Responses to Major Comments on Technical Support Document

Public Health Goal
For
1,1-Dichloroethane
In Drinking Water

Prepared by

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INTRODUCTION

The following are the combined responses to major comments received by the Office of Environmental Health Hazard Assessment (OEHHA) on the proposed public health goal (PHG) technical support document for 1,1-dichloroethane, based on the review draft. Changes have already been made in response to these comments, and have been incorporated into the final version posted on the OEHHA website. 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, Davis

Comment 1: "Overall, I found the 1,1-dichloromethane PHG draft document to be only moderately complete, but the lack of thoroughness in the review of toxicity data appears not to have compromised the calculations of the PHG. I've provided three references below, but a review of the literature from 1993 to the present revealed several additional references that are available at the UCD libraries."

Response 1: The references provided have been incorporated into the PHG document. Citations in PHG documents are not intended to be comprehensive, but tend to be limited to those that would affect the data interpretation and the PHG calculation.

Comment 2: "Also, the designation of 1,1-DCA as a carcinogen is somewhat tenuous given the results of the NCI (1978) study (cited in the text) and a second study by Klaunig *et al.* (1986) (not cited in the text, but readily available). Neither of these studies found sufficient evidence for declaring 1,1-DCA a carcinogen. The conclusion that 1,1-DCA is a carcinogen apparently is based on a re-evaluation of the NCI data by Gold and Zieger (1997). However, the inclusion of 1,1-DCA on the Proposition 65 list of potential carcinogens probably makes this concern mute."

Response 2: We agree that the evidence for carcinogenicity of 1,1-DCA is not as strong as for several other small halogenated hydrocarbons. For this one, the weight of evidence including structure-activity considerations has resulted in OEHHA's presumption of carcinogenicity for protection of public health.

Comment 3: "A second carcinogenicity study by Klaunig *et al*. (1986) was not cited in the PHG document. The Klaunig *et al*. study found no effect of 1,1-DCA on the incidence of liver or lung tumors in diethylnitrosamine-initiated or in B6C3F1 mice receiving 1,1-DCA alone at 835 ppm 1,1-DCA in drinking water."

Response 3: The study by Klaunig *et al*. (1986) was not a standard chronic bioassay, utilizing less-than-lifetime exposures and an inadequate number of treated animals. Negative results with this limited exposure protocol did not appear meaningful. However, the results of this study are now discussed in the PHG document.

Comment 4: "The data and methods used to generate the PHG are standard and are appropriate."

Response 4: No response needed.

Comment 5: "There is a reference in the text (p 16-17) to the use of the methodology of McKone (1987) to determine that the ingested dose and inhalation dose are approximately equal, and therefore justifies the use of the 4 L_{eq}/d for daily exposure by all routes. Viewing those calculations would be helpful, especially given the range of values for the terms such as Henry's constant that can be used in the calculations. Perhaps placing the calculations in an appendix would be more appropriate than placing them in the text, but since these types of calculations do appear in other PHG documents."

Response 5: The specific method used for the calculation, the CalTOX program, has now been cited.

Comment 6: "There is essentially no discussion of uncertainty in the PHG document. I suggest that a short section on the use of uncertainty factors be included in the document."

Response 6: The PHG is based on cancer potency, and cancer potencies do not have explicit uncertainty factors. However, a discussion of the uncertainty in cancer risk extrapolation is nevertheless appropriate, and has been added to the risk characterization section.

Comments from University of California, Davis

Comment 1: "The information included in the present report is largely accurate however limited. The one clear error is on page 10 in which this report states: "1,1-DCA has not been tested in many standard assays (e.g. sister chromatid exchange (SCE) chromosomal aberrations, mutations in mouse lymphoma cells)…." In fact, NCI looked for and found evidence of increased frequency of SCE using the Chinese Hamster Assay. Perhaps this is a typographical error or this reviewer is misinterpreting the text."

Response 1: The text has been changed to eliminate SCE from the list.

Comment 2: "There are several additional reports that are not cited that address the acute toxicity of 1,1-dichloroethane in laboratory animal models. For example rats survived an exposure of 4,000 ppm for 8 hours but were killed by an exposure of 16,000 ppm (Smyth, Am. Ind. Hyg. Assoc. 17:129, 1958) and a later report established a LC_{50} of 13,000 ppm also for rats (Klinkhead and Leahy, Evaluation of Selected Groundwater Contaminants: 17, 1987). In addition to the rat data included in the present document similar data was observed with guinea pigs with doses up to 750mg/Kg BW 1,1-dichloroethane failing to have observable adverse effects (Divincenzo and Krasavago, Ind. Hyg. Assoc. 35:21, 1974). Unpublished data from the Dow Chemical Company extended the observations to rabbits and dogs and apparently reached a similar conclusion in terms of its relative low capacity to produce adverse effects even at high doses. Cats were included in studies by Hoffman and colleagues (Hoffman, Birnstiel and Jobst, Arch. Toxicol.27:248, 1971).

These additional animal studies seem important since no information is available for potential adverse effects in primates. It is not clear if the current report is meant to be comprehensive or representative."

Response 2: The Smyth (1958) and Divincenzo and Krasavago (1974) studies have now been cited in the section on acute toxicity. We were not able to identify or obtain the Klinkhead and Leahy (1987) paper from the information provided, but it seemed largely to corroborate the Smyth observation. The study published in German by Hofmann *et al.* is summarized and is now the basis of the non-cancer health-protective concentration. In general, PHG documents cite only the most relevant papers to support the estimation of health-protective values in drinking water.

Comment 3: "The limitation of the existing data is that most studies reported evaluated selected and relatively gross adverse effects (lethality, weight loss, hepatotoxicity, cancer, etc) and, mainly mouse and rat models were used to generate experimental data. Despite this limited approach, clear species and gender differences were observed with rats more sensitive than mice and males more sensitive than females in terms of survival. In terms of cancer induction male mice were possibly more sensitive in terms of the induction of hepatic and lung tumors while the female rats were more sensitive for the development of vascular and reproductive tract tumors. Albeit at relatively high doses, these results may reflect the potential for species-specific toxicities of 1,1-DCA and reaffirm a gender-specific difference in its carcinogenic action. The occurrence of hyperplastic disease in estrogen-sensitive tissues, e.g. mammary gland and endometrium) may suggest interaction with sex steroid signal transduction which has now been demonstrated for other halogenated hydrocarbons. ... Extrapolation of mouse and rat data to humans is not appropriate for species specific traits such as reproduction, gametogenesis and embryonic development. This report does properly use the dose for mammary tumor induction rather than that for the male rat lethality in estimating a dose that could be toxic when interacting with female sex steroid hormones."

Response 3: We agree. No changes needed.

Comment 4: "A risk assessment for humans is extremely difficult with the current limited data in rodents, a complete absence of data for primates and no data for adverse effects on reproduction. While all of the existing data indicate a low risk at even at relatively high exposures for cancer, hepatic and pulmonary effects, adverse effects on reproduction and development that could occur at lower exposure levels were not assessed. This may be an important consideration as emerging evidence indicates that other small halogenated (e.g., bromodichloromethane) molecules have the potential to cause fetal loss in rats and possibly abortions in humans."

Response 4: We tend to agree with the comments but are not aware of any studies on adverse effect on reproduction that could be used as a basis to address these concerns. It could be argued that an additional uncertainty factor (UF) for database deficiencies should be used in the calculation of a health protective value for non-cancer effects. In this case, a factor of three might be incorporated, based on current OEHHA and U.S.

EPA policy to limit combined UF to no more than 3,000, in most cases. However, even with such a factor the PHG would still be based on the lower value from the cancer endpoint.

Comment 5: "Experiments utilizing non-human primate may provide information that is more relevant to human health issues and provide critical data for making a risk assessment."

Response 5: We are not aware of any studies in primates.

Comment 6: "There are several uncertainty issues but two are critical. The first is that there is very limited controlled, experimental data presented from which the risk assessment can be made. Only the most general type of exposure assessments has been reviewed in this document. Since this reviewer identified several reports which were not included in the present document, it is possible that additional data exist that could be useful, if not important. Second, based on what is known about other small halogenated hydrocarbons, it is most likely that if adverse effects were to be found they could be specific, gender and life-stage specific. Thus, extrapolating the current data which was produced largely in adult rats leaves open the possibility that some specific kinds of toxicity are overlooked."

Response 6: We agree with the uncertainty due to data limitations, but are not aware of noncancer studies showing effects at low enough doses to supersede or replace the estimate of health-protective levels based on cancer. The PHG value of 3 ppb should be adequate for protection of sensitive populations.