Responses to Major Comments on Technical Support Document

Public Health Goal
For
Hexachlorobenzene
in Drinking Water

Prepared by

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TABLE OF CONTENTS

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 hexachlorobenzene, based on the pre-release review draft. Changes have already been made in response to these comments, and have been incorporated into the draft 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, Riverside

Comment 1. "This Public Health Goal (PHG) document on hexachlorobenzene (HCB) is well written and contains exhaustive review and analysis of existing studies on HCB as related to its exposure, metabolism, toxicology, and dose-response. The review is up to date and studies are properly selected for drawing main conclusions. Key studies have been identified and used in analyzing dose-response for HCB in animals and humans.

The approach used in developing the draft PHG is technically sound, and the data sets used for deriving the PHG are from two scientifically-credible studies (Bleavins *et al.*, 1984; Arnold *et al.*, 1985). The selection of these studies is well justified. Risks of HCB are well characterized in the "Risk Characterization" section and the summary is comprehensive and yet to the point."

Response 1: Comments noted.

Comment 2. *However*, "The PHG of 0.03 ppb is much lower than the Maximum Contaminant Level (MCL) proposed by the U.S. EPA (0.001 mg/L or 1.0 ppb). The feasibility of detecting [HCB] in water samples at or below the draft PHG merits some discussion, if needed."

Response 2. Specific discussion regarding the feasibility of detecting HCB in water samples at or below the PHG level is not included in the document because PHGs are based exclusively on public health considerations. The PHG is defined and described in the preface of the document, which should provide the reader with some clarification as to what the PHG is and how it is used.

Comment 3. "Additional information on distribution of HCB between sediment (or soil) and water may be helpful when discussing "Environmental Occurrence and Human Exposure." The distribution coefficient *Kd* between the sediment phase and the overlying water will determine the potential release of HCB from previously contaminated sediment in a water source (e.g., a reservoir or creek). If possible, it may be also useful to include information on the persistence of HCB in sediment or aquatic systems. Such information will help the reader to better understand the magnitude and time-scope of the potential HCB exposure from drinking water."

Response 3. Text was revised to include a brief discussion on the distribution of HCB in water, sediment, and aquatic systems.

Comment 4. "On Page 3, under "Physical and Chemical Properties", it might be helpful to include the dimensionless Henry's Law constant, which may give the reader a more direct feeling about the volatility of HCB."

Response 4. The Henry's Law constant is included in the Physical and Chemical Properties Section of the document.

Comment 5. *Minor editorial comments were provided.*

Response 5. Changes to the text were made where appropriate.

Comments from University of California, Davis

Comment 1. "The document on hexachlorobenzene is well written and provides the essential information. The calculated [PHG] is reasonable. … Data on toxicity, metabolism, modes of action and exposure are generally presented in a clear and concise manner."

Response 1: Comments noted.

Comment 2. *However*, "[o]n page 20, last paragraph before 'Developmental and Reproductive Toxicity' ('Although HCB was not mutagenic…') the text is almost a verbatim quotation from a chapter in a textbook. First, it would seem that the information does not belong into the genetic toxicity chapter, but into 'Developmental'. Second, there are no references to the original observations, whether with regard to mutagenicity or developmental toxicity. This may be acceptable for the textbook (i.e., the chapter by Ecobichon), but in the present document it is not acceptable. The paragraph should be deleted or the information be moved into the appropriate place with references."

Response 2. Agreed. The text was correspondingly revised.

Comment 3. "There are many good data sets on the toxicity of Hexachlorobenzene available and the document has made a good use of them. PHGs have been calculated by standard procedures. Safety factors are conservative, but appropriate."

Response 3. Comments noted.

Comment 4. "In reading through the data presented that deal with Hexachlorobenzene toxicity in Turkey in the 1950ies, one is struck by the fact that apparently infants and toddlers were a particularly sensitive group (page 34, 3rd paragraph under 'Porphyria'). It is mentioned someplace that data on exposure are rather incomplete. Nevertheless, would it be possible to come at some, even if crude, estimate of exposure levels between the groups at higher risk (infants) compared to adults? This might be an interesting exercise, because it might give some clues whether the usually by rote applied safety factor for intraspecies variation of 10 is reasonably accurate. While such a consideration hardly would affect the outcome of the PHG calculation (based on carcinogenicity in

animal studies), it nevertheless would offer the opportunity to do a "reality check" on a common assumption. An additional possibility along these lines would be to compare exposure data and the ensuing toxicity of HCB in breast-feed infants and compare it to the toxicity in newborn ferrets (which also seem to become adversely affected after birth, presumably through the milk, depending on how long ferrets nurse; Table 7, page 22). Such a comparison could give some indication on the interspecies safety factor to be applied."

Response 4. The question of a "reality check" is raised in two different contexts - for setting uncertainty factors of 10 for sensitive population (adult to child difference), and 10 for intraspecies variation (ferret/mink to human comparisons). For the first part, the child or newborn is clearly more sensitive than the adult following exposure to HCB. The incident in Turkey and the findings by Bleavins *et al*. (1984a) and others demonstrate this effect. Courtney (1979) reported a 95 percent incidence of infant mortality as compared to 10 percent mortality in adults. A 10-fold uncertainty factor seems appropriate in this case, but a more precise value cannot be calculated.

For the interspecies comparison, the findings are similar between offspring of humans exposed to HCB and offspring of ferret and mink exposed to HCB. For the animal studies, a clear exposure level is known; for the human studies the exposure is not as clear. At the end of page 41 of the document, we state that similar exposure levels (0.8 mg/kg-day to 4 mg/kg-day) are observed for the infant mortality in both species. However, this is an estimate; the precise exposure level in women who had the infant mortality is not known. The rates of transfer of the HCB from the mothers to the infants in milk are unknown in both species. Thus, the available data are inadequate to accurately compare exposure between human infants and the newborn ferrets, so that the default 10-fold interspecies uncertainty factor seems most appropriate.

Comment 5. "I would agree with the second paragraph on page 43 under: "Carcinogenic Effects", that not enough mechanistic information is available that would justify to use a non-linear dose-response approach."

Response 5: Comment noted.

Comment 6. *Several editorial comments were provided.*

Response 6. Changes to the document were made, where appropriate.

Comments from U.S. Environmental Protection Agency

Comment 1. "The document is well written and gives a detailed explanation of studies used and good justification for the derived PHG."

Response 1: Comments noted.

Comment 2. *Several minor editorial comments were provided.*

Response 2. Changes to the document were made, where appropriate.

Comments from The Dow Chemical Company, Midland, Michigan

Comment 1: "Dow supports the decision of the Office of Environmental Health Hazard Assessment (OEHHA) not to set the Public Health Goal (PHG) for HCB at zero. Even for carcinogens, the state needs to determine the differing toxicity to assist decisions people need to make as to where money should be appropriately spent. This is far more appropriate than simply adopting a zero, as did EPA."

Response 1: Comment noted.

Comment 2: *However*, "Dow notes that one of the key studies relied upon for setting the PHG based on animal carcinogenicity data (Lambrecht *et al*., 1983a) is simply a non peer-reviewed abstract presented in Federation Proceedings/FASEB meetings in 1983. The second Lambrecht *et al.* paper (Lambrecht *et al.*, 1983b) could not be located in a TOXLINE® online search but also appears to be an abstract. However, Dow found a 1982 abstract by Lambrecht *et al*. from a previous FASEB meeting entitled *Hepatotoxicity and tumorigenicity of heaxahloobenzene (HCB) in Syrian Golden Hamsters (H) after subchronic administration*. This might be a similar abstract. Thus, both of the cancer endpoints in the Draft technical guidance are inappropriate as they are based on abstracts only or even on an abstract that cannot be readily located.

In contrast, EPA based their slope factor derivation for HCB on the study by Erturk *et al*., 1986 and did not mention the abstracts of Lambrecht *et al* (EPA IRIS HCB document). The tumor data from Arnold *et al.*, 1985 reported in a letter in a 1988 volume of Food and Chemical Toxicology, reports adenomas and not carcinomas as elevated for certain organs. Adenomas alone do not support a derivation of a cancer slope factor. To ensure that only real results are used, OEHHA needs to rely on peer reviewed studies. Therefore, OEHHA needs to re-review the appropriate scientific literature and redraft this technical support document based on appropriate, reliable scientific studies."

Response 2. In general, the literature is reviewed for all data related to the chemical of interest in the calculation of the PHG. In this case, the two articles noted by the commenter (Lambrecht RW, Erturk E, Grunden EE, Peters HA, *et al*., 1983a; Lambrecht RW, Erturk E, Grunden EE, Peters HA, *et al*., 1983b) are abstracts of presentations at two separate scientific meetings (AACR and Carcinogenesis, respectively) and are included in the document for completeness of the literature review. However, the same data presented in the two citations were included in the third citation mentioned by Dow (Erturk E, Lambrecht RW, Peters HA, *et al*., 1986). Thus, both OEHHA and the U.S. EPA used the same article and data in their respective documents. As such, we disagree with Dow that the calculation of the PHG needs to be re-drafted; the use of the data is indeed appropriate.

Comment 3. "HCB is a chemical that is in declining production as noted in the Production and Uses section of this Draft technical support document. The estimated production 20 years ago cited on page 3 of the Draft technical support document has decreased by approximately 25% to 3,219 tons based on EPA's 2000 TRI Executive Summary (available on EPA's web site).

"The use of HCB as a fungal growth inhibitor in the 1980s had very high historical emissions that are now eliminated. Additionally, the effectiveness of HCB waste treatment is better than it was in the 1980s. Environmental concentrations of HCB are certainly decreasing given the significant decrease in new HCB emissions and the reported half lives of HCB in the various media. We note that this is supported by the >30% decrease in human HCB concentrations (Adipose) over the five years from the average (1973 to 1983) to the 1983, see Draft technical document, p 10. OEHHA should redraft this technical support document to include additional, more recent information should to confirm that human body burdens are continuing to decrease."

Response 3. Comment noted. The most recent data on human body burden were included in the document.

Comment 4. "We also note that the Draft technical support document, on page 6, notes that the largest releases are in Louisiana and Texas. Thus, there is no potential for the most exposed US HCB population to reside in California. OEHHA needs to re-draft the technical support document to either eliminate or explain why it is concerned about historical, non-California media HCB concentrations. Given all of these factors [*including comments 2 and 3*], the implicit safety factors imbedded in an one in a million cancer risk is inappropriately applied to calculating an appropriate California HCB cancer risk. OEHHA should redraft the technical support document using a cancer risk of one in one hundred thousand, the same lifetime cancer risk used in the Proposition 65 risk assessments for chemicals that may have unknown human cancer risks and may be of increasing environmental exposure in California."

Response 4. The most recent data for levels of HCB found in California drinking water were included in the document. The other data provided in the document were included for completeness of the review. While the PHG level is based on an estimated cancer risk of 1 in 1 million (10^{-6}), levels equivalent to cancer risk levels of 10^{-4} and 10^{-5} are provided in the PHG document. The cancer risk level used in developing regulations on HCB exposure (i.e., the MCLs) are derived by the California Department of Health Services.

Comment 5. "The Public Health Goal For Hexachlorobenzene stated no NOAEL existed for HCB based upon data in Arnold *et al.*, 1985. This appears to contradicts the EPA's characterization of Arnold *et al.*, 1985 in which the USEPA derived a NOAEL of 1.6 ppm and a LOAEL of 8.0 ppm in the diet (EPA IRIS HCB document). Further, EPA IRIS states:

Although significant ($p<0.05$) increases were observed in the incidences of periportal glycogen depletion at 1.6 ppm, peribiliary lymphocytosis at 0.32, 1.6 and 40 ppm, and peribiliary fibrosis at 0.32 and 40 ppm in the F1 male rat groups, these effects are not being considered hexachlorobenzene-induced adverse effects because they were observed in a large number of F1 control males as well. The 8.0-ppm F1 groups were reported to have an increase ($p<0.05$) in hepatic centrilobular basophilic chromogenesis. The 40-ppm F1 groups showed increases ($p<0.05$) in pup mortality, hepatic centrilobular basophilic chromogenesis, and severe chronic nephrosis (males only)."

Response 5. Based on the data of the Arnold *et al.* (1985) study, OEHHA did not feel a NOAEL was established in the study. The dose-related increases in centrilobular basophilic chromogenesis observed in both male and female rats are significant at 8 and 40 ppm. Given the clear trend, the increases seen in the females at the 0.32 ppm (5/49) and 1.6 ppm concentrations (7/50), compared to controls (2/49), while not statistically significant, may be biologically significant (i.e., representing a toxic effect at these doses). The increases in hepatic lymphocytosis and fibrosis in males are of uncertain physiological significance because of the absence of any dose-related trend. HCB has been clearly shown to be hepatotoxic in humans and experimental animals, and the Arnold *et al*. (1985) results indicate that modest hepatotoxic effects can be seen at low HCB exposure concentrations. As such, the 0.32 ppm (0.01 mg/kg-day) used in this study was considered a LOAEL and a NOAEL was not identified.

Comment 6. "Additionally, since a NOAEL has been determined from the Arnold *et al.*, data (EPA IRIS HCB document), the uncertainty factors used in the noncarcinogenic effects are inappropriate. Given the fact that there is a NOAEL for the Arnold study, there should be no correction for using a LOAEL for the Arnold study. Given the slight effect of the Bleavins study, the correction for using a LOAEL rather than a NOAEL should be 2, not 3 for the Bleavins study.

"Further, given the relatively well documented human response to HCB and the decreasing exposure, 10 is an appropriate uncertainty factor for the combined interspecies extrapolation and human variability.

"These changes to the UFs will give a total UF of 20, not the 300 for the Bleavins study and a total UF of 10, not 300 for the Arnold study. These changed total UFs result in a calculated C of 16.5 ppb based on the Bleavins endpoint and C of 6.9 ppb based on the Arnold endpoint."

Response 6. We disagree with the comment and feel the uncertainty factors used in calculating the non-cancer PHG are appropriate and justified. Further changes to the non-cancer PHG are not needed.

REFERENCES

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Erturk, E, R Lambrecht, H Peters, D Cripps, A Gocmen, C Morris, G Bryan (1986). Oncogenicity of hexachlorobenzene. In: *Hexachlorobenzene: Proceedings of an International Symposium*, R.R.M.J.R.P. Cabral, ed., IARC Sci Publ 417-23.

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