Responses to Major Comments on Technical Support Document

Public Health Goal

For

Dichloromethane (Methylene Chloride, DCM)

In Drinking Water

Prepared by

Pesticide and Environmental Toxicology Section

Office of Environmental Health Hazard Assessment

California Environmental Protection Agency

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INTRODUCTION

The following are responses to selected comments received by the Office of Environmental Health Hazard Assessment (OEHHA) on the proposed public health goal (PHG) technical support document for dichloromethane (methylene chloride, DCM) as of March 15, 2000. For the sake of brevity, we have selected the more important or representative comments for responses. Comments appear in quotation marks where they directly quoted from the submission. Responses to all other minor comments mainly editorial in nature are incorporated in the revised document.

These comments and responses are provided in the spirit of the open dialogue among scientists that was 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

U.S. Environmental Protection Agency, National Center for Environmental Assessment

Comment 1: "The description of the methodology used for the cancer quantitative risk assessment was very confusing. Also, more sample calculations should be provided. For example, I was unable to replicate the results in the third row of Table 21 for the oral CSF using the regression from Table 20, so I'm not really sure how this was done."

Response 1: Additional examples and explanations have been added to Table 21 and the supporting text. In addition the inhalation calculations have been revised and are now based on sex averages for each endpoint.

Comment 2: "My interpretation is that a mouse PBPK model was used to get the GST metabolites, then slope factors were obtained and converted using ¾-power scaling to human equivalents of GST metabolites, but then these were not converted back to exposure levels so that the PHG reflects a level of GST metabolites in water. That is not a meaningful number."

Response 2: Rows one and two in Table 21 give values solely based on the internal dose without conversion to external exposure. Rows three through five in the original Table 21 give values based on different estimates of external exposures. This table has been extensively revised. The internal dose of glutathione sulfotransferase (GST) metabolites (mg/L_{tissue}-day × L_{tissue}/kg body weight) is a dose surrogate more closely related to the process of tumor generation in the target tissues than is the applied dose of dichloromethane (DCM). Our concern over the accuracy of extrapolation to external concentrations of DCM equivalents led us to base the proposed Public Health Goal (PHG) on the surrogate dose. In the light of these and other comments, we have changed the potency values used in the PHG calculations to the values based on external exposure given at the bottom of Table 21..

Comment 3: "It also appeared that a regression line based on mouse PBPK doses vs. applied doses was considered as a methodology for converting the human PBPK doses back to applied doses. This methodology was ultimately rejected, but not early enough... The mouse regression line reflects mouse uptake and metabolism and would not be appropriate to use for humans… The regression line should have been forced through zero…" since they have negative intercepts.

Response 3: In the revised Table 21, all the values are based on zero intercept regressions.

Comment 4: "The appropriate way to use the PBPK data would be to use mouse model to get the mouse GST metabolites and then use a human PBPK model to back calculate to human exposures. Apparently this was not done because the human PBPK model was deemed too uncertain. If this is the case, in my opinion, PBPK modeling should not be used at all, and a default exposure methodology should be used."

Response 4: Office of Environmental Health Hazard Assessment (OEHHA) staff members do not agree with this comment that, short of a human physiologically based pharmacokinetics (PBPK) model, no use can be made of animal PBPK model estimates of DCM internal doses. Our objective was to model the dose in the animal studies where DCM-induced cancer was

observed, not to project directly to an uncertain human PBPK model based on inadequate evidence of carcinogenicity in any specific target organ. We did apply the human PBPK model to estimate the generation of liver and lung GST metabolites resulting from current maximum allowable exposures via DCM in drinking water (see Risk Characterization). However, there is considerable uncertainty as to whether these are the target sites in humans (as they are in mice) and whether the human carcinogenic response is similar to that seen in mice. In view of these uncertainties, we chose to develop a number based on known sites in the mouse and to scale these to any potential site in humans. We understand that our approach on DCM and other chemicals with respect to the use of human PBPK models differs significantly from that of the U.S. Environmental Protection Agency (U.S. EPA). In the interest of completeness we have added slope values based on a default (applied dose) methodology for comparison.

Comment 5: "…the Draft reports what …other authors concluded without … CalEPA's position…conclusions."

Response 5: This is a matter of style in writing. The chapter and section the reviewer referred to, that is, "Toxicological Effects in Animals" and specifically "Summary of Evidence of (Animal) Carcinogenicity" is written as reviews of existing work. The California Environmental Protection Agency's (Cal/EPA) position and conclusions are presented in details later in "Dose-Response Assessment" and "Calculation of PHG."

Halogenated Solvents Industry Alliance, Inc.

Comment 1. "It is remarkable that the epidemiological evidence is essentially dismissed as having no value." "Although risk extrapolations to low doses may not be possible on studies that have no demonstrable effect, the absence of such effects certainly ought to modify the interpretations and calculations based on the much less relevant animal studies."

Response 1: The epidemiological data were evaluated in detail and summarized in about 14 pages in the PHG document. The evidence was used as support for DCM's carcinogenicity as the basis for calculation of the PHG. The data might imply upper bounds on the carcinogenic potency, but the studies were judged to be inadequate for such use. We also agree with the latest IARC (1999) review that "epidemiological evidence for carcinogenicity in humans was… judged inadequate." The animal data therefore appeared to be most relevant for a quantitative risk assessment.

Comment 2: "Regarding the Serota et al. drinking water study in mice, the evidence to support a positive interpretation of this study for liver tumors is weak. The supposed elevated incidences are hard to separate from concurrent controls (selection of the control group so that a statistically significant elevation can be reported is suspect), let alone historical control incidences. Rather than attempt calculations of carcinogenic potency on this study in isolation, it would be possible to combine the tumor incidences for the drinking water study and the inhalation study in an overall PBPK treatment – since the generation of GST product in the liver is common to both calculations. This should improve the quality of modeling and does not require deciding whether Serota is a positive or negative study."

Response 2: The tumor response in the Serota et al. mouse drinking water study is lower than that seen in the inhalation studies, most likely due to the much lower doses achieved by the oral route. Although the response is weak, there does appear to be a shallow dose-response and this exposure route is the most relevant to drinking water exposure of humans. In principle, it might be possible to combine tumor incidences and dosimetry by both inhalation and oral routes via the PBPK model. But this is not typically done and has not been done in this case. Because of the disparity of the inhalation and oral doses, number of doses, and general dissimilarity of study design. Simultaneous oral and inhalation exposures were used with the human PBPK model to estimate GST product generation from "typical" household DCM exposure (see Risk Characterization).

Comment 3: "The decision not to use human PBPK modeling for inter-species dose conversion in completely irrational. That the GST pathway is responsible for induction of tumors in mice is thoroughly well established (Green, 1997 and sequence of papers leading to this analysis). Whilst it is true that the response of humans to a given level of metabolite generated via GST pathway is unknown (the pharmacodynamic elements), it must be better to use PBPK calculations when the level of understanding is as good as it is for DCM. The extent of the human polymorphism is well understood from human in vivo and in vitro data and the PBPK treatments have been developed using information from subjects clearly heterozygous for GSTT1-1. A large number of human liver samples have now been examined. Even after the PBPK treatment has been applied, it is clear that man may be even further removed from the sensitivity of the mouse to DCM (Green, 1997). This could be a "pharmacodynamic" factor but may be linked to the site of generation of a short-lived reactive species – a refinement of the PBPK modeling is being developed to account for this localization phenomenon."

Response 3: As noted in the comment, there are still a number of uncertainties about the extrapolation of animal cancer data to humans in this risk assessment. The use of the human PBPK model for interspecies extrapolation presupposes a "level of confidence" that the liver is the primary target site in humans exposed to DCM and that humans respond to the carcinogenic effects of DCM as mice do. OEHHA does not presently have that level of confidence. We therefore chose to model the dose in the species where tumors were observed and to scale the animal dose-response to any potential tumor site in humans. As noted above, we used the human PBPK model as a check on the likely production of GST product under typical human exposure conditions. Whether the GST metabolites are acting in the human liver, lung, or elsewhere is unknown.

Comment 4: "The current PHG analysis has many minor flaws. These, however, pale into insignificance in contrast with the failure to use robust evidence from epidemiology studies and the refusal to apply well established PBPK treatments when converting the results of animal experiments to man."

Response 4: OEHHA disputes the adequacy of the epidemiological findings, as limited as they are. Also we note limitations of the human PBPK model for interspecies extrapolation although we did use it as a check on potential internal doses of GST metabolites under typical DCM exposure conditions for comparison with animal based extrapolations.

Comment 5: "Such overly conservative risk assessments draw attention to situations that are, in reality, of negligible risk whilst circumstances of true concern are overlooked."

Response 5: OEHHA has revised the PHG for DCM upward indicative of less theoretical cancer risk to the public potentially consuming DCM as a drinking water contaminant. The revised cancer potency estimate is similar to that used earlier by OEHHA and U.S. EPA. The PHG is based on a 10^{-6} lifetime risk level; the actual regulatory levels, maximum contaminant levels (MCLs), can be set at higher risk levels if appropriate to reflect competing concerns, including allocation of resources to address other, higher risks. MCLs are developed in California by the Department of Health Services.

University of California, Berkeley

Comment 1: "The mechanisms of generation of the mutagenic (genotoxic) metabolite of DCM could be discussed at greater length. In particular, the PBPK models cited are somewhat out-of-date (published by EPA in 1986, 1987), and the genetic polymorphism in the enzymology of glutathione transferases is only mentioned later (papers by El-Masri). A diagram showing the conversion of DCM to formaldehyde via a glutathione conjugate would have been helpful."

Response 1: PHG technical support documents are meant to focus on the information most relevant to assessing lifetime risks via potentially contaminated drinking water rather than representing comprehensive reviews of all the data.. In the case of PBPK, OEHHA decided to take DCM modeling developed for the Occupational Safety and Health Administration (OSHA), published in their 1997 final rule on DCM in the Federal Register, and adjust it slightly to allow both oral and inhalation inputs. At the time the draft was under development this was considered the most up-to-date and heavily reviewed DCM model in existence, although not exempt from expert criticism. A diagram showing the conversion of DCM to formaldehyde via a glutathione conjugate has been published by the ATSDR (1993, p. 31).

Comment 2: "I am really not very persuaded that DCM is a potent carcinogen that acts via genotoxic mechanisms. The solvent has been around too long and familiarity reduces awareness of long-term risks. On the other hand, the danger signals are clearly there in the experimental data. I think setting a PHG below routine detection limits will create problems of regulatory interpretation and enforcement."

Response 2: The proposed PHG has been revised upward indicative of lower chronic and cancer risk. DCM is not a potent carcinogen and it seems to be one of the less potent among a group of carcinogenic halogenated solvents and related compounds. The revised potency value is about the same as used previously by both OEHHA and U.S. EPA. The PHG is by law not a regulation and the Department of Health Services takes detection limits and other factors into account when revising a state maximum contaminant level (MCL) based on any new PHG. The MCL is the enforceable regulation. We appreciate your comments on this matter and forward them to the Department of Health Services for consideration when they evaluate the need to revise the current MCL.

University of California, Davis

Comment 1: "The information provided is both very complete and accurate. In fact, this is the largest document of this type I have seen and review of the literature was very thorough. The presentation of these studies is well done and the writing is very good. The data reviewed and

studies used in support of the development of the PHG were appropriate. The evaluation of the usefulness of the various studies, especially the epidemiological studies, was quite good. These studies are always difficult to evaluate, and it is often difficult to determine if evaluations for PHG documents are reasonable. ….The format used in this document allows one to determine if the conclusions about the studies are reasonable. ….the assumption seems very appropriate. At the least, the assumption leads to a conservative approach to the development of the PHG. This document presents the most thorough dose-response assessment I've seen for one of these analyses. The depth of the analysis is impressive. Incorporation of the results of the PBPK modeling, and use of the Bogen et al. methodology to generate the pathway absorbed dose rates is a major improvement over previous analyses. Parameter values used in the analysis are reasonable, and the results are quite reasonable given the assumptions."

Response 1: OEHHA staff members appreciate the comments.

Comment 2: "The methodology used is valid and provides a conservative PHG value for DCM. Consequently, the PHG can be used with confidence. However, I would like to see a probabilistic framework incorporated into these analyses."

Response 2: Per this comment together with other reviewers' comments mentioned above on the values used for calculating the PHG, OEHHA staff members have adjusted the proposed PHG number from 0.13 ppb to 4 ppb. This is a more realistic but still conservative value, utilizing a cancer potency value (q_1*) which is very similar to previous estimates. The probabilistic framework has been incorporated into these analyses through both the exposure analysis and the cancer potency analysis. Also probabilistic methods, while present in some PHG assessments when it is possible, have not been applied to all PHG documents. OEHHA's draft guidance in this area is only now nearing completion and has still not been approved by the Scientific Review Panel.

Comment 3: "I would like to see a section explicitly labeled Uncertainty Analysis with a quantitative evaluation (where possible) of the uncertainty."

Response 3: As in all supporting documents for PHG, the important uncertainties are covered mainly in the Risk Characterization section. Some discussions about uncertainties are also included in the Exposure Assessment and Dose-Response Assessment sections. Adding a new section on uncertainty analysis would be duplicate as well as cause a significant delay in the document with little except cosmetic gains. In addition, OEHHA would have to change the format for all the other PHG documents if we change the basic approach by adding a section on Uncertainty Analysis for the DCM document. This PHG document is already one of the largest we have done to date and the result is similar to previous assessments by U.S. EPA, OSHA and OEHHA. We do not believe much would be added in terms of public health protection by delaying the document for relatively marginal improvements.