chemical properties reported here the values that were used for the CalTOX calculations reported on page 47 or were the values in the CalTOX data set used."

Response 8. Table 2 contains the physical and chemical properties of PCE as described by IARC and ATSDR. These parameters were not the ones used in the CalTOX calculations, from the standard CalTOX data set. The values used in the CalTOX calculations were values that were obtained following a survey of the literature. The average value calculated from this search was incorporated into the CalTOX data set. Some slight differences exist in the values presented in Table 2 compared to those obtained from the survey and used in CalTOX.

Comment 9. "Why is there no consideration of Pharmacodynamics? Metabolism serves as a loss mechanism in a PBPK model. Pharmacodynamics provides a somewhat broader assessment of the rate of and products of a various metabolism processes. I suggest that this section be renamed "Pharmacokinetics and Pharmacodynamics" and include more information on the behavior of metabolism products. In particular there should be some discussion of metabolism pathways."

Response 9. Discussion of the metabolic pathways and pharmacokinetics can be found in the Metabolism and Pharmacokinetic Section of the document. A general discussion regarding the absorption, metabolism, distribution, and excretion is presented. In addition, metabolism and the behavior of the metabolic products were briefly considered in this section. The addition of more detailed information on pharmacodynamics could be of general interest, but would not appear to be directly relevant to the calculation of the PHG value. In the document, previous reviews (OEHHA, 1992; IARC, 1995; ASTDR, 1997) on this topic are cited for readers who would like to obtain more detailed information.

Comment 10. "There is no information provided here on tissue distribution and its importance for assessing the ratio of metabolism to intake. Why not?"

Response 10. A discussion of tissue distribution is found within the Metabolism section. A more detailed discussion is not provided in the document because the distribution of PCE among tissues is extensive once the material is absorbed; no particular sensitivities related to differential distribution are noted.

Comment 11. "There is no discussion here on the use of biomarkers in human studies of PCE and cancer. There should be some discussion of the feasibility of biomarkers and if possible some discussion of who has attempted this or on why no one has yet attempted biomarker-based studies."

Response 11. A discussion of biomarkers in human studies of PCE and cancer has not been incorporated into this document because the mechanism(s) of PCE carcinogenicity is/are not well characterized. Further elaboration of the feasibility of biomarkers or as to why no one has attempted biomarker-marker studies is outside the scope of a PHG document at this time, since it cannot currently contribute to setting a PHG.

Comment 12. The last paragraph of page 40, "provides a good discussion and illustration of the use of the linear extrapolation approach with the LED_{10}. However, use of this new methodology raises some questions and concerns. First, how sensitive are the results of the analysis to the benchmark selected. That is what happens for example if the approach is applied to the LED_5 instead of the LED_{10}? Also, the assumption is made here that the EPA will follow through with the proposed 1996 guidelines. The guidelines have not be[en] finalized or issued. What happens if there are major revisions to these guidelines?"

Response 12. Yes, the PHG values are sensitive to the assumptions used, but formal sensitivity analyses are not conducted. LED_{10} was selected as a point of departure for risk assessment

because it is generally the lowest (round number) point within the observable range. This makes it a good stable point for low-dose extrapolation. Extrapolations based on a LED_5 might be half the value that they would be if based on an LED_{10}, but that depends on both the slope of the dose-response curve and any decision as to whether the same uncertainty factors should be applied from the lower effect level. As required by the Safe Drinking Water Act, we will review and revise as necessary any public health protective concentration when new scientific data are available or significant regulatory changes occur. OEHHA utilizes the methodology described in U.S. EPA's 1996 draft guidelines where appropriate and will review any subsequent versions and incorporate them as appropriate.

Comment 13. "In using the CalTOX model, the authors of this study missed an opportunity to carry out a quantitative uncertainty analysis on the absolute and relative exposure by different pathways. The CalTOX model was designed to provide easy access to uncertainty/variability assessments. The Datacal.xls data set that is referred to includes both a mean value and coefficient of variation of exposure factors such as drinking water intake. At a minimum these values should be reported and discussed."

Response 13. An uncertainty analysis only of the exposure aspects appeared to us to be of limited utility, whereas a comparable evaluation of the entire analysis really was not feasible. Only the CalTOX model includes uncertainty analysis as a built-in functionality, and CalTOX has been used in only a few of the PHGs to date. For all these reasons, sensitivity analysis is not a standard part of the PHG development process.

Comment 14. "Why report the PHG as 0.056 ppb? Given the overall uncertainties in the parameters used and the reliability of the calculations provided, there is no justification for reporting more than 1 significant figure for the PHG, that is write it as 0.06 ppb."

Response 14. We agree that the PHG values have no more than one significant figure. Our use of two digits in some cases may serve to emphasize the value as the result of a simple calculation. However, in this case we have decided to go ahead and round off the PHG to 0.06 ppb. .

Comment 15. "[O]ne area that is left out is the "para-occupational" exposure. That is, the exposure to non-workers as a result of chemicals brought home from work by a worker residing in their household. PCE has been proposed and evaluated as an example of a significant para-occupational exposure…" (*reference provided*).

Response 15. The appropriate data were included in the PHG document under the "Indoor Exposures" subsection.

Halogenated Solvents Industry Alliance, Inc.

Comment 1. "Risk assessments that accumulate worst case assumptions and that predict risks that are patently too high at low dose are not in the best interests of the public. Such overly conservative risk assessments draw attention to situations that are, in reality, of negligible risk whilst circumstances of true concern are overlooked."

Response 1. The Safe Drinking Water Act of 1996 requires protection of the public from drinking water contaminants, using prudent assumptions as necessary to assure absence of adverse health effects. Lack of explicit knowledge about human health effects requires incorporation of some assumptions about toxic mechanisms and cross-species extrapolations. Our evaluation involved an extensive analysis of the available scientific literature and acknowledgement of several types of uncertainty; none of the steps involves a worst-case scenario. When new scientific data are available to reduce the uncertainty, the conclusions can be reevaluated.

Comment 2**.** *Regarding animal tumor types:*

"Mouse Liver – Passing mention is made of the mechanisms of induction of rodent liver tumors in association with peroxisome proliferation. European regulators, the US Food and Drug Administration, and many scientists now acknowledge that rodent liver tumors associated with peroxisome proliferation have no relevance for man (and are therefore not a basis for calculating human risk). If regulatory conservatism prevents this conclusion despite substantial evidence regarding perchloroethylene (PCE) and its principle metabolite trichloroacetic acid (TCA), the relationship between mouse liver tumors and peroxisome proliferation should, at least, be reviewed. This is critical in the light of the decisions regarding linear versus non-linear dose response relationships analyzed below."

"Rat mononuclear cell leukemia (MNCL)– The incidence of MNCL in control rats in the NTP inhalation study on PCE was 56 % in males and 37 % in females. The background incidence in the F344 rat is known to be "very high and variable." The human analogue of rat MNCL is extremely rare and there are no types of spontaneous tumor in man that approach the levels of incidence of this rat tumor type. Since it is likely that the natural propensity for developing MNCL can be triggered by mechanisms not normally associated with tumorigenesis, it is doubtful whether an increased incidence should be regarded as an indicator of carcinogenicity. However, even if considered of relevance on a qualitative basis, there is no justification for using the increased incidence in a quantitative calculation of risk because of the special susceptibility of the F344 rat strain."

Response 2**.** Cancer risk assessments do not assume concordance between species in particular tumor types, because of species- and strain-specific differences, as rightly pointed out above. The important point is that a particular chemical interacts with cells to produce tumors. We agree that the F344 strain may be unusually sensitive to some carcinogenic mechanisms, compared to other rodent strains. Its relative sensitivity for chemical-induced carcinogenesis, compared to humans, is unknown. Because of the multiple tumor types resulting from administration of PCE and its metabolite TCA, the argument that tumors secondary to

peroxisomal proliferation are not relevant to humans is of limited significance; the overall pattern of carcinogenicity is more compelling.

Comment 3**.** "Mention is made in several places of the possibility of the formation of PCE oxide, a metabolite, that if generated as a free molecule, could be expected to be genotoxic. There is no evidence that this metabolite is formed as a free molecule. Moreover, the negative results of various types of in vivo or in vitro genetic toxicity tests, where active metabolism occurred, show that PCE oxide is unlikely to be of any significance. It is likely that PCE oxide, if it exists at all, never leaves the site of formation on the enzyme before further chemical alteration occurs."

Response 3. Several investigators consider PCE oxide to be a credible potential genotoxin in the PCE metabolic pathway. We acknowledge the diversity of scientific opinion on this point in the Metabolism and Pharmacokinetic and Genetic Toxicity sections, but feel that this is a relevant postulate regarding carcinogenic mechanisms.

Comment 4. *The amount of dose assumed to be metabolized is too high. The work of Reitz et al. (1996) should have been used for the calculation.*

Response 4. The work by Reitz et al. (1996) was reviewed and considered in the preparation of this document. The various model predictions, available experimental data, and the fraction of dose metabolized used by Reitz et al. (1996) were found to be consistent with results of Chen and Blancato (1987), Bois et al. (1996), and the Bogen et al. (1987) approach used in this document for dose-response modeling of the animal cancer data.

Comment 5. "The evidence indicates that exposure to PCE is not associated with substantial risk but is not sufficiently robust to show that PCE is not carcinogenic to man. However, it can be said that there is no clear evidence of carcinogenicity – this is a more accurate conclusion than "possibly carcinogenic" (p. 35). Of the tumor sites identified, the incidence of esophageal cancer cannot be evaluated without the confounders of smoking and drinking being taken into account. It should be noted that both factors individually are associated with elevations in esophageal cancer but together display a very large degree of synergy. It is not clear which part of the "lymphatic system" is identified. There is no indication that PCE exposure is associated with leukemia and the result for non-Hodgkin's lymphoma was only reported in a proportion of the studies (suggesting "unremarkable" findings when not reported) and statistically significant elevations were not observed."

Response 5. We think the varied evidence justifies a positive statement (possibly carcinogenic) rather than a disclaimer (no clear evidence of carcinogenicity). We are aware of the significant role confounders can play. As discussed in Appendix 1 of the document, predictions made using the animal data support our conclusion of "possibly carcinogenic." In addition, the IARC has judged PCE as a probable human carcinogen while the U.S. EPA has listed PCE as a probable/possible human carcinogen based on support of the limited findings in humans to the sufficient evidence of cancer in animals.

Comment 6. "The existing human neurobehavioral studies are not a suitable basis for setting a PHG. The authors of the PHG document have identified some of the problems with these studies but there are many other concerns. For example, it is very difficult to avoid bias, the selection of appropriate control subjects is critical, and multi-endpoint studies are prone to showing occasional statistically significant differences that have arisen by chance."

Response 6. OEHHA considers that there are sufficient data available to support the use of the human neurobehavioral effects as the non-cancer effects observed with PCE exposure. In order to account for the different strengths and weaknesses of the three studies cited in the document, a geometric mean of the estimates of a human health protective concentration was used in the risk assessment calculations.

Comment 7. "The study by Verplanke et al. (1999) reported no changes in those parameters normally used as clinical indicators of kidney damage. The one possible change reported, increased urinary retinol binding protein, was considered to represent possible minor alterations only in kidney tubules."

Response 7. OEHHA considers the findings by Verplanke et al. (1999) to be important in supporting the possibility of an alternative mechanism for renal toxicity by PCE. The nearly two-fold increase in mean urinary concentration of retino-binding protein reported by Verplanke et al. (1999) for one group of exposed workers confirms the changes in at least one renal parameter observed in six of eight rodent studies, where nephropathy has been observed in female rats and both sexes of mice.

Comment 8. The effects that can be considered to be associated with exposure to PCE are the onset of anesthesia (human information) and liver effects (rodent). Since rodents may be more sensitive to liver effects than man, the quantitative interpretation may be difficult. The effects on rat kidney would also require careful quantitative interpretation, if they are relevant to man at all, given the information in Volkel et al. (1998).

Response 8. These points are noted and considered.

Comment 9. "The selection of an extrapolation model for a PCE should be discussed on an end point basis. Thus "halothioketenes" relate to kidney responses and should not be used to justify a linear treatment of mouse liver tumors. In fact, the evidence that PCE does not induce mouse liver tumors by a genotoxic mechanism is extensive and fits with what is known for a wide range of rodent liver carcinogens associated with peroxisome proliferation. If a risk assessment is based on mouse liver tumors (despite the probable irrelevance to man), the extrapolation model should not be linear. An example of the type of analysis that is appropriate has been published for diethylhexylphthalate (Doull, J et al., Reg Tox Pharmacol **29**:327-357). For any kind of credible risk assessment for PCE, there has to be a full discussion of peroxisome proliferation (and associated phenomena such as cell proliferation, apoptosis and oxidative stress) and the role of trichloroacetic acid (TCA)."

Response 9. The evidence that liver tumors caused by PCE are related to peroxisomal proliferation is rather tenuous, and we have not assumed so in our evaluation. In that regard, the amount of detail provided on peroxisomal proliferation in the PHG document seems appropriate for our purpose. The calculation method we utilized is appropriate for the assumed genotoxic mechanism.

Comment 10. "The assumption that a "bodyweight to the power ¾" conversion should be applied despite the use of metabolized dose in both rodents and man is unjustifiable. The suggestion that it is needed to adjust for "sensitivity" means that it is being used as an uncertainty or safety factor that has no basis in biology. Every piece of mechanistic information relevant to PCE (and TCA) and mouse liver tumors leads to the conclusion that man, if he or she responds at all, is less sensitive than the mouse to a given metabolized dose. The absence of an induction of rat tumors provides support for this view. The power conversion should only apply when the metabolism in two species cannot be related by a PBPK treatment and, even then, the scientific justification for its use is very weak."

Response 10. OEHHA does not share the commenter's optimistic interpretation of the nature and direction of uncertainties in the interspecies comparison for PCE carcinogenic effects. Indeed, as noted in an appendix to the PHG document, the limited evidence from epidemiological studies is broadly consistent with the estimate proposed based on the mouse data and using the default interspecies extrapolation procedure applied in other PHG risk assessments. In the absence of more definitive evidence, OEHHA elected to use this standard default approach which is both consistent with the available data and protective of public health. OEHHA has previously emphasized that interspecies extrapolation needs to allow for toxicodynamic as well as toxicokinetic differences between species, and that variation and uncertainty from both these causes is accommodated by the default interspecies extrapolation procedure, in the absence of better information. The power conversion used in this document also follows the current proposed U.S. EPA guidelines.

Comment 11. "EPA does <u>not</u> classify PCE as a Group B carcinogen (page 54). The EPA Science Advisory Board rejected that classification and the IRIS database currently shows no official classification."

Response 11. EPA considers PCE as an intermediate between a probable and possible human carcinogen (Group B/C); this is now correctly noted in the document. Other groups, such as the IARC, have classified PCE as a probable human carcinogen (Class 2A).

Comment 12. "When the imperfections of the epidemiology data and the uncertainties of the animal-based calculation of risk are considered, this comparison should not appear in any public document. OEHHA recognized many of the difficulties in interpreting the epidemiology data for PCE and admit that it is inappropriate for calculating risk. The epidemiology studies used are an insecure basis for calculations for a number of reasons (including exposures to other solvents, potential uncorrected confounders of drinking and smoking, no correction for socioeconomic status). It should also be noted that the "PCE-only" sub-cohort does not show an overall

increase in cancer (and remains true for a very recent update of this cohort). As discussed above, the calculation of risk based on animal tumors has a number of flaws. The comparison is thus being made on the weakest possible sets of data and certainly should not be taken as supporting the calculations of the PHG."

Response 12. OEHHA believes that the animal data on PCE carcinogenicity are adequate for deriving a carcinogenic risk factor, and that the human data provide supporting evidence.

Association of California Water Agencies

Comment 1. The suggestion was made to include two recent publications associated with PCE exposure and percutaneous absorption (references provided).

Response 1. The identified articles were reviewed. The PHG document was revised to include some of the findings reported by Paulu et al. (1999).