Responses to Major Comments on Technical Support Document

Public Health Goal

For

1,2-Dibromo-3-chloropropane (DBCP)

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 1,2-dibromo-3-chloropropane. 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

The Dow Chemical Company

Comment 1. "Dow supports this newer methodology which has gone through extensive peer review and public comment. Unfortunately, OEHHA did not consistently use this methodology not withstanding your stated intent to do so."

Response 1. In a few cases OEHHA chose not to use the newer methodology on chemical contaminants that did not present significant new data to evaluate. This was a matter of resource management and it was more expeditious and economical to retain the older cancer potency value. Even if OEHHA had applied the newer methodology, based on our current view of the mode of action of DBCP, essentially a genotoxic carcinogen, we would have adopted a linear dose-response approach rather than a nonlinear or margin of exposure (MOE) based approach. The paragraph stating our intent to use this methodology was inadvertently left in the technical support document and has been deleted from the current version (page ii, item 2 of the preface).

Comment 2 "The PHG of 1.7 ppt is based upon the concept that there should be a total risk from all exposure pathways of 10^{-6}. Only the ingestion pathway is estimated, however, and it is arbitrarily assumed that since exposure could occur from inhalation and from dermal exposure, the allowable exposure from water will be 1/3 of the total; i.e. it is assumed that inhalation and dermal exposures are already imposing 2/3 of the allowable 10^{-6} total criteria. If this aspect were corrected the derived standard would be 5 ppt, not the draft standard of 1.7 ppt DBCP."

Response 2. No correction is needed. OEHHA has considered multi-route exposures from volatile organic chemicals (VOCs) in drinking water for over a decade. This approach is based on largely on the work of McKone et al. (1988) and the showering exposure default of U.S. EPA's Risk Assessment Forum (1991). More recently on the advice of the Risk Assessment Advisory Committee (RAAC, 1995) we have also employed an environmental fate and transport model (CalTOX) to estimate exposure via inhalation and dermal routes from VOCs in tap water (e.g., MTBE). OEHHA, unlike U.S. EPA, has endeavored to apply multi-pathway exposure concepts usually considering multiple sources (water, food, ambient air) via a relative source contribution (RSC), with defaults of 20, 40 and 80%, and multiple routes for VOCs (inhalation, ingestion, dermal) to the source, drinking water. In general OEHHA has followed U.S. EPA's practice of not applying the RSC in a calculation based on cancer potency and a negligible lifetime cancer risk criterion of 10^{-6}. This is clearly explained in the technical support document. However, due to changes in risk assessment methodologies, this practice may need more critical evaluation on a case-by-case basis.

Comment 3: Dow Chemical is concerned about "incorrect risk apportionment."

Response 3: The risk has not been apportioned. The PHG is based upon exposure to DBCP exclusively from the use of contaminated groundwater. No other sources of exposure have been taken into account. This comment appears to be based on an assumption that the exposures attributed to the inhalation and dermal routes were from sources in addition to contaminated drinking water. This is not the case.

Exposure to DBCP by these other routes is due to volatilization of the chemical and contact (e.g., showering and bathing) with contaminated water. This is clearly stated in the document and suitably referenced. No changes have been made.

Comment 4. "Regulatory risk criteria have historically varied from 10-6 to 10-4 depending upon the regulatory statute, the agency and the risk assessment scenario used in the assessment. ……OEHHA should select a risk criterion; 10^{-6}, 10^{-5}, 10^{-4} then regulate drinking water on that basis from the risk due to exposure of a hypothetical person in exposures to DBCP in drinking water. The methodology does not allow non-arbitrarily accounting for other unknown, unspecified exposures."

Response 4. The cancer risk criterion for the PHG is the de minimis lifetime excess theoretical cancer risk of 10^{-6}. This would apply to the sum of all exposure routes for a VOC like DBCP in contaminated drinking water. PHGs are not regulations. The management of DBCP risks is conducted by a separate agency, the California Department of Health Services, where the Maximum Contaminant Level (MCL) is set. The MCL is a regulation. The law does allow the PHG to be set at zero but OEHHA generally does not consider this practical option, unlike U.S. EPA which routinely sets MCL goals (MCLGs) for many carcinogens at zero. The fact that other environmental exposures (e.g., arsenic, radon, and benzene) may exceed the PHG criterion of an individual drinking water contaminant is not sufficient reason to add additional theoretical risks from that contaminant.

Shell Oil Company

These comments, found in a 10-page cover to the individual comments of Drs. Bruckner, Sielken, Whorton, and Wilson, were submitted by Shell Oil on the behalf of Shell Oil, Dow Chemical, and Occidental Chemical were prepared by Steven W. Jones of Sedgwick, Detert, Moran, and Arnold for Shell Oil Company. The major points of these comments are covered in the responses to the comments by the Dow Chemical Company (above) and/or the responses to the individual scientists, which are found below.

Dr. James V. Bruckner

Comment 1. " …the inappropriate use of the Rao inhalation study to set a water standard. Since the Foote study was a water ingestion study, it is more appropriate."

Response 1. Ingestion, inhalation and dermal exposures could occur from DBCP-contaminated water. Since inhalation exposure alone may exceed that by the ingestion route (McKone et al, 1988) it is entirely appropriate to use an inhalation study, particularly since it indicates more sensitive adverse effects via that route.

Comment 2: "Some of the interpretations/assumptions made about NOAELs and LOAELs are innacurate":

Response 2: The decrease seen in sperm count seen after 10 weeks in the rat study by Rao et al. (1983) was significant and supports the scientific hypothesis of a cumulative effect of DBCP. Therefore, the adjustment to the Foote et al. (1986 a,b) 10 week NOAEL is appropriate. It should be noted that the

NOAEL derived from the Foote et al (1986 a,b) study was not used in setting the PHG. According to Rao et al. (1982, 1983), the NOAELs for the rabbit and rat are indeed both 0.1 ppm. The NOEL calculated by Reed et al. (1987) was not used in the technical support document, the value they derived was provided solely for comparison.

Comment 3. "The mouse is not an appropriate animal model for assessing chemical carcinogenesis in humans." "The metabolites of DBCP are responsible for cytotoxicity and carcinogenesis. Mice have greater P450 activities than rats or humans, and therefore, are more susceptible to DBCP-induced toxicity/cancer than humans."

Response 3. The commenter has submitted a number of published articles on the subject of the metabolism of DBCP and related chemicals. The metabolism includes transformation by glutathione S-transferases, the generation of reactive metabolites, including epoxides, the alkylation of cellular macromolecules by reactive DBCP metabolites, and DNA adduct formation by a similar chemical, 1,2,3-trichloropropane. Covalent binding of DBCP to proteins in vitro as a result of activation by microsomal oxidase was also described. The commenter argues that these data indicate a greater susceptibility to toxicity/carcinogenesis of DBCP in mice than in humans or rats. In OEHHA's view these data do not clearly support that hypothesis since all of the DBCP studies submitted by the commenter were conducted in rats. Similar arguments have been made previously for other carcinogens (e.g., trichloroethylene, 1,3-butadiene). It is difficult predicting the potency and target sites of a carcinogen between experimental rodents much less between rodents and humans. It is true that rats are (marginally) closer to humans in size than are mice but that alone does not provide sufficient reason to discount mouse based cancer data for use in human cancer risk assessment. Therefore, the cancer potency was derived from the experimental data in mice.

Comment 4. "Dermal and inhalation exposure contribute substantially less than does ingestion to total DBCP exposure of persons using DBCP-contaminated water."

Response 4. OEHHA does not agree with this conclusion. As noted in an earlier response above, OEHHA's analysis to provide some allowance for possible multi-route exposures to VOCs via showering, bathing, flushing of toilets etc. For DBCP we have used 2 Leq/day each for inhalation, and dermal exposure and 2 L/day for ingestion, totaling 6 Leq/day. McKone (1987) estimated the ratio of inhalation to ingestion uptake for DBCP to range from 0.8 to 4.0 or 1.6 to 8.0 Leq/day for inhalation only. U.S. EPA's Risk Assessment Forum (1991) recommended a default of inhalation exposure from showering in VOC contaminated water equal to ingestion of that water. For ingestion of 2 liters/day, the default for showering only would be 2 Leq/day. This default was based on the average of a number of VOCs studied by U.S. EPA. The exposure to VOCs via inhalation and dermal routes has been studied by several researchers notably Bogen (1992), Jo et al. (1990 a,b), Weisel et al. (1992), McKone et al. (1993), Blancato et al. (1993) and Weisel and Jo (1996). The latter authors concluded that "approximately equivalent amounts of volatile contaminants from water can enter the body by three different routes, inhalation, dermal absorption, and ingestion, for typical daily activities of drinking and bathing." These studies were conducted in human volunteers exposed to water containing TCE or chloroform.

The commenter has provided two relatively obscure documents (Thomas letter, 1987; U.S. EPA, Superfund Supplemental Guidance, 1998) purporting to show that that inhalation and dermal exposures to VOCs in general, and DBCP in particular, amount to only 5-15%. These documents provide no data and appear to be based on only calculations from experimental animals. The commenter has not mentioned the above-cited studies of far greater relevance in humans exposed to VOCs in typical household exposure situations and has not provided significant and relevant new data on DBCP exposure. Therefore, OEHHA concluded that inhalation and dermal exposures to DBCP via drinking water are significant based on the available scientific information.

Comment 5. "There is evidence in support of a threshold for DBCP carcinogenesis, for both a cytotoxicity/regenerative hyperplasia mechanism and a genotoxic mechanism."

Response 5. The commenter has provided information purporting to show a threshold for cancer (stomach cancer in rats) and genotoxicity, a mechanism based on irritation and cytotoxicity, and a nonlinear (quadratic) dose response based on DNA damage in rat liver (Kitchin & Brown, 1994). OEHHA concluded that the data do not provide sufficient support for a biologically-based risk assessment model for DBCP. Other studies provided show that DBCP metabolites (possibly epoxides) could act via covalent adduct formation with DNA and other critical macromolecules. The dose-response data based on liver DNA damage (only three data points for DBCP) is not adequate to establish a nonlinear dose-response. OEHHA has determined that the current database supports a linear mechanism of action for DBCP. OEHHA has concluded that the claims of hormesis, or low level beneficial effects, based on the limited data are not scientifically defensible.

Dr. Robert L. Sielken, Jr.

Comment 1: Dr. Sielken suggests that a margin of exposure analysis as described in the 1996 U.S. EPA Guidelines for Carcinogen Risk Assessment should be applied to DBCP.

Response 1: Even if the 1996 draft proposed guidelines were applied to the DBCP bioassay data, a MOE approach would not be appropriate. This is because the bulk of the evidence suggests DBCP to be a genotoxic carcinogen, thus, linearity in response would be assumed and the cancer slope factor approach would be taken (deriving a cancer potency as the slope of the straight line through the point of departure and the origin). This approach is further supported by the lack of a plausible threshold mechanism (See also Comment/Response 5, above).

Other major comments by Dr. Sielken have been addressed as responses to other commenters.

Dr. Donald Whorton

Comment 1: Dr. Whorton made several editorial suggestions.

Response 1: Most of these suggestions were incorporated into the document, particularly those relating to human toxicity. Numerous changes were made to the document, which improve the clarity and accuracy of the discussion of the human toxicity of DBCP. The majority of these changes can be found in the text of the document on pages 24 through 27.

Comment 2: Dr. Whorton suggests that the conclusion of the epidemiology section which states that "the epidemiologic data are inadequate for establishing or refuting the carcinogenic potential of DBCP in humans" is misleading.

Response 2: The statement has been changed to reflect the fact that the epidemiological data have not shown DBCP to be carcinogenic in humans. An additional statement regarding the clear evidence of the animal carcinogenicity of DBCP has been added, however.

Comment 3: Dr Whorton provides additional references regarding epidemiological studies.

Response 3: These references have been incorporated into the document.

Comment 4: On the basis of a personal communication (Wyrobek), Dr. Whorton states that the effect reported by Kapp et al., 1979 and Kapp and Jacobsen, 1980 of non-disjunction of the Y-chromosome is currently considered to be chromatin clumping rather than non-disjunction (last entry in Table 4, Genotoxicity of DBCP).

Response 4: More information is needed to change the results as reported by the investigators. Since there is some doubt as to the reliability of their report, discussion of this observation when it is used as a possible explanation for other effects have been deleted from the document (page 24, 3rd paragraph; page 26, 5th paragraph).

Other major comments by Dr. Whorton have been adressed as responses to other commenters.

Dr. Richard Wilson

Comment 1: Most of Dr. Wilson's comments address issues such as the choice of 10^{-6} as the *de minimis* risk level and choices of certain defaults in the calculations.

Response 1: Selection of default values and de minimis risk are clearly explained in the technical support document and scientifically or statutorily justified. No changes in the document were made as a result of these comments.

Other major comments by Dr. Wilson have been addressed as responses to other commenters.

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