Responses to Major Comments on Technical Support Document

Public Health Goal

For

Vinyl Chloride

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 vinyl chloride 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.org. OEHHA may also be contacted at:

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RESPONSES TO MAJOR COMMENTS RECEIVED

Comment from the U.S. EPA Office of Water

Comment 1: *Comment that the U.S. Environmental Protection Agency is currently evaluating new methods for inhalation and dermal exposures due to showering or bathing. The U.S. EPA will consider these routes in the future, but currently uses only drinking water to derive maximum contaminant (MCLs).*

Response 1: Multi pathway exposure calculations were performed in accordance with the Office of Environmental Health Hazard Assessment (OEHHA) methods. We consider exposure to contaminants derived from other media in development of PHGs.

Comment 2: *The U.S. EPA does not use 1×10^{-6} as the de minimis exposure level, instead they calculate a range of risk from 1×10^{-4} to 1×10^{-6} and factor in feasibility to derive the MCL.*

Response 2: PHGs are to be based exclusively on health considerations, according to the California Safe Drinking Water Act. For carcinogens, we use a *de minimis* risk level of 1×10^{-6} but provide estimates of levels which correspond to other risk levels for use by risk managers, including derivation of the California MCLs.

Comment 3: *Comment that U.S. EPA's MCLGs (which are goals) are zero for vinyl chloride (a known human carcinogen).*

Response 3: PHG value was derived in accordance with OEHHA methods. PHGs may be set at zero if necessary; however, our estimate is intended to provide the level of contaminant that would pose no significant health risk to individuals consuming water on a daily basis over a lifetime. For carcinogens, we use a *de minimis* risk level of 1×10^{-6}.

Comment 4: *The PHG was calculated using recent computer models. U.S. EPA is currently undertaking a major effort to revise the existing Integrated Risk Information System (IRIS) risk assessment for vinyl chloride.*

Response 4: The draft U.S. EPA vinyl chloride risk assessment has been considered, but the calculations could not be verified from the draft version available at the time this PHG was developed.

Comment 5: *Comment that for the noncancer health-protective concentration calculation OEHHA used a relative source contribution of 28 percent. For comparison, U.S. EPA does not use relative source contribution (RSC) factors for carcinogens.*

Response 5: The RSC factor was used only in calculating the health protective concentration based on the non-cancer endpoint. However, we have changed the non-cancer RSC to 20 percent in our final PHG version.

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

Comment 1: "The U.S. EPA's draft vinyl chloride assessment has evaluated and incorporated a current physiologically-based pharmacokinetic (PBPK) model to obtain human equivalent doses from the animal studies of Til et al., Feron et al., and Maltoni et al. Using this model removes uncertainties related to the pharmacokinetic part of the customary uncertainty factor of 10 in extrapolating from animals to humans. Therefore, the interspecies uncertainty factor is reduced to 3 to account for only the pharmacodynamic part of the extrapolation factor. Cal EPA is encouraged to use such a model, since it not only reduces the uncertainty factor for non-cancer effects but also could be used to base the cancer risk estimates on internal dose to the target site (liver)."

Response 1: OEHHA identified some concerns about the Clewell (1985) PBPK model and its use in risk assessments. These concerns include the methods used to parameterize the model for humans, the treatment of oral uptake, the lack of statistical assessment of fit, and in general, limited documentation. Vinyl chloride has produced cancer in animals in multiple sites, including liver, lung, brain, mammary gland, and Zymbal gland, whereas the PBPK model is based on tumors in only one tissue. It thus seemed to us that there was more uncertainty in the extrapolation than represented in the PBPK model. We will examine the final version of the U.S. EPA toxicological review for appropriateness of the PBPK model to use in a subsequent update of the vinyl chloride PHG.

Comment 2: "Considerable published information exists on the age-related susceptibility, in particular early life in animals, of the carcinogenic effects of vinyl chloride. The U.S. EPA's draft assessment has addressed this information by adjusting the risk estimates obtained from modeled dose values and tumors in adult animals by a factor of 2. Cal EPA is encouraged to carefully review and at least acknowledge this information on age-related susceptibility in their assessment."

Response 2: Cancer incidence relating to age of exposure is included in the discussion several times in the PHG document, especially within the descriptions of the rat, hamster, and mouse inhalation studies by Drew *et al.* (1983). The PHG value was derived from the Drew *et al.* (1983) mouse inhalation data. We chose the most sensitive study to account for increased susceptibility in females and in the young. U.S. EPA chose a less sensitive study and added a factor of 2 to protect children. Our review of currently available information does not justify using a factor of 2 to adjust for risk estimates from exposure occurring early in life compared with estimates from lifetime exposure. However, we will continue to consider this approach in our assessments. In addition, we added a paragraph on age related differences in DNA adduct formation and carcinogenesis of vinyl chloride in rats as cited in Swenberg et al. (1992b).

Comment 3: "Page 5: While it is true that vinyl chloride is well absorbed, it should be mentioned that metabolic saturation occurs at high concentrations and under these conditions uptake decreases to replace the amount metabolized."

Response 3: We feel that the Gehring (1978) model takes saturation kinetics into account; however, the commenter is correct that a textual description of metabolic saturation at higher doses should be emphasized in the metabolism section. See also Response # 4.

Comment 4: "Page 8, first paragraph: Several studies demonstrate metabolic saturation beginning at about 250 ppm. Therefore, failure of metabolism to increase in proportion to concentration is unlikely to be detectable at concentrations as low as 9 ppm."

Response 4: The metabolism section was revised to include the following: "Studies by Hefner *et al.* (1975) and Bolt *et al.* (1977) suggested that the enzyme systems responsible for vinyl chloride metabolism in rats become saturated at atmospheric concentrations greater than 250 ppm, and higher concentrations produce relatively little additional reactive metabolite."

Comment 5: "Page 8: The genetic toxicity section should include recent important studies by James A. Swenberg and associates. "The formation and repair of DNA adducts in vinyl chloride and vinyl flouride cocarcinogenesis," (IARC, 1999)."

Response 5: We added summaries of two studies, Swenberg *et al.* (1992) and Swenberg *et al.* (1999) to the genotoxicity section. The studies describe the formation and persistence of certain etheno DNA adducts with known potential for genotoxicity. The authors observed dose related increases in epsilon G in non-parenchymal cells, the target cells for carcinogenesis as noted in the revised PHG.

Comment 6: "Page 9: A two-generation reproduction and developmental toxicity study in CD rats has recently been completed. It was conducted under contract by Huntingdon Life Sciences, Inc. for the Chemical Manufacturers Association. This study provided strong support for the conclusion that the liver and not the reproductive system is the critical target site for vinyl chloride."

Response 6: This was a valuable comment. A summary of the CMA (1998) study, in which the authors observed no developmental toxicity in rats, was added to the Developmental and Reproductive Toxicity section of the report.

Comment 7: "Page 13: The U.S. EPA has acquired the individual animal data for the Feron et al. study. All the rats with lung tumors, with one exception, also have liver tumors. This is probably due to metastases. In any case, including rats with lung tumors will not alter quantitative risk estimates if individual animal data is available. If not, their inclusion will result in an erroneous increase in risk estimates. In Table 5, it would be informative to note that mammary fibroadenomas actually decreased with increasing dose."

Response 7: We acknowledge these potentially important points on dose-response assessment of the Feron *et al.* (1981) study. We no longer use this study as part of the multipathway calculation for the PHG value.

Comment 8: "Page 23 near the bottom: The U.S. EPA in their latest draft found only suggestive evidence for the brain, lung and digestive tract tumors in humans."

Response 8: The conclusions at the end of the epidemiology section were revised to reflect that the potential association between vinyl chloride exposure and increased risk for other cancers is not as clear as that for liver cancer. The evidence associating exposure to vinyl chloride with

increased mortality ratios for brain cancer, lung cancer, and lymphoma is more suggestive than conclusive.

Comment 9: "Page 24: The review of the epidemiology studies is out of date. Newer studies that should be included are: Jones et al., Scand J. Work Env. Health 14:153-160 (1988); Pirastu, et al. Am. J. Ind. Med. 17:155-161 (1990); Pirastu, et al. Epidemiol Prev. 22: 226-236, (1988); Simonato, et al. Scand J. Work Environ. Health 17:159-169, (1991); Wong, et al. Am. J. Ind. Med. 20: 317-334 (1991); Wu, et al. J. Occup. Med. 31: 518-523 (1989); CMA, et al. 1998, unpublished but done under contract."

Response 9: The review of epidemiology studies was expanded to include summaries of several of the above-mentioned studies. The section was significantly strengthened as a result.

Comment 10: "Page 27: It was not stated which tumors were actually used in quantitating the oral data. It is true that use of male rat data results in higher risk if only angiosarcomas are considered. If rats with angiosarcoma or hepatocellular carcinoma, or rats with angiosarcoma or hepatocellular carcinoma or neopolastic nodules combined, are used, then females provide a greater risk. Because both hepatocellular carcinoma as well as liver angiosarcoma occur in humans, and because neoplastic nodules can progress to liver cancer, the U.S. EPA believes the conservative approach of including rats exhibiting any of these endpoints should be included for quantitating cancer risk. In any case, the tumor types and actual tumor counts used should be listed."

Response 10: We acknowledge the potentially important issues raised about the Feron *et al.* (1981) study; however, it is no longer used in our multipathway calculation.

Comments from the Chemical Manufacturers' Association

Comment 1: *The CMA suggests that the OEHHA PHG for vinyl chloride should conform more closely with U.S. EPA's draft Toxicological Review for Vinyl Chloride. Pertinent quotes from the CMA comments follow:* "OEHHA proposes a PHG of 0.043 µg/L…for vinyl chloride in drinking water… [T]he methodology used to derive the cancer slope factor on which this extremely low proposed PHG is based is flawed and inappropriate. A scientifically supportable slope factor has recently been derived by the U.S. Environmental Protection Agency after external peer review by leading scientific experts on risk assessment. No reason is given in the [PHG] document for discarding the product of this three-year effort in favor of a slope factor based on a study of rats exposed to polyvinyl chloride (PVC) powder in their diet." *And,* "More generally, [U.S.] EPA's Toxicological Review, now almost complete following a three-year process including public comment and two rounds of scientific peer review, provides a scientifically supportable risk assessment for vinyl chloride. OEHHA should reject the results of this process only if it can articulate strong reasons to do so and only after comparable independent scientific review."

Response 1: As mentioned in responses to U.S. EPA comments 1 and 2, OEHHA has reviewed the currently available version of U.S. EPA's Toxicological Review for Vinyl Chloride (which is labeled "Draft-do not cite or quote") and in general, found it difficult to assess the quantitative analysis due to incomplete documentation. As one example, animal potencies were not given. Because of this and other problems, OEHHA was unable to replicate the analysis that produced the oral potency value. OEHHA has identified several concerns about the Clewell *et al.* (1985)

PBPK model and its use in the risk assessments. These concerns include the methods used to parameterize the model for humans, the treatment of oral uptake, and the lack of statistical assessment of fit, as well as the very limited documentation. We look forward, however, to an updated final version of this toxicological review. We will update our PHG value for vinyl

chloride on a periodic basis, and we would very much like to examine and include new and verified PBPK modeling and methods such as might be found in a complete and final version of the U.S. EPA toxicological review for vinyl chloride.

Comment 2: *A comment related to above, but centered on inhalation potency said, in part:* "The draft PHG places OEHHA in the position of disagreeing with [U.S.] EPA and its external review committee. The net result of OEHHA's incomplete evaluation of the data base on vinyl chloride is that it has developed an inhalation potency factor that is approximately nine-fold higher than that in the draft Toxicological Review. [U.S.] EPA's potency factor is expected to be further lowered following the most recent peer review by the elimination of the two-fold safety factor included in the draft to account for other potential tumor sites…OEHHA should be prepared to explain why its model greatly overpredicts the actual incidence of angiosarcomas observed in exposed worker populations."

Response 2: The modeling used by OEHHA was reviewed and accepted by our Scientific Review Panel. While we are certainly open to new modeling approaches, new methods need to be published in a completed, well-documented form to allow us to utilize them to change our approach. For example, the above comment states that "[U.S.] EPA's potency factor is expected to be further lowered following the most recent peer review…" suggesting that the U.S. EPA's approach is undergoing additional modifications. Prudent policy dictates waiting for new methods and values to be finalized before adopting them. It should be noted that upper 95% cancer potency estimates are used in risk assessments, which may exceed actual rates; however, if the human cancer data had been considered adequate, the PHG risk assessment would have been based on it.

Comment 3: *The Feron et al. rat study on exposure to vinyl chloride from dietary exposure to PVC powder should not be used to evaluate risks from exposure to vinyl chloride in drinking water.*

Response 3. We have eliminated use of the Feron study for risk calculation.

Comment 4: *The CMA indicated that on page 14 the draft PHG incorrectly stated that…* "the inhalation potency factor derived by OEHHA from Bi et al. (1985) may be underestimated because of the small number of animals per group in the study." *Further, the CMA stated that* "Small numbers of animals may make it more difficult to detect a significant effect, but once an effect has been detected small numbers of animals do not bias the estimates upward or downward."

Response 4: The comment is reasonable and the phrase has been eliminated.

Comment 5: *The CMA suggests that the discussion on developmental and reproductive toxicity should be expanded to include a multigeneration study in rats sponsored by the CMA Health Committee and performed in conjunction with the ATSDR. (Copy kindly supplied with comments.)*

Response 5: The CMA (1998) study was added to the Developmental and Reproductive Toxicity section of the PHG.

Comment 6: *The CMA suggested, as did the U.S. EPA, that statements in the PHG draft suggesting an increased risk of brain and lung cancer as the result of human exposure to vinyl chloride are not supported by the epidemiological data. CMA suggested (and kindly supplied) several recent epidemiological study reports.*

Response 6: The epidemiological section has been updated and several new studies were added. The section now concludes with the following: "The evidence associating exposure to vinyl chloride with increased mortality ratios for brain cancer, lung cancer, and lymphoma is more suggestive than conclusive."

Comment 7: *The CMA noted that the statement in the PHG draft under Environmental Occurrence and Human Exposure that vinyl chloride can leach directly into drinking water from PVC pipes, with a historic level of 0.3 percent of the U.S. population exposed to levels exceeding 5 mg/L, is outdated and the current possibility of significant vinyl chloride exposure from PVC pipes under realistic use conditions is nil.*

Response 7: We removed the statement regarding "…estimated potential vinyl chloride exposure…" and added the following sentence. "Current certification standards regulating the residual level of vinyl chloride monomer in polyvinyl chloride pipe are sufficiently stringent that significant vinyl chloride exposure from leaching into drinking water is not likely (CMA, 2000)."

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