Responses to Major Comments on Technical Support Document

Public Health Goal
For
Toxaphene
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 toxaphene as discussed at the PHG workshop held on July 22, 2002, or as revised following the workshop. 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, Los Angeles

Comment 1: "Thus, with every mixture of congeners there is the possibility that it is more toxicologically potent than the mixtures that have been tested for the purpose of establishing the regulatory levels. Furthermore, the issues associated with enantiomers of the congeners…"

Response 1: There is no question that the toxicity of a mixture will vary with the components of a mixture. The set of toxaphene congeners that persons ingesting toxaphene-tainted water will be exposed to can be expected to vary. However, the only sources of toxicity information utilize commercially available toxaphene or selected congeners. Therefore it is not possible to produce a more specific risk assessment for environmental exposures to toxaphene congeners and their enantiomers in drinking water. This has now been noted in the document.

Comment 2: "In general, I am not a proponent of the risk assessment methodology that has been utilized in this document and that is routinely used to determine risk associated with non-carcinogenic environmental exposures. The overall process of estimating the threshold for toxicity by the NOAEL or LOAEL and then dividing these values by a number of uncertainty factors (which are generally either 3 or 10) seems somewhat arbitrary and non-scientific…. However, this is the process that has gained acceptance among the various constituencies, and I am not in a position to suggest a better system for making such evaluations."

Response 2: The procedures used in the risk assessment are the standard procedures used by our office and U.S. EPA for assessment of threshold-based health effects.

Comment 3: "...for the determination of the relative source contribution (RSC) for the non-carcinogenic health-protective concentration, the chosen value does not seem to be well substantiated. In this instance, it appears that the RSC of 0.80 is just a guess from the information that appears on page 20. Is there data to substantiate this value?"

Response 3: The RSC is a rough estimate of the contribution of drinking water and non-drinking water sources to the overall human exposure. Data are not usually adequate to quantify the actual sources, and certainly were not in this case. Our default estimates generally range from 20 to 80 percent, where the lower estimate acknowledges major contributions from sources other than drinking water, and the higher estimate assumes a small/minimal contribution from other sources. Reevaluation of the extent of toxaphene residues in fish led to the decision to assume a small/minimal contribution from that source. As a result, the RSC was changed from the low default of 20 percent to 80 percent.

Comment 4: *Referring to a statement on page 2 of the document,* "The toxaphene health-based protective level of 0.003 ppb proposed by OEHHA (1991) was based on the cancer risk level of 10^{-6}," *the commenter notes that* "This statement seems to contradict the previous sentences where 0.003 mg/L represents a cancer risk of 10^{-4} level. It seems the 10^{-6} level should be 0.03 ppb. Was there different information used to derive this value in 1991?"

Response 4: Yes, the 10^{-6} level corresponds to 0.03 ppb. The typo has been corrected.

Comment 5: "Page 7, Metabolism section: The first paragraph seems to indicate that toxaphene is primarily excreted in the feces, whereas the second paragraph indicates that the primary route of excretion is the urine. It is my understanding that urinary excretion is minimal compared to the fecal excretion except for the pregnant animal (Wen and Chan, 2000)."

Response 5: The studies reported in the document appear to show that both urine and feces are major excretion routes, but which is predominant appears to vary. Pollack and Hillstand (1982) found no difference in the manner of excretion for pregnant vs. virgin rats. No change made.

Comment 6: "Page 8, lines 1 through 5: Are the enzymes that can perform this biotransformation known? It appears incongruous to suggest that the process was intestinal metabolism when rat liver microsomes were used for the process."

Response 6: The determination that anaerobic pathways were operating was based on *in vivo* metabolism of toxaphene. The experiment with rat liver microsomes merely confirmed that point. This has been clarified.

Comment 7: "Developmental and Reproductive Toxicity: It would be advantageous to indicate the treatment duration in the two-generation study."

Response 7: Done.

Comment 8: "Developmental and Reproductive Toxicity, 2nd and 3rd paragraphs: There are conversions from ppm to mg/kg/day that could be made more transparent by including the assumptions for the calculation. For example, the grams of intake per day and the weight of the animals would allow the calculations to be made. These assumptions could be stated throughout the document wherever the conversions have been made (it is possible that there are large intraspecies differences in these values)."

Response 8: Dose calculations have been problematic. When dose assumptions made by the study authors or earlier reviewers were used, this was stated. In some cases, it was not clear how they arrived at their determinations. When the calculations were made by OEHHA, the values and assumptions used are provided.

Comment 9: *Quoting from pg. 13 of the draft PHG,* "Weanling female mice were fed 10, 100 and 200 ppm (approximately 1.5, 15 and 20 mg/kg-day)," *the commenter notes*, "It seems that the 20 mg/kg-day should be a 30 from the ratios of the numbers."

Response 9: Yes. This has been corrected.

Comment 10: *Referring to p. 14*, "The study described indicates that there were initially 40 rats, and 20 were sacrificed at each of 4 time-points that equals 80 rats."

Response 10: The study description was clarified.

Comment 11: "It seems that there should be mention that Chu *et al*. (1988) reported thyroid adenomas after toxaphene exposure.

Response 11: Done, although there was only one such tumor per group, which is below the level of statistical significance.

Comment 12: *Referring to the PHG draft, p. 15,* "If 0.60 to 1.47 mg/kg is the range for the 10 ppm dose, then this could be clarified in a more clearly worded statement."

Response 12: Done.

Comment 13: "The time-averaged concentration does not seem to be a valuable concept. Different stages during carcinogenesis exhibit different susceptibilities. So, to give a chemical substance for 6 months at 100 mg/kg/day and then to give 0 for 6 months, could have a different outcome than giving 0 for 6 months followed by 100 mg/kg/day for the next 6 months, even though the time averaged concentration was the same. I believe that the exposures just have to be described but that the time-averaged concentrations do not have meaning."

Response 13: A number of studies, particularly the chronic ones, had their doses adjusted lower due to frank toxicity. We agree that this introduces extra uncertainty into the dose required to produce various toxic effects. However, it does not seem inappropriate to use the time-averaged daily dose as an approximation of the dose that might be associated with the observed adverse effects, for public health protective risk assessment. We agree that this is a simplification.

Comments 14: "It would be beneficial to describe the rationalization for having diets with and without corn oil."

Response 14: The effect of toxaphene administered in oil was noted.

Comment 15: *Referring to page 23, line 20, the statement that U.S. EPA proposed a MCLG of zero and MCL of* $3x10^{-2}$ *mg/L or 30 ng/L (30 ppt) is mentioned, with the comment,* "$3x10^{-2}$ mg/L is not equal to 30 ng/L. Perhaps $3x10^{-2}$ μg/L."

Response 15: This was a direct quote. However, we will modify the way this is presented to avoid appearing to support an erroneous statement.

Comment 16: *Consider using another study for risk assessment: "*A more recent NOAEL of 0.1 mg/kg/day and LOAEL of 0.4 mg/kg/day was determined based on effects on humoral immunity in female cynomolgus (*Macaca fascicularis*) monkeys (Tryphonas *et al.*, 2001)."

Response 16: This study was released after the first draft of the report, and we appreciate the commenter pointing out the article. The results of Tryphonas *et al*. (2001) appear to be supportive of Chu *et al.* (1988), and are now described in the document. We prefer to retain the study of Chu *et al*. (1988) for the risk assessment calculations because the NOAEL from Chu *et al*. (1988) is lower than the LOAEL of Tryphonas *et al*. (2001) (0.35 vs. 0.4 mg/kg-day).

Comments 17: "My previous comments have already addressed the lack of scientific basis for various aspects of the overall risk assessment procedure. More specifically, the uncertainty factors which are 10 for the three extrapolations used in this risk assessment are not well justified from a scientific perspective, but are the standard values used in risk assessments of this sort performed by multiple federal and state agencies. Likewise, the relative source contribution utilized in this study does not seem to be well justified, as mentioned previously. Since the actual values used for these parameters are relatively moot in the final analysis because the carcinogenic concentration value is orders of magnitude lower than the noncarcinogenic concentration value, it is assumed that the overall analysis yields a value that is relatively protective for the public health due to both types of outcomes.

Response 17: We agree. As stated earlier, the relative source contribution factor was increased based on additional data on concentrations of toxaphene congeners in fish.

Comments 18: "The alteration of the slope factors predicated on information from the 1996 EPA publication does not appear well delineated in this document. From my reading, the carcinogenic slope factor utilized in this assessment was 1.2 $(mg/kg\text{-}day)^{-1}$, which is the same slope factor that was used by OEHHA in 1991 and is based on information derived from the Litton (1978) study. This interpretation is based on information found on Page 22 of the draft study. If there have been major changes in the assumptions used to derive the slope factors, as indicated by the question posed by OEHHA on Page iii, then these new assumptions and the impact on the carcinogenic slope factors should be clearly stated in the document."

Response 18: The assumptions used to calculate the potency factor for toxaphene predate the 1996 U.S. EPA guidelines; nevertheless, use of the new guidelines would not have resulted in a significant change in the risk assessment. The same is true for the most recent versions of the U.S. EPA draft cancer guidelines in 1999 and 2002.

Comment 19: "From my perspective, the initial position of the regulatory community should be a level of 1 x 10^{-6}, with potential alterations of this level possible by consideration of other factors…. In essence, it is my assessment that the regulatory level for toxaphene as well as other carcinogens should be relatively conservative (e.g. either using a PHG of zero or a value that causes a risk of one cancer per million of exposed population) as opposed to less stringent cancer risk values such as one cancer per ten- or one hundred- thousand exposed population.

Response 19: While we might agree with the intent, it should be pointed out that PHGs are non-regulatory in nature. PHGs are guidance values to be considered in developing regulations for chemicals in water. No change.

Comments from University of California, Davis

Comment 1: "Toxaphene is produced by chlorination of camphene. However, toxaphene mostly consists of chlorinated bornenes and bornadienes, not camphenes."

Response 1: Toxaphene is commonly described as chlorinated camphenes in numerous references. Although describing toxaphene as a collection of bornenes and bornadienes may be more precise, these classes are not as recognizable to less technically-oriented audiences as that of camphenes. Slight modification in the wording was made to indicate that toxaphene is not precisely chlorinated camphenes.

Comment 2: "I do not know what the selection criterion the authors used to pick these structures. If the most toxic congeners are to be listed, toxicant A should be included (Matsumura F., Howard R.W., and Nelson J.O., 1975. Structure of the toxic fraction A of toxaphene. Chemosphere 5:271-276). If the indicator compounds for stable residues are to be listed, they should include compounds 1,2 and 3 of DeGeus *et al*. (1999) as done by H. Karl *et al*. (Karl H, 1999. Chemosphere 39: 2497-2506)."

Response 2: With so many to choose from, many different congeners could have been illustrated. The illustration was selected for its clear presentation of some characteristic toxaphene structures, not because the focus was on any particular attribute or characteristic.

Comment 3: "Despite the mention of "use" in the subheading, I do not find any mention of toxaphene's "use" in California. Data on the use of toxaphene on cotton is available, and, if this public-health document is intended for situations in California, the use patterns must be indicated since the contaminated soil serves as the source for subsequent environmental distribution."

Response 3: Data on the pattern of toxaphene use in California during its peak use period of the 1960s and 1970s are not readily available. The lack of detections of toxaphene in drinking water in recent years indicates that residual levels of toxaphene in soil from earlier agricultural uses are not having a significant effect on drinking water supplies.

Comment 4: "The write up does not convey the general picture that toxaphene indeed persists for decades in soil. Certainly Dr. Seiber's experiment under that experimental condition must have shown the loss of toxaphene through soil-surface volatization. However, toxaphene in deeper locations would stay much much longer. The fair way is to cite additional references to indicate the half life (t ½) in deep soil.

Response 4: The write-up does not convey specifically that toxaphene persists for decades in soil, because confirmatory data are not available. The presumption of a long-term persistence in soil is mentioned.

Comment 5: "There is no mention of fish accumulating toxaphene. In the case of the Great Lakes situation, toxaphene from the Southwestern cotton growing areas transported through the atmosphere is enough to cause accumulation of several ppm of toxaphene.

Gooch J.W. and Matsumura F. (1985). Evaluation of the toxic components of toxaphene in Lake Michigan lake trout. J. Agric. Food Chem. 35(3): 844-848.

Gooch J.W. and Matsumura F. (1987). Toxicity of chlorinated bornane (toxaphene) residues isolated from Great Lakes lake trout (Salvelinus namayeush). Arch. Environ. Contam. Toxicol. 16(3): 349-355.

The above studies show that toxaphene residues found in those fish are at least as toxic as the original toxaphene."

Response 5: Toxaphene accumulation in fish was mentioned as a source of concern for human exposure. Newer data indicate, however, that levels in fish have decreased greatly. This has been acknowledged in the document.

Comment 6: "This section does not cover the major difference in metabolism capabilities between some terrestrial mammalian species and others. In humans, laboratory test mammals, and terrestrial food animals, toxaphene is degraded fast, resulting in very low toxaphene residues while high toxaphene residues are found in fish, aquatic mammals (seals, whales, frogs, etc). The first paragraph of the metabolism section should be re-written."

Response 6: It is not the intent of this section to provide a survey of relative toxaphene pharmacokinetics in wildlife. For PHG development, study results in the most relevant species, laboratory animals and man whenever possible, are cited. Results in other species are described only with respect to exposure sources or other data supporting the human risk assessment.

Comment 7: "While this document is not meant for specialists, it would be more credible if the authors could mention that is main mode of action is to affect the $GABA_A$ receptor so that its chloride channel cannot be closed. Cite a review to make sure the fundamental aspect is covered.

e.g., Casida J.E. (1995). Insecticide action at the GABA-gated chloride channel, recognition, progress, and prospects. Arch. Insect. Biochem. Physiol. 22:13-23."

Response 7: Done.

Comment 8: "If CalEPA is going to enforce 0.03 ppb of toxaphene in drinking water, there must be a clearly written statement on the analytical feasibility and approaches. There are questions about the definition and verification of toxaphene, whether or not to exclude particulates in drinking water, the specific detection method (ECD-GLC or GC-MS) and their sensitivities, the methods of extraction and purification, and the quantification method. They are not trivial tasks and not must make sure that such a standard is enforceable."

Response 8: PHGs are not enforceable standards; the comments would apply to Maximum Contaminant Levels (MCLs), developed by the California Department of Health Services after consideration of just such issues. As specified in California Health and Safety Code 116365 (described in more detail in the Preface to each PHG document), PHGs are based only on public health considerations.

REFERENCES

Wen YH, Chan HM (2000). A pharmacokinetic model for predicting absorption, elimination, and tissue burden of toxaphene in rats. Toxicol Appl Pharmacol 168(3):235-243.

Tryphonas H, Arnold DL, Bryce F, Huang J, Hodgen M, Ladouceur DT, Fernie S, Lepage-Parenteau M, Hayward S (2001). Effects of toxaphene on the immune system of cynomolgus (*Macaca fascicularis*) monkeys. Food Chem Toxicol 39:947-958.