DISPOSITION OF PEER REVIEW COMMENTS FOR TOXICOLOGICAL PROFILE FOR HEXACHLOROBUTADIENE

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

March 2019

Peer reviewers for the third pre-public comment draft of the Toxicological Profile for Hexachlorobutadiene were:

Wei-Hsiang Chen, Ph.D.
Associate Professor
Institute of Environmental Engineering
National Sun Yat-sen University

Shane Que Hee, Ph.D.
Associate,
Department of Environmental Health Sciences
University of California, UCLA
UCLA Fielding School of Public Health

James V. Bruckner, Ph.D.
Professor of Pharmacology & Toxicology
Department of Pharmaceutical & Biomedical Sciences
College of Pharmacy
University of Georgia
Athens, Georgia

Comments provided by Peer Reviewer #1

General Comments

COMMENT: Chapter 1. In general it is a good summary

RESPONSE: *No response needed.*

COMMENT: Chapter 2. The most recent research reference dates to 2013. There are some references that need inclusion relative to kidney effects and metabolism

RESPONSE*: See Responses to specific comments.*

COMMENT: There were no recent studies that might be candidates for MRL setting.

RESPONSE: *No response needed.*

COMMENT: The below should be included:

The Cristofori et al Cell Biol Toxicol 31: 1-13, 2015 review should be included since it discusses glutathione bioactivation of HCBD to form a cysteine conjugate via the β-lyase pathway, oxidative metabolism to the more toxic sulfoxide, and the gender specific cytochrome P-450 3A of adult male rats and rabbits. Add on p44 L16; p46 L23; p57 L21.

Sadeghnia et al Renal Failure 35:1151-1155, 2013 should be included since it examines the protective effect of rutin on acute HCBD effects at 100 mg/kg (ip). Cite near Bouroshaki et al 2010 who studied the protective effect of pomegranate seed oil on acute HCDB effects at 50 mg/kg (ip). Cite both at p65 after L18 as interactions. Can't find where Bouroshaki et al (2010) is cited in the text but it would be appropriate also on p 46 at L2 for the 50 mg/kg (ip) dose that caused elevation of serum creatinine and urea and urinary glucose and protein at 24 h relative to controls as well as increases in total thiol and thiobarbituric acid species in kidney homogenates. Sadeghnia is in the same research group and reports the same biomarkers as Bouroshaki et al (2010). Similarly Bouroshaki et al 2015 Iran J Med Sci 32: 173-176, 2015 reported on the protective effect of safranal and should be cited in the Interactions section too.

RESPONSE: *The Cristofori et al. (2015) paper was added to the discussion of the mechanisms of action in Section 2.10:*

> Much of the data related to the mechanism of hexachlorobutadiene toxicity indicate that the intermediates produced by modification of the cysteine derivative, S-(1,2,3,4,4-pentachlorobuta-1,3-dienyl)-L-cysteine (PCBC), are responsible for the observed effects on the proximal tubules. PCBC is formed from the hexachlorobutadiene conjugate S-1,2,3,4,4-pentachlorobuta-1,3-dienyl)-L-glutathione in the liver, intestines, and/or kidney through the action of γ-glutamyl transferase, which removes the glutamate from the glutathione tripeptide followed by the action of a peptidase that removes the glycine from the carboxy terminus (Cristofori et al. 2015).

The updated format for the toxicological profile no longer includes a discussion of methods for reducing toxicity. Thus, the Boroushaki et al. (2010) study was not cited in the profile (citation was removed from the reference list in Chapter 8) and Sadghnia was not added to the profile.

COMMENT: Acute Duration (revised): reasoning appears sound as to revisiting the Harleman and Seinen, 1979 study. I would delete the 1st paragraph and note and put the note at the end in the new text that would then begin with "Three studies…" It is less confusing. p83 L12 states "two studies". It should be "Two inhalation studies".

RESPONSE: *The Reviewer appears to be referring to the note to the MRL Workgroup in the MRL rationale statement. This is an internal review note that was removed in the final document.*

COMMENT: Intermediate duration (revised). Same comment re order. In the Note: "LOAEL" is meant not "LAOEL."

RESPONSE: *The Reviewer appears to be referring to the note to the MRL Workgroup in the MRL rationale statement. This is an internal review note that was removed in the final document.*

COMMENT: Chronic –Duration MRLs p84 L2: The oral study should be identified.

RESPONSE: *The Kociba et al. (1977a) citation was added to the Chronic MRL subsection of Section 6.2:*

One chronic-duration oral study was identified (Kociba et al. 1977a).

COMMENT: Chapter 7. What is the policy on dates? The current recommendation or the date on which a recommendation/standard was made? Thus ACCIH (2018) recommends an air HCBD concentration of 0.02 ppm that was established in 1979 with a cancer notation of A3 and a skin notation. Probably need the most up to date reference? If so, the EPA data conflict. All the dates should be 2018 or the Year of Publication of the Toxicological Profile? The reader wants to know the current guidance level, I would think.

RESPONSE: *The dates listed are the most recent version of the guidance document, with the exception of guidelines listed in EPA's Integrated Risk Information System (IRIS) database (reference concentration [RfC], reference dose [RfD], and cancer classification) where the date used for the citation is the date that the document was last revised.*

COMMENT: Appendix A. See comments above on MRLs. They are compatible with what is in the text.

RESPONSE: *No response needed.*

COMMENT: Appendix B. I would include Scifinder Scholar/Chemical Abstracts as a data base. For example for hexachlorobutadiene, it has 3,177 references after removal of duplicates with 577 references on toxicity, 179 on health, and 559 on environment

RESPONSE: *It has been ATSDR experience that the PubMed, TOXLINE, and TOXCENTER databases reliably identify relevant published toxicological and environmental chemistry papers.*

Comments provided by Peer Reviewer #2

General Comments

COMMENT: Chapter 1 adequately summarizes the health effects studies in Chapter 2.

RESPONSE: *No response needed.*

COMMENT: Chapter 2 is very comprehensive and well written. The experimental protocols and findings are clearly and accurately presented. The tables and figures are a good way to present the key findings of the different studies, so the reader can readily compare data from one study with another. I was not able to locate any additional, more recent investigations that were relevant to derivation of MRLs.

RESPONSE: *No response needed.*

Acute-Duration Oral MRL

COMMENT: The 14-day hexachlorobutadiene (HCB) feeding study of Harleman and Seinen (1979) was a reasonable choice for derivation of the acute duration MRL. I do not concur, however, with ATSDR's designation of a 14-day repeated exposure as an acute exposure. I have always considered an acute exposure to be a single exposure that can vary in duration. Use of a LOAEL from a 14-day study as the basis for an acute guideline certainly introduces conservatism into (i.e., lowers) the MRL.

RESPONSE: *ATSDR defines acute exposure to be 1–14 days; thus, basing an acute MRL on a 14-day study would not be overly conservative.*

COMMENT: I also have a problem with the routine application of a 10-fold uncertainty factor (UF) for extrapolation from animals to man, irregardless of scientific evidence. A species-to-species UF of 1 should be used, although a science-based interspecies UF would be 0.25. Green et al. (2003) clearly showed that rates for key steps in the HCB metabolic activation pathway are 3 to 5 times higher in rats than in humans. It is widely recognized that renal B-lyase-dependent biotransformation of cysteine S-conjugates is significantly higher in rats than humans (Iyer and Anders, 1996; McGoldrick et al., 2003).

RESPONSE: *The Green et al. (2003) physiologically based pharmacokinetic (PBPK) model, which was designed to extrapolate from an oral dose to an inhalation concentration, is discussed in Section 3.1.6 of the profile. As noted in the profile, the results of the model should be interpreted cautiously since it was constructed using limited data and has not been validated in rats or humans. Thus, ATSDR did not consider the results of the model sufficient to derive chemical-specific uncertainty factors for hexachlorobutadiene.*

COMMENT: A total UF of 100 is adequate for calculation of the acute duration oral MRL.

RESPONSE: *No response needed.*

Intermediate-Duration Oral MRL

COMMENT: There is a solid basis for derivation of the intermediate-duration MRL. There have been a substantial number of oral studies of appropriate duration employing gavage and ingestion of the chemical. The nephrotoxicity findings are quite consistent, in terms of the reported LOAELs and NOAELs. Interestingly, the same LOAEL was observed for females of two different species by NTP (1991) and Schwetz et al. (1977).

RESPONSE: *No response needed.*

COMMENT: Again, the UF of 10 for interspecies extrapolation is not scientifically justified. Nevertheless the total UF of 100 and the MRL of 0.002 mg/kg/day are reasonable. This relatively low MRL is justified, I believe, b the fact that HCB is carcinogenic in rats.

RESPONSE: *See the previous response in the Acute-Duration Oral MRL subsection.*

Chapter 7

COMMENT: Hughes et al. (2001) did derive what they termed a "tolerable intake" of 0.34 ug/kg for use in Canada. This appears to be a chronic, or long-term health protection guideline. The DOE PACs are not very informative, as the reader will have to locate and consult another literature source in order to interpret them.

RESPONSE: *Given the large number of regulations/guidelines that can be available for a particular chemical, ATSDR has established a list of types of values to be included in Chapter 7. These primarily focus on values established by U.S. government agencies; thus, the Hughes et al. (2001) tolerable intake value was not added. Because PAC values could be based on Acute Exposure Guideline Levels (AEGLs), Emergency Response Planning Guidelines (ERPGs) or Temporary Emergency Exposure Limits (TEELs) values, it was not possible to give specific definitions for each PAC value, which is why ATSDR provided a link to DOE's website for an in-depth discussion of the values.*

Appendix A

COMMENT: Unfortunately, data from HCB inhalation toxicology studies are inadequate and unsuitable for deriving acute, intermediate, or chronic MRLs. The document's authors have done an excellent job describing the dearth of applicable data and the detailed logic for not calculating inhalation MRLs.

RESPONSE: *No response needed.*

COMMENT: The authors have been detained and accurate in their description of the databases and justifications for selection of the critical effects, principal studies, points of departure, and uncertainty factors for derivation of the acute and intermediate duration MRLs. See my previous comment about the lack of scientific justification for an interspecies uncertainty factor of 10.

RESPONSE: *See previous Responses to comments regarding the interspecies uncertainty factors.*

Appendix B

COMMENT: I would like to see a "Mechanism" or "Mode of Action" section added after the Toxicokintics section of each Toxicological Profile. Mechanism(s), if understood to some degree, allow the reader to better interpret, or understand why metabolism and disposition are important and why the bioactive moiety is selectively toxic to certain biological systems, cells, organs, species, genders, etc.

RESPONSE: *In ATSDR's revised toxicological profile format, the mechanisms of action are discussed in the appropriate health effects section. For the hexachlorobutadiene toxicological profile, the mechanisms of renal toxicity are discussed at the end of Section 2.10. For chemicals in which there is a common mechanism of action for most endpoints, the mechanistic data are discussed in a separate section (Section 2.21).*

COMMENT: The literature search appears to have been adequate. HCB has received very little attention since the early 2000s.

RESPONSE: *No response needed.*

Additional References

COMMENT: The Reviewer suggested the addition of the following papers

Iyers RA, Anders MW. 1996. Cysteine conjugate β-lyase-dependent biotransformation of the cystine S-conjugates of the sevoflurane degradation product compound A in human, nonhuman primate, and rat kidney cytosol and mitochondria. Anesthesiology 85: 1454-1461

McGoldrick TA, Lock EA, Rodilla V, Hawksorth GM. 2003. Renal cysteine conjugate C-S lyase mediated toxicity of halogenated alkenes in primary cultures of human and rat proximal tubular cells. Arch Toxicol 77:365-370.

Hughes K, Idris B, Meck ME. 2001. Hexachlorobutadiene: Hazard characterization and exposure-response analysis. Environ Carcino Ecotox Revs C19"267-280.

RESPONSE: *The Iyers et al. (1996) and McGoldrick et al. (2003) papers were not added to the profile since they do not discuss hexachlorobutadiene. The Hughes et al. (2001) paper was not added since it is a review article and it is ATSDR practice to rely on primary sources for hazard identification and dose-response data.*

Comments provided by Peer Reviewer #3:

ATSDR Charge Questions and Responses and Reviewer Comments

Chapter 1

QUESTION: Does Chapter 1 adequately summarize the published literature regarding health effects for this substance?

COMMENT: Figures 1-3 and 1-4: It is suggested that the ranges of experimental times applied in these studies or the definitions for Acute (<14 days), Intermediate (15–365 days), and Chronic (≥365 days) are given in these two figures for discussion.

RESPONSE: *ATSDR will consider the Reviewer's suggestion in future versions of the toxicological profile guidance document.*

COMMENT: By reading through the texts below, the processes of deriving the provisional acute and intermediate MRLs are understandable. However, it is difficult to relate the numbers listed in Figures 1-4 with the provisional acute and intermediate MRLs by going through Table 1-1. For example, a lowest LOAEL of 5.9 mg/kg/day (Harleman and Seinen 1979) was selected as the PoD with a total uncertainty factor of 1,000 (10 for the use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability) for the acute MRL. Nevertheless, the value of 5.9 mg/kg/day is not shown in Figure 1-4. Similarly, the value of 0.5 mg/kg/day as the LOAEL in NTP (1991), which reported 0.2 mg/kg/day as the NOAEL and used as the PoD for the intermediate MRL, is not shown in Figure 1-4.

RESPONSE: *The Summary of Sensitive Targets figures in Section 1.3 do not necessarily show the PODs for the MRLs. The figure is intended to provide an overview of the lowest LOAEL values for the most sensitive targets of toxicity. The information in Figure 1-4 has been corrected. The LOAEL for renal effects following acute exposure was changed from 6.1 mg/kg/day to 5.9 mg/kg/day and the LOAEL for renal effects following intermediate exposure was corrected to 0.5 mg/kg/day.*

Chapter 2

QUESTION: First, does Chapter 2 adequately reflect the published literature regarding health effects for this substance? Are you aware of any studies that are not included that may be relevant in the derivation of MRLs for this chemical?

COMMENT: The current version of Chapter 2 adequately reflects the publications associated with the health effects of hexachlorobutadiene. To the best knowledge of the reviewer, no studies associated with the derivation of MRLs for hexachlorobutadiene are not included in this document.

RESPONSE: *No response needed.*

QUESTION: Second, we would like you to focus on the current data assessment which resulted in the changes noted above and presented in detail below.

COMMENT: Page 32, Table 2-2: The statement of section c is incorrect. The uncertainty factor used to derive a provisional intermediate oral minimal risk level (MRL) of 0.002 mg/kg/day should be 100 (10 for extrapolation from animals to humans and 10 for human variability).

RESPONSE: *The footnote in Table 2-2 was corrected:*

> [c]Used to derive a provisional intermediate oral minimal risk level (MRL) of 0.002 mg/kg/day; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Chapter 7

QUESTION: We would like to know your thoughts on the regulations and guidelines that are presented and any that should be added or removed. Are you aware of any additional regulations or guidelines that we should add? Please provide citations. Are there any that should be removed? Explain.

COMMENT: In Table7-1, the links of two references including EPA 2012 and DOE 2016b are not working. Please update.

RESPONSE: *The links have been corrected.*

COMMENT: To the best knowledge of the reviewer, the regulations and guidelines provided in this chapter are fine. No addition or removal is needed.

RESPONSE: *No response needed.*

Appendix A

QUESTION: Please address the MRL worksheet based upon the questions provided above about the MRLs.

COMMENT: Page A-11, starting from line 10: The reason (Because the LOAEL identified in the NTP (1991) was lower than that identified in the Schwetz et al. (1977)…) is sufficient to select NTP (1991) as the principal study. However, one additional statement emphasizing the shorter duration time but the same NOAEL in NTP (1991) could be a plus to strengthen the selection of NTP (1991) for the main study.

RESPONSE: *ATSDR does not agree with the Reviewer that the shorter duration of the NTP (1991) study, as compared to the Schwetz et al. (1977) study, provides support for selecting the NTP study as the basis of the MRL.*

Appendix B

QUESTION: Please provide comments about the process utilized in this section.

COMMENT: The process utilized in this section is fine. No revisions is needed.

RESPONSE: *No response necessary.*