REVIEW OF "DRAFT TOXICOLOGICAL PROFILE FOR

HEXACHLOROBENZENE"
Reviewer #1

This document summarizes available information on the characteristics, exposure, and health effects of hexachlorobenzene. It is prepared in the standard format for the ATSDR Toxicological Profiles, and discusses health effects in relationship to route of exposure (inhalation, oral, dermal).

Overall, the document is well written, in a clear style, and well documented. Tables and Figures are good comprehensive compilations of information, and are useful for comparison of data and values. At difference with similar document, this one is not overly repetitious or redundant, though some modifications are suggested below. Some issues may also need additional corrections and/or clarifications, as suggested in the specific comments below. Furthermore, some sections would benefit of an overall conclusion statement, as some data can be subject to different interpretations.

Specific comments are listed below; they are divided by chapters, with indications of the page number and line.

CHAPTER 1. PUBLIC HEALTH STATEMENT

The intended audience for this chapter is the lay public, and this chapter is written in a simple and direct style. All major information on hexachlorobenzene is summarized in a simple and clear manner. However, there seems to be too much emphasis on exposure through water, which would be unlikely given the very low solubility of hexachlorobenzene in water (see also p. 10, 2nd paragraph). Also, indications on potential contamination of bottled water (p. 6) do not appear to be warranted.

The USEPA advisories for drinking water are puzzling. It is stated (p. 8) that an adult can be exposed to up to 0.2 mg/L of hexachlorobenzene for several years without any adverse effect. Assuming consumption of 2 L of water/day in a 70 Kg person, exposure would be 0.4 mg/day, i.e. 0.006 mg/kg/day. This value is significantly higher than the MRLs for intermediate and

chronic oral exposures. I am afraid this may create some confusion. If my interpretation is correct, then a comment on this may be useful.

CHAPTER 2. RELEVANCE TO PUBLIC HEALTH

p. 10, 2nd paragraph: It would be of interest to present data on potential exposure to hexachlorobenzene through food, in the context of which foods may be most contributing to body burden (see Tables 6-5, 6-6). Also, it could be indicated that infant exposure occurs because of exposure through breast milk.

p. 11, last paragraph: As exposure of toddlers and infants may be lower (see above, though it may have been different in this episode), is there a differential age-dependent susceptibility, or differential exposure may explain the *in vivo* outcomes in humans?

p. 12, 1st paragraph: Typo on line 7 (hyperpigmentation)

p. 12 last paragraph: I would change "The primary target systems… are hepatic toxicity, reproductive toxicity…" into "The primary targets of toxicity… are the liver…." or "The primary manifestations of toxicity…. are…".

p. 13, line 2: …inherited and/or acquired diseases…

p. 13, 2nd paragraph: …hepatomegaly and increased liver weight… Is this repetitious?

p. 13, last paragraph: On the first line: …doses as low as 16 mg/kg/day…. I would delete as low as.

p. 15, 2nd paragraph: On third line from bottom, change to italics (*possibly carcinogenic to humans*)

Figure 2-1 Good and useful.

p. 18, last paragraph
p. 19, top paragraph: Add some doses from the indicated studies.

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CHAPTER 3. HEALTH EFFECTS

Section 3.1 INTRODUCTION

Section 3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

In this as in the following sections, I will comment only when I disagree with some statements of have suggestions to change text etc. In the absence of any specific comments, I agree with the writing, the choices and the conclusions.

p. 25, line 18: It would be useful if actual blood levels of hexachlorobenzene were indicated.

p. 37, line 13: Arthritis is indicated as an adverse effect of hexachlorobenzene observed in humans. It is discussed briefly in the section on musculo-skeletal events. The other information provided from animal studies are much different from arthritis. A possibility would be to move this brief section (lines 13-18) to the section on metabolic effects (p.53), as the main issue here is inflammation.

p. 60, line 18: Here a statement could be added that the Goldey and Taylor, 1992 study was utilized to derive the acute MRL, as it was indicated on p. 63 for the intermediate MRL.

p. 62, line 24: The Bourque et al. (1995) study it is the only to report effects in Cynomolgus monkeys at 0.01 mg/kg/day, yet similar effects were found in other studies at higher doses (see p. 63, line 6 et al.). Is there any information on the purity of hexachlobenzene in these different studies?

p.71, line 16: Perhaps “casual” should be “causal”, i.e. porphyria is seen as a potential “precursor” of hepatic cancer.

Section 3.3 GENOTOXICITY

This section would benefit of an overall conclusion. Most often, results from genotoxicity studies provide constrasting results, with both positive and negative findings, and an overall conclusion related to the potential genotoxicity of a compound must rely on a weight-of-evidence approach. The two Tables are useful. The paucity of information available may also be indicated in this section.

Section 3.4 TOXICOKINETICS

This section is extremely comprehensive as it discusses a large number of studies on absorption, metabolism, distribution, and excretion after exposure through the different routes. Fig. 3-3 is informative. It is apparent that most hexachlorobenzene is excreted unchanged in the feces, while metabolites are excreted through the urine. What does not easily emerge from the text is the potential contribution that this "minor" metabolism may have in overall toxicity.

p. 107, line 24: I would delete this sentence (lines 24-26).

p. 109, line 13: What is the usefulness of determining the effect of partial hepatectomy on distribution of hexachlorobenzene?

p. 109, line 16: At the beginning or at the end of the section on PBPK models, it should be stated why none of these models was used for any risk assessment. Where they not adequate, or there was no interest?

p. 110, line 20: On p. 109 (lines 8-10) it is stated that the Yessair (1986) model modeled humans as well as rats.

Section 3.5 MECHANISMS OF ACTION

p. 112, line 23: The whole section on pharmacokinetic mechanisms (p. 112-115) is very repetitive of the previous toxicokinetic section. Some sentences are reproduced verbatim. It would be useful to delete this section and add any new information to the section on toxicokinetics, or to significantly shorten it.

p. 115, line 23: The section on mechanism of toxicity is somewhat difficult to follow. Perhaps it would be possible to rewrite it in part to facilitate the reader.

Section 3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

p. 121, line 32: typo: thyroxine

p. 121-122: The information given is scarce. Perhaps there is not much; thus it would be useful to add for instance some considerations on doses/concentrations eliciting endocrine effects. How do they compare with those causing other adverse health effects?

Section 3.7 CHILDREN'S SUSCEPTIBILITY

p. 123, line 24: A sentence may be added indicating that in several cases the increased susceptibility of children to adverse health effects involves the central nervous system.

p. 125, line 19: It may be here indicated that exposure to hexachlorobenzene in the Goldey and Taylor (1992) study occurred in the mother before conception. The high retention and long half-life of hexachlorobenzene caused some exposure *in utero* and most exposure in the early postnatal period through lactation.

Section 3.8 BIOMARKERS OF EXPOSURE AND EFFECT

p. 128, line 23: The section on Biomarkers of Effects may be expanded by adding some details on the few studies which are available.

p.129, lines 7-10: This sentence may be deleted. Its significance is obscure.

Section 3.9 INTERACTIONS WITH OTHER CHEMICALS

p. 129, line 14: It may be stated at the beginning that certain chemicals may modify the toxicity of hexachlobenzene and that this compound in turn may modify the toxicity of other chemicals.

p. 129, line 31: These two sentences are unclear. It is said that hexachlorobenzene is an enzyme inducer. "Thus" exposure of any of these enzyme inducers …. There is no direct relationship between the two statements.

p. 131, line 17: The effect of hexachlorobenzene on malathion toxicity represents an interaction, but its significance is doubtful.

Section 3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

p. 133, line 21: As there was an entire section devoted to childrens' susceptibility, this may be acknowledged at the beginning of this paragraph.

p. 134, line 4: I wonder whether certain genetic polymorphisms (e.g. in metabolic enzymes, such as CYPs, or in enzymes involved in the porphyrin cascade) may influence hexachlorobenzene toxicity. Perhaps, even if data are not available, it may be mentioned as a theoretical possibility.

Section 3.11 METHODS FOR REDUCING TOXIC EFFECTS

p. 136, line 16: The mechanism indicated here (i.e. interference with sodium channels) refers only to p,p'-DDT, not to all other organochlorine insecticides. Rather, their neurotoxicity is ascribed to a block of the chloride channels, such as those associated with the GABA-A receptors. This should be corrected.

Section 3.12 ADEQUACY OF THE DATABASE

This section contains a further summary of all aspects discussed in previous sections, and emphasizes those aspects which would benefit of further data. I agree with most considerations, with a couple of exceptions.

p. 147, line 6: This reviewer feels that biomarkers to measure exposure to hexachlorobenzene are already adequate.

p. 151, line 14: It is unclear how the ongoing studies indicated in Table 3-5 will contribute to fill any data gap for hexachlorobenzene. They look as epidemiological studies in which hexachlorobenzene will possibly be measured in blood or other media together with other contaminants. Some details on these studies may be added here.

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

Acceptable as is.

CHAPTER 5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

Acceptable as is.

CHAPTER 6. POTENTIAL FOR HUMAN EXPOSURE

This section contains a very thorough discussion of all possible route of exposure to hexachlorobenzene. Some additional discussion on the potential exposure of the general consumer through the diet, based on the data presented in the Tables, would be useful.

p. 221, line 4: The same ongoing studies indicated before (p. 151) are mentioned here. What would be their specific contribution to these specific data needs?

CHAPTER 7. ANALYTICAL METHODS

No further comments.

CHAPTER 8. REGULATIONS AND ADVISORIES

The list of studies available for acute, intermediate and chronic toxicity was reviewed. Papers describing the studies selected for determination of the MRLs were also reviewed, as well as Appendix A.

This reviewer agrees on the selection of the studies used for determining the acute MRL (Goldey and Taylor, 1992), intermediate MRL (Bourque et al. 1995), and chronic MRL (Arnold et al., 1985). On p. 236, line 16, it is indicated that the LOAEL in the two-generation study by Arnold et al. (1985) was 0.016 mg/kg/day, while in reality it was 0.022 mg/kg/day. Also, though effects were seen at this dose level, dose-dependency appears to be weak. This may be mentioned.

CHAPTER 9. REFERENCES

Very comprehensive list of references.

UNPUBLISHED STUDIES (IF APPLICABLE TO REVIEW)

None known.

ADDITIONAL COMMENTS

1. Hexachlorobenzene is one of the "dirty dozen" chemicals which have been outlawed by the Stockholm convention on persistent organic pollutants. This may be mentioned somewhere in the document.
2. There is increasing concern about the prevalence of autistic spectrum disorders and on their possible etiology. Recent studies have pointed out at the fact that alterations of porphyrin metabolism and excretion may be an important characteristic of these disorders. Though information on hexachlorobenzene and autism may not be available, given that effects on porphyrin metabolism are a primary adverse health effect of

hexacholorobenzene toxicity, this may be mentioned as one of the potential consequences of developmental exposure to this chemical, certainly deserving some attention.

Some recent references on this topic are:

Woods et al. Env. Health Perspect. 118: 14501457, 2010.

Youn et al. J. Toxicol. Environ. Health. 73: 701-710, 2010

Heyer et al. Autism Res. 5: 84-92, 2012.

Reviewer #2

Review of: DRAFT TOXICOLOGICAL PROFILE FOR HEXACHLOROBENZENE

Specific suggestions for improving the document were provided as annotations on the word file as "comments". 45 specific comments were provided.

Summary:

This is an outstanding document reviewing the literature and current state of knowledge on the toxicological profile of hexachlorobenzene. While hexachlorobenzene has not been produced commercially in the USA for over 30 years, it is still used and occurs as a by-product in industrial processes. The long persistence in the environment, and the concentration in fat depots in animals and humans, results in persistent concerns regarding human exposures, particularly with regards to infant exposure in breast milk.

The DRAFT is very well organized and written. The review of the literature is thorough.

Suggestions for improving the draft largely fall into the two following groups (as annotated in the document):

1. The outstanding research presented in the bulk of the text (3. HEALTH EFFECTS), is not faithfully summarized in either 1. PUBLIC HEALTH STATEMENT FOR HEXACHLOROBENZENE, or 2. RELEVANCE TO PUBLIC HEALTH. Key issues that are given inadequate presentations in sections 1 or 2 include:
    a. Persistence in environment
    b. Concentrations in fat depots in animals and humans
    c. Sources of ingestion
    d. Persistence in the human body
    e. Concerns regarding infant exposure via breast milk
    f. Others, as noted in specific comments
2. Given the persistence in the environment and in animals, and either known or potential broad dispersal, more attention should be given to international commercial production (in all 3 sections of the text).
    a. A new subsection of Section 2 (Relevance to public health) should be devoted to international efforts to study and control hexachlorobenzene. The exposures of US

residents are not limited to hexachlorobenzene produced or used in the US. Thus, the document should be less US-centric, and describe:

i. International production and use
ii. Better description of possible sources of importation to the US
iii. Efforts of the EU or other international groups to review sources of exposures, risks associated with exposures, and regulatory efforts to control these.

b. A new subsection of Section 1 should list access to information internationally (any EU developed web sites or documents, or other international studies).

HEXACHLOROBENZENE (My responses are bolded and numbered)

Reviewer #3

-Are there any data relevant to child health and developmental effects that have not been discussed in the profile and should be?
-Are there any general issues relevant to child health that have not been discussed in the profile and should be?
-If you answer yes to either of the above questions, please provide any relevant references.

CHAPTER 1. PUBLIC HEALTH STATEMENT

-The tone of the chapter should be factual rather than judgmental. Does the chapter present the important information in a non-technical style suitable for the average citizen? If not, suggest alternate wording.

1. The use narrative on p2 does not actually address the question of what HCB is actually used for in the United States but rather in what media HCB is detected. See revised text. Transfer most of the text to Where is HCB Found on p3.

2. p3 Where is HCB found: Add the sentence about the food chain since the reader is not prepared to see food in the table. Added new refs Antunes et al 2012;Wegiel et al 2011. Biodegradation in soil should be mentioned.
-Major headings are stated as a question. In your opinion, do the answers to the questions adequately address the concerns of the lay public? Are these summary statements consistent, and are they supported by the technical discussion in the remainder of the text? Please note sections that are weak and suggest ways to improve them.
3. See #1.
4. p4 How does HCB enter body? Contaminated soil is another source important for children who eat soil/pica
5. p8: Add the ACGIH 8-hr TLV-TWA of 2.0 µg/m3 (skin) to the table and refer to the A3 carcinogen status on p16.
-Are scientific terms used that are too technical or that require additional explanation? Please note such terms and suggest alternate wording.

CHAPTER 2. RELEVANCE TO PUBLIC HEALTH

-Do you agree with those effects known to occur in humans as reported in the text? If not, provide a copy of additional references you would cite and indicate where (in the text) these references should be included.
-Are the effects only observed in animals likely to be of concern to humans? Why or why not? If you do not agree, please explain.
-Have exposure conditions been adequately described? If you do not agree, please

explain

6. p10 para 1 1st sent: hexachlorobenzene is fully chlorinated benzene and is just one compound. It is not a hydrocarbon.
7. p10 para 1 2nd last sent: HCB is still used in the U.S.-- it is not manufactured. They are not the same thing. Certain HCB supplies are imported, for example for laboratory standard use, research use, etc. as indicated in #1.
8. p11 para 1: it is worthwhile to draw attention to children playing in and on contaminated soils as being more likely to be exposed. Also see #4.
9. p13; include endometriosis as an example of a possible HCB correlated disease with a lowered fertility possible outcome.
10. p23 new last para: Biological monitoring equivalent MRLs proposed by Aylward et al 2010.

CHAPTER 3. HEALTH EFFECTS

Section 3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

Toxicity - Quality of Human Studies
-Were adequately designed human studies identified in the text (i.e., good exposure data, sufficiently long period of exposure to account for observed health effects, adequate control for confounding factors)? If not, were the major limitations of the studies sufficiently described in the text without providing detailed discussions. If study limitations were not adequately addressed, please suggest appropriate changes.
-Were the conclusions drawn by the authors of the studies appropriate and accurately reflected in the profile? If not, did the text provide adequate justification for including the study (e.g., citing study limitations)? Please suggest appropriate changes.
-Were all appropriate NOAELs and/or LOAELs identified for each study? If not, did the text provide adequate justification for excluding NOAELs/LOAELs including, but not limited to, citing study limitations? Please suggest appropriate changes.
-Were the appropriate statistical tests used in the studies? Would other statistical tests have been more appropriate? Were statistical test results of study data evaluated properly? **NOTE**: As a rule, statistical values are not reported in the text, but proper statistical analyses contribute to the reliability of the data.
-Are you aware of other studies which may be important in evaluating the toxicity of the substance? Please provide a copy of each study and indicate where in the text each study should be included

Toxicity - Quality of Animal Studies

-Were adequately designed animal studies identified in the text (i.e., adequate number of animals, good animal care, accounting for competing causes of death, sufficient number of dose groups, and sufficient magnitude of dose levels)? If not, does the inadequate design negate the utility of the study? Please explain.
-Were the animal species appropriate for the most significant toxicological endpoint of the study? If not, which animal species would be more appropriate and why?
-Were the conclusions drawn by the authors of the studies appropriate and accurately reflected in the text? If not, did the text provide adequate justification for including the study (e.g., citing study limitations)

-Were all appropriate NOAELs and LOAELs identified for each study? Were all appropriate toxicological effects identified for the studies? If not, please explain.
-If appropriate, is there a discussion of the toxicities of the various forms of the substance? If not, please give examples of toxicological effects that might be important for forms of the substance.
-Were the appropriate statistical tests used in the interpretation of the studies? If not, which statistical tests would have been more appropriate? Were statistical test results of study data evaluated properly? **NOTE**: As a rule, statistical values are not reported in the text, but proper statistical analyses contribute to the reliability of the data.
-Are you aware of other studies that may be important in evaluating the toxicity of the substance? If you are citing a new reference, please provide a copy and indicate where (in the text) it should be included.

LSE Tables and Figures

-Are the LSE tables and figures complete and self-explanatory? Does the "Users Guide" explain clearly how to use them? Are exposure levels (units, dose) accurately presented for the route of exposure? Please offer suggestions to improve the effectiveness of the LSE tables and figures and the "User's Guide."
-Do you agree with the categorization of "less serious" or "serious" for the effects cited in the LSE tables?
-If MRLs have been derived, are the values justifiable? If no MRLs have been derived, do you agree that the data do not support such a derivation?

Evaluation of Text

-Have the major limitations of the studies been adequately and accurately discussed? How might discussions be changed to improve or more accurately reflect the proper interpretation of the studies?
-Has the effect, or key endpoint, been critically evaluated for its relevance in

both humans and animals?
-Have "bottom-line" statements been made regarding the relevance of the endpoint for human health?
-Are the conclusions appropriate given the overall database? If not, please discuss your own conclusions based on the data provided and other data provided to you but not presented in the text.
-Has adequate attention been paid to dose-response relationships for both human and animal data? Please explain.
-Has the animal data been used to draw support for any known human effects? If so, critique the validity of the support.

11. p25-32 Inhalation: There are no persuasive workplace inhalation studies because of the presence of other chemicals.

12. p33-49: Oral ---OK

13. p49-52: Dermal…OK

14. p52: Ocular---OK

15 p52- 54: Body Weight Effects---OK

16. p54 : Metabolic Effects---OK

17. p54-59 : Immunological and Lymphoreticular Effects—OK

18. p59-61 : Neurological Effects---OK

19. p61-66: Reproductive Effects—OK

20. p67-71: Developmental Effects---OK

21. p72-77 : Cancer---OK.Added Pena et al 2012

22. p77 Dermal exposure: OK

Section 3.3 GENOTOXICITY p77-79 :….OK
Section 3.4 TOXICOKINETICS

-Is there adequate discussion of absorption, distribution, metabolism, and excretion of the substance? If not, suggest ways to improve the text.
-Have the major organs, tissues, etc. in which the substance is stored been identified? If not, suggest ways to improve the text.

-Have all applicable metabolic parameters been presented? Have all available pharmacokinetic/pharmacodynamic models and supporting data been

presented? If not, please explain.
-Is there adequate discussion of the differences in toxicokinetics between humans and animals? What other observations should be made?
-Is there an adequate discussion of the relevance of animal toxicokinetic information for humans? If not, please explain.
-If applicable, is there a discussion of the toxicokinetics of different forms of the substance (e.g., inorganic vs. organic mercury)?

23. Figure 3.3: Bottom reaction sequence

The glutathione conjugate structure is incorrect, the chlorinated benzene ring needs to be connected to the S of GS not to G, and there should be no H.

The N-acetyl cysteine derivative has an incorrect chemical structure. You need to add -S-CH_2- between the chlorinated benzene ring and the -NAc.

The formula for pentachlorothiophenol is incorrect. There is no O.

The formula for pentachloroanisole is incorrect. A methyl group should be attached to the S not CH.

You need to show GSH (glutathione) as a reaction participant

Section 3.5 MECHANISMS OF ACTION
The propose of this section is to provide a brief overview of known mechanisms of metabolism, absorption, distribution, and excretion, and then a discussion of any substance reactions or physiological processes that may affect these mechanisms.
Have all possible mechanisms of action been discussed? If not, please explain.

24. p115 L29: Schlummer: I get 0.854% not 85.4%. The 1st sentence does not make sense in common with the conclusion on p115. The statement about the fat flush mechanism on p116 does not make sense either. Unless you can clarify, I recommend you delete as I suggest and keep to facts not speculation
25. p117 para 2: Hexachlorobenzene has just one lipophilicity; there needs to be a parameter that differs for blood and breast milk that accounts for the difference in hexachlorobenzene concentration.
26. p123 L5-11: Dioxin –like behavior from results of Mundy et al 2010,2012 provided as additional evidence for mechanism of toxicity.
27. p125 L5 : Add hirsutism as an axis effect.
Section 3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

28. p129: New reference (Pena et al 2012) reporting estrogenic effects in rats provided.

Section 3.7 CHILDREN'S SUSCEPTIBILITY

Section 3.8 BIOMARKERS OF EXPOSURE AND EFFECT

This section begins with standard language (in bold).
-Are the biomarkers of exposure specific for the substance or are they for a class of substances? If they are not specific, how would you change the text?
-Are there valid tests to measure the biomarker of exposure? Is this consistent with statements made in other sections of the text? If not, please indicate where inconsistencies exist.
-Are the biomarkers of effect specific for the substance or are they for a class of substances? If they are not specific, how would you change the text?
-Are there valid tests to measure the biomarker of effect? Is this consistent with statements made in other sections of the text? If not, please indicate where inconsistencies exist

29. p130 last para sent 1: New references for serum/blood for Cooney et al 2010; Den Hond et al 2011; Schettgen et al 2011 provided

Section 3.9 INTERACTIONS WITH OTHER CHEMICALS

Discuss the influence of other substances on the toxicity of the substance.
-Is there adequate discussion of the interactive effects with other substances? Does the discussion concentrate on those effects that might occur at hazardous waste sites? If not, please clarify and add additional references.
-If interactive effects with other substances are known, does the text discuss the mechanisms of these interactions? If not, please clarify and provide any appropriate references.

Section 3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

-Is there a discussion of populations at higher risk because of biological differences which make them more susceptible? Do you agree with the choices of populations? Why or why not? Are you aware of additional studies in this area?

Section 3.11 METHODS FOR REDUCING TOXIC EFFECTS

-Is the management and treatment specific for the substance, or is it general for a class of substances?
-Is there any controversy associated with the treatment? Is it a "well accepted" treatment?
-Are there any hazards associated with the treatment of populations that are

unusually susceptible to the substance (e.g., infants, children)

-Are treatments available to prevent the specific substance from reaching the target organ(s), or are the actions general for a class of substances?
-Is there any controversy associated with the treatment? Is it a "well-accepted" treatment? If the discussion concerns an experimental method, do you agree with the conceptual approach of the method?
-Are there any hazards associated with the treatment of populations that are unusually susceptible to the substance (e.g., infants, children)?
-Are there treatments to prevent adverse effects as the substance is being eliminated from the major organs/tissues where it has been stored (e.g., as a substance is eliminated from adipose tissue, can we prevent adverse effects from occurring in the target organ[s])?

-Are treatments available to prevent the specific substance from reaching the target organ(s), or are the treatment's actions general for a class of substances?
-Is there any controversy associated with the treatment? Is it a "well accepted" treatment? If the discussion concerns an experimental method, do you agree with the conceptual approach of the method?
-Are there any hazards associated with the treatment of populations that are unusually susceptible to the substance (e.g., infants, children)?

Existing Information on Health Effects of [Substance X]-- Figure 2-X
-Do you know of other studies that may fill a data gap? If so, please provide the reference

Identification of Data Needs
-Are the data needs presented in a neutral, non-judgmental fashion? Please note where the text shows bias.
-Do you agree with the identified data needs? If not, please explain your response and support your conclusions with appropriate references.
-Does the text indicate whether any information on the data need exists?
-Does the text adequately justify why further development of the data need would be desirable; or, conversely, justify the "inappropriateness" of developing the data need at present? If not, how can this justification be improved.

30. p142 end of para also p147 L5: Exploration of the dioxin-like behavior of HCB is recommended (Mundy et al 2010,2012) and on apoptosis (Luan et al 2012)

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

-Are you aware of any information or values that are wrong or missing in the chemical and physical properties tables? Please provide appropriate

references for your additions or changes.
Is information provided on the various forms of the substance? If not, please explain
31. p157 para 1 L5: :HCB is not a hydrocarbon.
32. p157 para 2: The fumes contain chlorine --they are not chlorides

CHAPTER 5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL
-Are you aware of any information that is wrong or missing? If so, please provide copies of the references and indicate where (in the text) the references should be included
33. p164 para 1 new last sent: Recent review reference for HCB re disposal and remediation is provided (Tong and Yuan 2012).

CHAPTER 6. POTENTIAL FOR HUMAN EXPOSURE
-Has the text appropriately traced the substance from its point of release to the environment until it reaches the receptor population? Does the text provide sufficient and technically sound information regarding the extent of occurrence at NPL sites? Do you know of other relevant information? Please provide references for added information.
-Does the text cover pertinent information relative to transport, partitioning, transformation, and degradation of the substance in all media? Do you know of other relevant information? Please provide references for added information.
-Does the text provide information on levels monitored or estimated in the environment, including background levels? Are proper units used for each medium? Does the information include the form of the substance measured? Is there an adequate discussion of the quality of the information? Do you know of other relevant information? Please provide references for added information.
-Does the text describe sources and pathways of exposure for the general population and occupations involved in the handling of the substance, as well as populations with potentially high exposures? Do you agree with the selection of these populations? If not, why? Which additional populations should be included in this section?
-For Sections 6.8.1, Identification of Data Needs and 6.8.2, Ongoing Studies, answer the same questions presented in Section 3.12.2, Identification of Data Needs and 3.12.3, Ongoing Studies.
34. p166 para 1 L10: The 1st sentence is incorrect. I can still buy HCB so it is still sold. It is true it is not manufactured in the U.S.
35. p166 para 2 L29: Emission data provided from specific sources (Antunes et al 2012; Liu et al 2012; Wegiel et al 2011
36. p168 para 1 L4: HCB used as referent compound for Bioconcentration factors in fish (Adolfsson-Erici et al 2012).
37. p178 new last para in soil section: Earthworms used as biosentinel for HCB (Vampre et al 2010)

CHAPTER 7. ANALYTICAL METHODS

-Are you aware of additional methods that can be added to the tables? If so, please provide copies of appropriate references.
-Have methods been included for measuring key metabolites mentioned previously in the text?
-If unique issues related to sampling for the substance exist, have they been adequately addressed in the text? What other discussion should be provided?
-For Section 7.3.1, Identification of Data Needs, answer the same questions presented in Section 3.12.2, Identification of Data Needs

CHAPTER 8. REGULATIONS AND ADVISORIES

-Are you aware of other regulations or guidelines that may be appropriate for the table? If so, please provide a copy of the reference.
38. p243: Use the 2012 ACGIH TLV-TWA (8-hr) of 0.002 mg/m^3 for workplace air (skin, A3 carcinogen). The notations (skin, A3 carcinogen) should be included.Change the date too.

CHAPTER 9. REFERENCES

-Are there additional references that provide new data or are there better studies than those already in the text? If so, please provide a copy of each additional reference.
39. See new references

UNPUBLISHED STUDIES (IF APPLICABLE TO REVIEW)

-For each of the unpublished studies included with the profile, prepare a brief evaluation that includes your assessment of the:
-Adequacy of design, methodology, and reporting;
-Validity of results and author's conclusions; and
-Study inadequacies or confounding factors.
-Provide a summary of your conclusions? Do you agree or disagree with those of the author? If not please explain why.