DISPOSITION OF PEER REVIEW COMMENTS FOR TOXICOLOGICAL PROFILE FOR 1-BROMOPROPANE

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Comments provided by Reviewer #1:

Comments on Charge Questions and Statements from the Guidelines for Peer Review of ATSDR's Toxicological Profiles

Charge question and statement: "Are there any data relevant to child health and developmental effects that have not been discussed in the profile and should be?"

COMMENT: All available information or data relevant to child health and developmental effects have been discussed in the profile.

RESPONSE: *No response is necessary.*

Charge question and statement: "Are there any general issues relevant to child health that have not been discussed in the profile and should be."

COMMENT: I do not find any issue.

RESPONSE: *No response is necessary.*

CHAPTER 1. PUBLIC HEALTH STATEMENT

Charge question and 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."

COMMENT: Page 4, line 8-9, It is better to add the concentration of exposure (see comment in the text). Also the relevance of these finding to human is unknown. It is very confusing to understand. I would suggest to revise, "since the exposure level of 1-bromopropane was very high, and not expected to occur in human exposure, the relevance of these findings to human is unknown."

RESPONSE: *The exposure levels was added. Also added was the text suggested by the Reviewer.*

Charge question and statement: "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. Are scientific terms used that are too technical or that require additional explanation? Please note such terms and suggest alternate wording."

COMMENT: See previous comments

RESPONSE: *No response is necessary.*

CHAPTER 2. RELEVANCE TO PUBLIC HEALTH

Charge question and statement: "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."

COMMENT: I agree with those effect known to occur in human.

RESPONSE: *No response is necessary.*

Charge question and statement: "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."

COMMENT: The effects only observed in animals are likely to be of concern to humans. There is limited data on human exposure and potential effects. Current observation or current data are not strong enough to conclude that these effects were only observed in animals. These is no study to examine whether exposure to 1-brompropane increase the risk of cancer. Further comparative studies between animals and human, especially the difference on the metabolism should be conducted.

RESPONSE: *The need to conduct further studies on differences in the metabolism between species is mentioned in the data needs section (Comparative Toxicokinetics).*

Charge question and statement: "Have exposure conditions been adequately described? If you do not agree, please explain."

COMMENT: Yes.

RESPONSE: *No response is necessary.*

CHAPTER 3. HEALTH EFFECTS
Section 3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE
Toxicity - Quality of Human Studies

Charge question and statement: "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)?"

COMMENT: Page 167 "MINIMAL RISK LEVEL (MRL) WORKSHEET"
There is a significant concern to use the data from this paper to deduce the MRL, Page 167 "MINIMAL RISK LEVEL (MRL) WORKSHEET"

This is a cross-sectional study, the cause-effect relationship could not be determined in this studies. The changes of these endpoints did not necessary relate to the exposure of 1-bromopropane.
There are several issues in this publication.

The first one is the selection bias. Even it was claimed that age, sex, and region-matched controls were conducted, it was unclear the criteria was used to **randomly** select

these controls. What was the pool population for the control selection? Convenience selection from an adjacent factories was not "random" selection. Declaration in the paper that "random sampling of the control" was conducted does not guarantee the fact that the selection of the sex and age-matched controls was a random process in the paper. The selection bias of the controls significantly affect the creditability of this study, especially there were no clear dose-dependent effect of endpoint observed within the low, medium and high exposure groups. As shown in Table 3, the highest dose did not reveal the highest changes of these endpoints.

Secondly, there are several factories involved in this study. As indicated in the paper, some factories previously produced 2-bromoprppane. 2-Bromopropane is confirmed to have reproductive and hematopoietic effects on workers. Also as indicated by the measurement of passive air samples, there were certain levels of 2-bromopropane. Therefore, the potential interaction of 1-bromopropane with 2-bromopropane has to be considered.

Thirdly, the seasonal difference in the 1-bromopropane exposures was significant in these small-scale factories. The door and windows were open during summer while the door or windows were closed during the winter. There were no indication of the dates of these personal samplers were taken. It seemed that most of these samples were taken during the summer times. Therefore, the passive samples were significantly under-estimated the actual exposure levels. Furthermore, there was no indication of the temperature of the day of these passive sampling. The temperature and atmosphere pressure are essential to convert the mass concentration (mg/m^3) to ppm. Although the paper cited their previous literature to support the number of rate used in the in the calculation of the TWA (ppm), no more information were found. This is the text from the one of papers cited, "The TWA concentration of each solvent was calculated based on the formula: TWA = absorbed solvent (mg)/sampling rate (mg/ppm X min) X sampling time (min). In our calculations, the values of 0.134 and 0.117 were used as the sampling rates of 1-bromo propane and 2-bromopropane, respectively." The key element of this measurement is the determination of the sample rate. It is not clear what kind of calculation led the author to get the number of 0.134 and 0.117. Obviously, these sample rates were be different under the different temperature and pressure level. The authors have used these sample rates regardless of the different temperature conditions. Therefore, the assessment of the concentration of exposure was questionable. The actual concentration (TWA) could be much higher than reported in the paper.

There were general discussion of jobs of these worker involves, but the specific job type of these individual female workers involved were not included in the analysis. The physical activities of these workers among the job types were significantly different, and inhalation rate were different, therefore, it might significantly affect the level of exposure. As indicated in the paper, dermal absorption could occur during the handling of the solvents. These factors also led to the under-estimation of actual exposure.

Although linear regression analysis was performed to confirm the trend with the exposure level or the product of exposure level and period of exposure, it was unclear what kind of levels for the selected control. It seemed that "zero" exposure were assumed for these workers in the control. However, there were no any measurements for the controls, and this assumption that the "Zero" exposure for the control workers might not true. This assumption-based investigation significantly affected the quality of the paper.

All together, the exposure assessment of 1-bromopropane might be significantly under-estimated, especially for the cumulative exposure. The use of the questionable assessment of exposure of 1-bromopropane might be somehow misleading in the risk assessment. As demonstrated by the huge variation of TWA from these workers, even within the one or two investigation periods, the grouping of low, mid and high exposure levels, especially cumulative exposures were questionable.

It is noted that ACGIH used this report to derive the TLV for 1-bromopropane. However, concern remains due to the exposure assessment of 1-bromoprpane in these workers, selection of the control works. I suggest a careful discussion before to use this data.

RESPONSE: *An extended discussion of the limitations of the Li et al. (2010) study is now presented in the revised MRL Rationale Statement document. Some of this discussion has also been incorporated into Appendix A.*

Charge question and statement: "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."

COMMENT: See previous comments.

RESPONSE: *No response is necessary.*

Charge question and statement: "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."

COMMENT: See previous comments.

RESPONSE: *No response is necessary.*

Charge question and statement: "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."

COMMENT: See previous comments.

RESPONSE: *No response is necessary.*

Charge question and statement: "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."

COMMENT: See previous comments.

RESPONSE: *No response is necessary.*

Charge question and statement: "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."

COMMENT: No more studies.

RESPONSE: *No response is necessary.*

Toxicity - Quality of Animal Studies

Charge question and statement: "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."

COMMENT: No concern.

RESPONSE: *No response is necessary.*

Charge question and statement: "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?"

COMMENT: Species differences in the toxicity of 1-bromopropane were observed. Discussion should be included since extrapolation from animal studies to human is a critical component. Mice is more hepatotoxic to 1-bromopropane and few studies were reported the neurotoxicity in mice. The extrapolation of animal studies to human should be discussed. Different metabolism of 1-bromopropane, especially the P450s seems to be involved in the neurotoxicity and reproductive toxicity (Garner et al 2006).

RESPONSE: *Section 3.5.3, Animal-to-Human Extrapolations, discusses the role of oxidative metabolism and conjugations reactions in the liver and sperm toxicity of 1-bromopropane in rats and mice. It also mentions that because nothing is known regarding the oxidative and conjugation capacities of the liver of humans towards 1-bromopropane, which species, rats or mice, is the better model to assess potential liver and sperm toxicity in humans is unknown. Gardner et al. (2006) do not discuss the role of metabolism in the neurotoxicity or reproductive toxicity of 1-bromopropane. Gardner et al. (2007) discuss the role of oxidative metabolism on the sperm toxicity of 1-bromopropane in mice; there is no discussion of neurotoxicity.*

Charge question and statement: "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)?"

COMMENT: Yes.

RESPONSE: *No response is necessary.*

Charge question and statement: "Were all appropriate NOAELs and LOAELs identified for each study? Were all appropriate toxicological effects identified for the studies? If not, please explain."

COMMENT: Yes.

RESPONSE: *No response is necessary.*

Charge question and statement: "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."

COMMENT: No discussion. The isoform of 2-bromopropane should be included.

RESPONSE: *It is unclear what the reviewer means by isoform. 2-Bromopropane is a different chemical. It would be inappropriate to include information on 2-bromopropane in the toxicological profile for 1-bromopropane.*

Charge question and statement: "Were the appropriate statistical tests used in the interpretation of the studies?"

COMMENT: No concern.

RESPONSE: *No response is necessary.*

Charge question and statement: "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. Levels of Significant Exposure (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.""

COMMENT: Yes.

RESPONSE: *No response is necessary.*

Charge question and statement: "Do you agree with the categorization of "less serious" or "serious" for the effects cited in the LSE tables?"

COMMENT: Yes.

RESPONSE: *No response is necessary.*

Charge question and statement: "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?"

COMMENT: See comments in the text.

RESPONSE: *An extended discussion of the limitations of the Li et al. (2010) study is now presented in the revised MRL Rationale Statement document. Some of this discussion has also been incorporated into Appendix A.*

Evaluation of Text

Charge question and statement: "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?"

COMMENT: NO. Please refer previous comments in the Page 167 "MINIMAL RISK LEVEL (MRL) WORKSHEET".

RESPONSE: *An extended discussion of the limitations of the Li et al. (2010) study is now presented in the revised MRL Rationale Statement document. Some of this discussion has also been incorporated into Appendix A.*

Charge question and statement: "Has the effect, or key endpoint, been critically evaluated for its relevance in both humans and animals?"

COMMENT: Yes.

RESPONSE: *No response is necessary.*

Charge question and statement: "Have "bottom-line" statements been made regarding the relevance of the endpoint for human health?"

COMMENT: Yes.

RESPONSE: *No response is necessary.*

Charge question and statement: "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."

COMMENT: Yes.

RESPONSE: *No response is necessary.*

Charge question and statement: "Has adequate attention been paid to dose-response relationships for both human and animal data? Please explain."

COMMENT: NO. In the Page 167 "MINIMAL RISK LEVEL (MRL) WORKSHEET". Please refer previous comments. No typical dose-response were observed in the workers, but there was no discussion. Dose-response relationships between neurological tests (tibial motor DL, sural NCV and vibration test in females) and 1-bromopropane exposure level, which are the basis of their main conclusion, are not monotone (Table 3). In any of 3 tests, the mean level of the highest exposure group returns to the level of the control group, which poses a question on dose-dependent toxicity of the compound.

RESPONSE: *An extended discussion of the limitations of the Li et al. (2010) study is now presented in the revised MRL Rationale Statement document. Some of this discussion has also been incorporated into Appendix A.*

Charge question and statement: "Has the animal data been used to draw support for any known human effects? If so, critique the validity of the support."

COMMENT: Not really.

RESPONSE: *Without further elaboration, it is difficult to determine what the reviewer specifically means. Page 8, line 25 states: "**Results from animal studies support that exposure to 1-bromopropane can result in neurotoxicity."** At the end of every section (i.e., respiratory, renal, endocrine, reproductive, etc.), there are statements regarding the relevance of the animal findings to humans.*

Section 3.4 TOXICOKINETICS

Charge question and statement: "Is there adequate discussion of absorption, distribution, metabolism, and excretion of the substance? If not, suggest ways to improve the text."

COMMENT: Yes.

RESPONSE: *No response is necessary.*

Charge question and statement: "*Have the major organs, tissues, etc. in which the substance is stored been identified? If not, suggest ways to improve the text."*

COMMENT: No. Please use recent PBPK model to address this issue (Garner et al 2015).

RESPONSE: *The PBPK model of Garner et al. (2015) has been summarized in the appropriate section.*

Charge question and statement: "Have all applicable metabolic parameters been presented? Have all available pharmacokinetic/pharmacodynamic models and supporting data been presented? If not, please explain."

COMMENT: Yes.

RESPONSE: *No response is necessary.*

Charge question and statement: "Is there adequate discussion of the differences in toxicokinetics between humans and animals? What other observations should be made?"

COMMENT: NO. Please refer recent publication of PBPK model (Garner et al. 2015).

RESPONSE*: A summary of the PBPK model developed by Garner et al. (2015) has been included in the profile.*

Charge question and statement: "Is there an adequate discussion of the relevance of animal toxicokinetic information for humans? If not, please explain."

COMMENT: NO. Please refer recent publication of PBPK model (Garner et al. 2015).

RESPONSE: *Section 3.5.3, Animal-to Human-Extrapolations, has been expanded and includes a brief discussion on the relevance of animal toxicokinetic information for humans.*

Section 3.5 MECHANISMS OF ACTION

Charge question and statement: "Have all possible mechanisms of action been discussed? If not, please explain."

COMMENT: Yes.

RESPONSE: *No response is necessary.*

Section 3.8 BIOMARKERS OF EXPOSURE AND EFFECT

Charge question and statement: "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?"

COMMENT: Yes.

RESPONSE: *No response is necessary.*

Charge question and statement: "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."

COMMENT: Yes.

RESPONSE: *No response is necessary.*

Charge question and statement: "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?"

COMMENT: No.

RESPONSE: *No response is necessary.*

Charge question and statement: "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."

COMMENT: No.

RESPONSE: *No response is necessary.*

Section 3.9 INTERACTIONS WITH OTHER CHEMICALS

Charge question and statement: "Is there adequate discussion of the interactive effects with other substances?"

COMMENT: No. The potential interaction of 1-bromopproane with 2-bromopropane should be discussed.

RESPONSE: *No studies were located discussing interactions between 1-bromopropane and 2-bromopropane.*

Charge question and statement: "Does the discussion concentrate on those effects that might occur at hazardous waste sites? If not, please clarify and add additional references."

COMMENT: Yes.

RESPONSE: *No response is necessary.*

Section 3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

Charge question and statement: "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?"

COMMENT: Not found any discussion.

RESPONSE: *No information regarding sensitive human population was located in the studies available for review.*

Section 3.11 METHODS FOR REDUCING TOXIC EFFECTS

Charge question and statement: "Is the management and treatment specific for the substance, or is it general for a class of substances?"

COMMENT: No.

RESPONSE: *No response is necessary.*

Charge question and statement: "Is there any controversy associated with the treatment? Is it a "well accepted" treatment?"

COMMENT: No.

RESPONSE: *No response is necessary.*

Charge question and statement: "Are there any hazards associated with the treatment of populations that are unusually susceptible to the substance (e.g., infants, children)?"

COMMENT: No.

RESPONSE: *No response is necessary.*

Charge question and statement: "Are treatments available to prevent the specific substance from reaching the target organ(s), or are the actions general for a class of substances?"

COMMENT: No.

RESPONSE: *No response is necessary.*

Charge question and statement: "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?"

COMMENT: No.

RESPONSE: *No response is necessary.*

Charge question and statement: "Are there any hazards associated with the treatment of populations that are unusually susceptible to the substance (e.g., infants, children)?"

COMMENT: No.

RESPONSE: *No response is necessary.*

Charge question and statement: "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])?"

COMMENT: No.

RESPONSE: *No response is necessary.*

Charge question and statement: "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?"

COMMENT: No.

RESPONSE: *No response is necessary.*

Charge question and statement: "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)?"

COMMENT: No.

RESPONSE: *No response is necessary.*

Section 3.12 ADEQUACY OF THE DATABASE

Charge question and statement: "Do you know of other studies that may fill a data gap? If so, please provide the reference."

COMMENT: Physiologically Based Pharmacokinetic Modeling for 1-Bromopropane in F344 Rats Using Gas Uptake Inhalation Experiments Toxicol. Sci. (2015) 145(1): 23 36.doi: 10.1093/toxsci/ kfv018

RESPONSE: *Information from the Gardner et al. (2015) PBPK study was added to the profile.*

Identification of Data Needs

Charge question and statement: "Are the data needs presented in a neutral, non-judgmental fashion? Please note where the text shows bias."

COMMENT: Yes.

RESPONSE: *No response is necessary.*

Charge question and statement: "Do you agree with the identified data needs? If not, please explain your response and support your conclusions with appropriate references."

COMMENT: No. Please see listed in the text.

RESPONSE: *There is only one comment in the data needs section and it is regarding the PBPK model recently published by Gardner et al. (2015). That study was added to the profile.*

Charge question and statement: "Does the text indicate whether any information on the data need exists?"

COMMENT: No.

RESPONSE: *No response appears necessary.*

Charge question and statement: "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."

COMMENT: No.

RESPONSE: *No response appears necessary.*

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

Charge question and statement: "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."

COMMENT: No.

RESPONSE: *No response is necessary.*

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

Charge question and statement: "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."

COMMENT: No.

RESPONSE: *No response is necessary.*

CHAPTER 6. POTENTIAL FOR HUMAN EXPOSURE

Charge question and statement: "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."

COMMENT: Yes.

RESPONSE: *No response is necessary.*

Charge question and statement: "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."

COMMENT: Yes.

RESPONSE: *No response is necessary.*

Charge question and statement: "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."

COMMENT: Yes.

RESPONSE: *No response is necessary.*

Charge question and statement: "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?"

COMMENT: Yes.

RESPONSE: *No response is necessary.*

CHAPTER 7. ANALYTICAL METHODS

Charge question and statement: "Are you aware of additional methods that can be added to the tables? If so, please provide copies of appropriate references."

COMMENT: No.

RESPONSE: *No response is necessary.*

Charge question and statement: "Have methods been included for measuring key metabolites mentioned previously in the text?"

COMMENT: Yes.

RESPONSE: *No response is necessary.*

Comments provided by Reviewer #2:

The Reviewer noted that the present profile reviewed comprehensively epidemiological and experimental studies on health effects of 1-bromopropane, biomarkers of exposure and effects and proposed minimal exposure limit. Almost information collected is relevant, but there are some incorrect citations and interpretations on important research articles, as outlined below.

COMMENT: ***Endocrine effect:*** This profile mention that the limited human data and the animal data available do not indicate that the endocrine endpoints are sensitive targets of 1-bromopropane toxicity (p48, line 20-21), but the present reviewer believe that endocrine system may be involved with reproductive effects of 1-bromopropane through suppression of the central nervous system induced by exposure to 1-bromopropane. Weight of seminal vesicle is known to be a good biomarker reflecting blood testosterone level. In Ichihara 2000a study, seminal vesicle decreased at 200 ppm of the lowest exposure concentration, although testosterone deceased at 400 ppm or over. The profile missed the biological significance of decrease in seminal vesicle.

RESPONSE: *The comment refers to a summary statement that appears at the end of the section on Endocrine Effects on page 29 (not 48) indicating that the limited data in humans and the animal data do not suggest that endocrine end points are particularly sensitive targets for 1-bromopropane toxicity. ATSDR believes that the statement is correct because neurological and hepatic effects have been reported at lower exposure concentrations in other intermediate-duration studies. In the study that the reviewer suggested adding to the profile (Banu et al. 2007), also authored by Ichihara, absolute and relative seminal vesicle weights were significantly reduced in rats exposed for 6 weeks to 1,000 ppm 1-bromopropane, but not in rats exposed to 400 ppm 1-bromopropane. In any case, the Ichihara et al. (2000a) entry in the LSE table was revised and now indicates that the study LOAEL was 200 ppm 1-bromopropane for reduced weight of the seminal vesicle.*

COMMENT: ***Different mechanism depending on the exposure levels:*** On the other hand, the profile also should evaluate the different endpoints depending on the exposure levels. Character of reproductive effect of 1-bromopropane is very different depending on the exposure level. At lower exposure levels of 400 ppm, exposure to 1-bromopropane did not reduced spermatogenic cells including spermatogonia, preleptotene spermatocyte, pachytene spermatocyte and round spermatid at stage VII but only increased retained sperm in stage IX-XI, showing spermiation failure, but at 1000 ppm exposure to 1-bromopropane degenerated spermatogenic cells. The former change was reversible but the latter was irreversible during the observation period. The above study suggest different mechanism operates depending on the exposure levels.

RESPONSE: *Information from the study by Banu et al. (2007) was added to the profile and the possibility of two different mechanism operating at different exposure concentrations is mentioned in section 3.2.1.5, Reproductive Effects, and in the Mechanism of Toxicity section.*

COMMENT: Banu et al. 2007 should be cited.

RESPONSE: *Data from Banu et al. (2007) were added to appropriate sections of the profile, as well as to the LSE table.*

COMMENT: ***Decreased vibration sense is less serious or serious:*** The profiles classified the decreased vibration sense as less serious endpoint, but it is not known whether this end point is

accompanied by degeneration of peripheral nerve or deep sense pathway in the central nervous system. The latter explain 1-bromopropane-inducing sensory ataxia in human cases (Samukawa et al. 2010, Majersik et al. 2007).

RESPONSE: *There is some judgement involved in the in the classification of effects as less serious or serious. Decreased vibration sense, as reported in Li et al. (2010), does not seem as an effect that would lead to severe morbidity or mortality, which is why it is classified as less serious. The case described by Samukawa et al. (2012) occurred in an individual who was exposed to an estimated 553 ppm 1-bromopropane, 430 times higher than the mean exposure concentration of 1.28 ppm reported by Li et al. (2010). In the case described by Majersik et al. (2007), the individual was exposed to an estimated mean concentration of 130 ppm 1-bromopropane, 100 times higher than the 1.28 ppm reported by Li et al. (2010). Decreased vibration sense is a real effect and is probably a good indicator that serious neurological effects can occur, but at much higher exposure concentrations.*

COMMENT: ***Research Needs: Cognitive problem, exposure assessment and biomarker in epidemiological study:***

Human cases showed memory problem or cognitive dysfunction (Ichihara 2002, Majersik 2007) and an epidemiological study (Li et al. 2010) showed lower score of Benton's cognitive test in 1-bromopropane-exposed workers. As this end point is serious one, follow up study on intoxicated cases and also long-term cohort study on the workers is needed for investigating cognitive function in 1-bromopropane exposed workers.

Additionally, epidemiological study with improved exposure assessment is needed to obtain clearer dose-response relationship in humans that base the occupational exposure limit, as Li et al. 2010 study has limitation in estimating cumulative exposure level.

Along with development of PBPK model, development of biomarker which is involved in mechanism of 1-bromopropane neurotoxicity is also needed for extrapolation from animals to humans.

RESPONSE: *The existing text in the section on neurotoxicity in the data needs section states that prospective studies of 1-bromopropane workers are necessary and that these studies should pay especial attention to vibration sense as well as to neurophysiological and neurobehavioral parameters. Improved procedures for assessing exposure has also identified as a data need. A PBPK model has been developed for 1-bromopropane in rats and is now discussed in the profile.*

COMMENT: ***Child health and developmental effects*****:** As data relevant to child health and developmental effects, there is another BSOC' study conducted by Huntingdon Life Sciences, Study No. 98-4141 A developmental study in rat via whole body inhalation exposure. 23 August 2001. In small or home industry, it is possible that children be exposed to hazardous chemicals, as living room might not be separated from the workplace completely. Regarding the developmental effects, there is difference in development between human and rodents. In spite of the difference, the key events of neurological development is almost consistent between humans and rodents (Semple et al. Brain development in rodents and humans: Identifying benchmarks of maturation and vulnerability to injury across species. Progress in Neurobiology 2013)

RESPONSE: *ATSDR is trying to obtain a copy of the unpublished developmental study mentioned by the reviewer.*

LSE Table Comments:

COMMENT: Regarding entry #61 in Table 3-1, the Reviewer states that the reduced neurogenesis in the hippocampus, listed as a less serious effect might be a serious event. The Reviewer seems to suggest that it should be move to the serious column.

RESPONSE: *ATSDR agrees with the reviewer and the effect was moved to the serious column.*

COMMENT: Regarding entry #20 in Table 3-1, the Reviewer states that the alterations in the myofilaments in the soleus muscle, listed as a less serious effect might be a serious effect. The Reviewer seems to suggest that it should be move to the serious column.

RESPONSE: *ATSDR agrees with the Reviewer and the effect was moved to the serious column.*

Unpublished Studies:

COMMENT: ***Albemarle 1997:*** The design and methodology was adequate for evaluating general toxicity, but not designed for evaluating neurotoxicity. Pathological method was conventional and perfusion, which is absolutely required for evaluation of the central nervous system, was not conducted. For peripheral nerve, examination with unraveled nerve after post-fixation with osmium was not conducted. It is very difficult to find degenerated peripheral nerve unless this unravelling method is used. For observation on peripheral nerve on section, semi-thin or ultra-thin sectioning after embedding the samples with Epoxy resin. Regarding evaluation on reproductive toxicity, evaluation on seminiferous tubules of specified stages or counting of the oocyte or follicles using serial sectioning was not conducted. As a regular toxicological study, this is relevant, but is not sufficient for evaluation of neurotoxicity or reproductive toxicity.

ElfAtoChem 1993: This is an acute oral toxicity study. The study design is sound and well performed. The conclusion just gives LD_{50} of 1-bromopropane by oral route. It gives less information explaining health effects of 1-bromopropane in humans in occupational settings.

ElfAtoChem 1995: This study is acute dermal toxicity study. The study design is sound, but the result is negative. The study provide little information on dermal toxicity of 1-bromopropane.

ElfAtoChem 1997: This is an acute toxicity study to determine 50% lethal concentration. It is difficult to extrapolate the result of this study to humans exposed to 1-bromopropane in occupational settings, as the exposure level is extremely high.

WIL: This is a complete two generation study. Study design is sound and the reporting is very well. Conclusion is well written and summarized. Especially decrease in brain in F0, F1 and F2 must be very important, but this is written only in the result section, but in conclusion decrease in brain is just briefly written. Decrease in brain in pups might be very important, as it suggest neuro-developmental effect, which is one of major concerns with environmental chemicals.

RESPONSE: *No response is necessary.*

Comments provided by Reviewer #3:

Public Health Statement

COMMENT: p. 5, lines 16-21: Although these are "boiler plate" statements, it might be worth mentioning that regulations and recommendations may also be based on human studies.

RESPONSE: *The comment refers to boilerplate text in the section WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH? The reviewer's suggestion will be considered for incorporation into all Toxicological Profiles.*

Relevance to Public Health

COMMENT: p. 7, lines 18 & 19: Does 1-bromopropane (1-BP) or the hydroxy radicals have a half-life of 14 days? I assume this pertains to 1-BP.

RESPONSE: *The half-life of 14 days refers to 1-bromopropane. The statement was amended to make this more apparent.*

COMMENT: p. 11, lines 21, 25 & 28: Should an adverse effect that was initially manifest on day 14 of a 3-week study be utilized to derive an acute-duration MRL? This introduces considerable conservatism, as Honma et al. (2003) saw no significant effect of 1-BP on grip strength after 1 or 7 daily 8-hour 1,000-ppm exposures.

Use of the $BMCL_{1SD}$, in effect, introduces a 10-fold uncertainty factor (UF). Upon equivalent inhalation exposures, rats absorb significantly more volatile organic chemicals (VOCs) than do humans. Rats have a higher alveolar minute volume, higher blood:air partition coefficient, greater pulmonary perfusion rate and a higher 1-BP metabolic rate (Bruckner et al., 2013). All of these processes enhance systemic uptake (i.e., internal dose). This should offset the default 3x interspecies pharmacodynamic UF.

RESPONSE: *Using an adverse effect that manifested after 14 days of exposure is in accordance with ATSDR's guidance for MRL derivation and is in line with ATSDR's conservative approach to address public health issues. Acute-duration MRLs are supposed to protect for an exposure-duration window of up to 14 days.*

It is unclear what the Reviewer means by the $BMCL_{1SD}$ introducing a 10-fold uncertainty factor. Because rats would appear to be more susceptible to humans to volatile organic chemicals, based on the factors mentioned by the reviewer, the use of dosimetric adjustment to calculate the MRL obviates the need of a 10-fold UF for interspecies extrapolation, so a UF of 3 is used.

COMMENT: p. 12, lines 24-34: I concur with the document authors' dismissal of hepatotoxicity as a likely adverse effect of 1-BP in humans. More emphasis, however, should be placed on spermatoxicity as a sensitive end point. Spermatotoxicity occurs in rodents and humans in response to a number of brominated propanes and ethanes. 1,2-Dibromo-3-chloropropane (DBCP) is the classic male reproductive toxicant. 1,2,3-Tribromopropane and 1,3-dibromopropane also adversely affect a number of male reproductive parameters. Easley et al. (2015) reported that 2-bromopropane reduced human spermatocyte viability via formation of reactive oxygen species. Even 1,2-dichloropropane has been reported to cause testicular degeneration and reduced sperm counts in rats (Bruckner et al., 1989).

Brominated alkanes are more potent than chlorinated congeners, because they are more readily bioactivated by glutathione transferases to reactive, cytotoxic episulfonium ions (Lag et al., 1991). Liu et al. (2009) reported decreased sperm counts, decreased sperm mobility and increased sperm with abnormal heads in mice at 50 ppm, the lowest vapor concentration of 1-BP tested. The actual LOAEL may have been lower. The acute inhalation MRL for 1-BP has been based in this document on a LOAEL of 200 ppm for decreased grip strength. The intermediate duration MRL has been based on a LOAEL of 500 ppm for increase in spontaneous motor activity. The sperm abnormalities appear more overtly injurious than modified grip strength and locomotor activity, which are apparently reversible manifestations of sedation. Banu et al. (2001) reported that inhalation of 1,000 ppm 1-BP for 6 weeks cause substantial reduction in hindlimb muscular strength, as well as persistent depletion of spermatogenic cells in rats 14 weeks after cessation of the 1-BP exposure.

RESPONSE: *The comment refers to the discussion of the intermediate-duration data considered for derivation of an intermediate-duration inhalation MRL for 1-bromopropane. ATSDR would like to clarify that the acute-duration inhalation MRL for 1-bromopropane was based on a $BMCL_{1SD}$ of 97.40 ppm 1-bromopropane for decreased grip strength, not on a LOAEL of 200 ppm as stated by the Reviewer. In addition, the intermediate-duration inhalation MRL was based on a NOAEL of 10 ppm 1-bromopropane for increased spontaneous locomotor activity, not on a LOAEL of 500 ppm 1-bromopropane as stated by the Reviewer. ATSDR agrees with the Reviewer in that in the Liu et al. (2009) study, the true LOAEL may have been lower than 50 ppm 1-bromopropane, the lowest concentration tested.*

The Reviewer stated: "The sperm abnormalities appear more overtly injurious than modified grip strength and locomotor activity, which are apparently reversible manifestations of sedation." ATSDR would like to note that the intermediate-duration inhalation MRL is based on ***increased*** *locomotor activity, which is a response opposite to manifestation of sedation. As noted by Honma et al. (2003), however, sedation did occur in rats exposed to 1,000 ppm 1-bromopropane.*

Sperm parameters did not seem to be a particular sensitive target for 1-bromopropane in other studies in rodents. In the comprehensive 2-generation reproductive toxicity study in rats performed by WIL Research Laboratories (BSOC 2001), significant alterations in sperm parameters were reported at ≥500 ppm 1-bromopropane, but not at 250 ppm. The reported results of Banu et al. (2001) mentioned by the Reviewer are consistent with the finding of BSOC (2001). In the NTP (2011) 14-week study in mice, sperm alterations were also reported at ≥500 ppm 1-bromopropane, but not at 250 ppm.

In summary, ATSDR believes the neurological alterations reported in rats exposed to 10 ppm 1-bromopropane for 3 weeks in the study by Honma et al. (2003) are an appropriate choice for derivation of an intermediate-duration inhalation MRL for 1-bromopropane.

COMMENT: p. 13, lines 3-5: Honma et al. (2003) state in their Abstract that ambulation and rearing scores in their 50-ppm rats were increased over control values. Thus, 50 ppm is used as a LOAEL in calculation of the intermediate duration inhalation MRL. Scrutiny of data in their Figure 5 reveals overlap of control and 50 ppm SE bars for Freezing and Ambulation. There does not appear to be overlap of SE (or SD) bars for Rearing, although only the 200 ppm values for Rearing and Ambulation are designated as being significantly different from controls.

RESPONSE: *The intermediate-duration inhalation MRL is based on a NOAEL of 10 ppm for no significant changes in spontaneous locomotor activity, as shown in Figure 3 of Honma et al. (2003). The LOAEL was 50 ppm, but the LOAEL was not used in the calculation of the intermediate-duration inhalation MRL. The reviewer is correct in that, according to Figure 5 of Honma et al. (2003),*

ambulation and rearing are increased in the group exposed to 50 ppm compared to the control group, but the differences with the control group do not appear to be significant (there is no asterisk indicating statistical significance). This only means that the statement in the abstract in Honma et al. (2003) is not accurate. Figure 5 was not involved in the derivation of any MRLs for 1-bromopropane.

COMMENT: p. 14, lines 3 & 4: The effects on vibration sense, tibial motor distal latency, sural nerve conduction velocity and POMS indices do not appear to be dose-dependent, judging from the median and cumulative values for the low, middle and high exposure groups in Tables 3 and 6 of Li et al. (2010). What is the toxicological significance of diminished perception of vibration? The authors note that clinical vibration assessment using a tuning fork is inherently inaccurate.

RESPONSE: *An extended discussion of the limitations of the Li et al. (2010) study is now presented in the revised MRL Rationale Statement document. Some of this discussion has also been incorporated into Appendix A.*

COMMENT: p. 18, lines 9 & 10: Elf AtoChem S.A. (1997) observed acute inflammation with edema and PMN neutrophil accumulation, not emphysema.

RESPONSE: *The comment refers to the sentence: "At necropsy, pulmonary lesions consisting of edema and emphysema were observed' which appears in Section 3.2.1.1, Death. Page 20 of Elf AtoChem S.A. (1997), under CONCLUSION, states that: "Mortality induced by n-Propyl Bromide is due to an acute respiratory deficiency associated to an acute inflammation of lung, with pulmonary emphysema and oedema." There is no mention of PMN neutrophil accumulation as being related to death. The toxicological profile mentions the PMN neutrophil accumulation under Hematological Effects.*

Health Effects

COMMENT: p. 22, line 22: I believe the second "not" should be omitted. See Editorial change made in text.

RESPONSE: *The sentence was corrected.*

COMMENT: p. 24, line 10: Are the document's authors certain that the decrease in grip strength described by Honma et al. (2003) is solely of neurological origin, and not due to an effect on skeletal muscle?

RESPONSE: *There is no evidence of gross or microscopic alterations of skeletal muscle histological from other studies, at least at exposure concentrations ≤400 ppm 1-bromopropane, as the text in the profile indicates. No studies were available that evaluated electrophysiological parameters of skeletal muscles from animals exposed to 1-bromopropane.*

COMMENT: p. 25, line 31: Although the LOAEL for hepatotoxicity in the Albemarle Co. (1997) study is said here to be 600 ppm, they did report centrilobular vacuolation in 3 of 15 male rats and in 1 of 15 female rats at 400 ppm.

RESPONSE: *Unless otherwise stated, the effects mentioned in the text of the profile refer to statistically significant differences with controls. The NOAEL for histopathology is stated to be 400 ppm in the last paragraph of page 24 because 3/15 and 1/15 are not statistically different from control (0/15) according to Fisher's Exact Test.*

COMMENT: p. 33, lines 2-28: I noted previously that the findings of Li et al. (2010) about key parameters, judging from the raw data, do not appear to be dose-dependent. Have their data and statistical analyses been reviewed by statisticians? I would strongly advise this.

RESPONSE: *An extended discussion of the limitations of the Li et al. (2010) study is now presented in the revised MRL Rationale Statement document. Some of this discussion has also been incorporated into Appendix A.*

COMMENT: p. 36, lines 18-21: Please comment on the neurotoxicological significance of increased spontaneous locomotor activity. Could this be a manifestation of the initial excitatory phase of VOC-induced CNS depression? Kim et al. (1999), as related in lines 29 and 30 of the preceding page, saw decreased activity and mild ataxia at higher inhaled concentrations. Is increased spontaneous motor activity really a toxicologically-significant end point on which a MRL should be based? Please justify.

RESPONSE: *Spontaneous locomotor activity has been used for decades to evaluate the effects of chemicals. Both decreases and increases in activity are considered toxicologically significant effects. See for example Moser V. 2011, Functional assays for neurotoxicity testing. Toxicologic Pathology 19: 36-45, or U.S. EPA 1998, Guidelines for Neurotoxicity Risk Assessment, EPA/630/R-95/001F. As mentioned in EPA (1998), some chemicals (i.e., toluene, xylene, triadimefon) produce transient increases in activity by increasing neurotransmitter release, while other chemicals (i.e., trimethyltin) produce permanent increases in motor activity by destroying specific regions of the brain (i.e., hippocampus). It is not uncommon to see U-shaped responses due to inhibition of inhibitory pathways at low doses, resulting in increased activity, and inhibition of excitatory pathways as the doses increase, resulting in decrease activity (i.e., sedation). Increased activity relative to an untreated group can also occur due to delayed habituation to a novel environment.*

COMMENT: p. 51, lines 8-30: I could not locate any published papers on the absorption or pharmacokinetics (PK) of inhaled 1-BP. Nevertheless, it would be worthwhile to point out that 1-BP is a relatively small, volatile, uncharged, lipophilic molecule (i.e., a VOC). VOCs, as a class, are very rapidly and extensively absorbed from the alveoli (Bruckner et al., 2013). % Systemic absorption of 1,1,1-trichloroethane, a VOC with comparable physicochemical properties, varies from 50-60% in rats, depending on the inhaled concentration and duration of exposure (Dallas et al., 1989). Recent findings of Garner et al. (2015) suggest a rapid uptake of inhaled 1-BP by rats.

RESPONSE: *The absorption section was amended with information from Garner et al. (2015) about the rapid and extensive absorption by the respiratory tract.*

COMMENT: p. 51, lines 34 & 35: Garner et al. (2015) developed a PBPK model that predicted some accumulation of 1-BP in arterial blood and fat of humans exposed 8 hours/day for 5 days.

RESPONSE: *Discussion of simulated results from the Garner et al. (2015) rat and human PBPK models was added to Section 3.4.5.*

COMMENT: p. 52, line 29: I assume it is implied here that the glutathione (GSH) pathway is important quantitatively in humans.

RESPONSE: *The phrase "an important pathway in humans" was changed to "a quantitatively important pathway in humans."*

COMMENT: p. 59, line 23: Terminal elimination half-times increased (rather than decreased) with increasing air concentrations of 1-BP.

RESPONSE: *"Decreased" was replaced with "increased."*

COMMENT: p. 61, lines 23 & 24: See the recently published PBPK model by Garner et al. (2015).

RESPONSE: *A description of the rat and human models and an evaluation of their utility for risk assessment purposes was included.*

COMMENT: p. 63, lines 2 & 3: 1-BP will be readily absorbed by passive diffusion.

RESPONSE: *A similar statement was added.*

COMMENT: p. 63, lines 5-9: 1-BP, like other VOCs, will be widely distributed throughout the body according to tissues' blood flow and lipid content. The brain will initially receive a relatively high concentration, but the lipophilic chemical will largely redistribute to adipose tissue, from which release will be delayed/prolonged.

RESPONSE: *The text was modified to better reflect data on time aspects of distribution of 1-bromopropane, as suggested by the Reviewer's comment.*

COMMENT: p. 64, line 28: Please define PPI and CA1 the initial time they are used in this subsection, as well as other abbreviations on the following pages.

RESPONSE: *As many as possible have been defined. CA1 refers to a specific area of the mammalian hippocampus. CA stands for cornu Ammon, Latin for Ammon's horn, for the shape of the hippocampus. Including such an explanation in the text of the profile is unnecessary.*

COMMENT: p. 68, line 5: The authors of this section have not commented on the possible identities of neurotoxic moieties. Is the parent compound suspect, or are certain metabolites more likely suspects? Any studies on the influence of CYP or GSH inducers or inhibitors, or null strains of mice on neurotoxic potency?

RESPONSE: *ATSDR is not aware of studies that examined the influence of CYP or GSH inducers or inhibitors or null strains of mice on the neurotoxicity of 1-bromopropane. A summary statement was added at the end of the Mechanism of Neurotoxicity section indicating that the neurotoxic moiety(s) has*

not been identified. Text was added also to the data needs section stating that studies aimed at identifying the entity responsible for the neurotoxicity of 1-bromopropane would be valuable.

COMMENT: p. 68, lines 22-27: It should be pointed out that the findings of Liu et al. (2009) regarding species differences also support oxidative stress as a mechanism of 1-BP-induced hepatotoxicity and spermatoxicity. Mice are much more susceptible to both toxicities that rats. Mice have greater capacity via CYPs to oxidize 1-BP and are much less efficient in detoxifying the oxidative metabolites.

RESPONSE: *Data from Liu et al. (2009) regarding the role of oxidative stress in spermatoxicity was added to the section on Mechanisms of Testicular Toxicity.*

COMMENT: p. 68, lines 29-34: Cite the aforementioned findings of Liu et al. (2009), as well as the results of Garner et al. (2007), who found that CYP2E1-catalyzed oxidation contributes to spermatotoxicity.

RESPONSE: *Data from Liu et al. (2009) and Garner et al. (2007) were added to the section on Mechanisms of Testicular Toxicity.*

COMMENT: p. 69, lines 13-17: It would be worthwhile in this section to cite the NTP (2013) Monograph on 1-Bromopropane, as it contains considerable information on several aspects of the chemical's carcinogenicity in rodents, including the logic for its human cancer designation.

RESPONSE: *Citation to the NTP (2013) Monograph on 1-bromopropane was added to the section on Mechanisms of Carcinogenicity.*

COMMENT: p. 73, lines 1-4: It may be a good idea to cite a more recent and inclusive review article on the ontogeny of cytochromes P450. I suggest Hines (2007) (See Additional References).

RESPONSE: *The comment refers to boilerplate text. ATSDR will consider the Reviewer's suggestion.*

COMMENT: p. 73, line 14: You may want to cite a paper by Bruckner (2000) that gives an overview of the NRC (1993) panel process and some of its more important findings about potential susceptibilities and resistance of children to chemical injury.

RESPONSE: *The comment refers to boilerplate text. ATSDR will consider the Reviewer's suggestion.*

COMMENT: p. 75, lines 33-35: As mentioned previously, spermatotoxicity in rodents and humans is a relatively sensitive end point. Sperm counts, motility and morphology could readily be monitored in 1-BP-exposed male workers.

RESPONSE*: It is true that sperm parameters could readily be monitored in male workers exposed to 1-bromopropane. However, the point is that abnormal sperm parameters is not specific for 1-bromopropane exposure. Many other chemicals or conditions not related to exposure to 1-bromopropane can induce sperm abnormalities.*

COMMENT: p. 76, lines 17 & 18: Chemicals that deplete reduced GSH could enhance oxidant damage by 1-BP. Chemicals that significantly induce or inhibit CYP2E1 would logically be anticipated to alter 1-BP metabolic activation, resulting in increased or decreased toxicity.

RESPONSE: *The comment refers to the sentence: "In general, chemicals that interfere with CYP enzymes or glutathione are likely to affect the metabolism of 1-bromopropane," which appears in Section 3.9, INTERACTIONS WITH OTHER CHEMICALS. A statement was added indicating that this could result in increased or decreased toxicity.*

COMMENT: p. 77, line 13: It would be worthwhile to point out that mice are considerably more susceptible to 1-BP-induced hepatotoxicity and spermatoxicity than rats. As recounted in the discussion section of the paper by Liu et al. (2009), the greater susceptibility of mice is likely due to higher CYP2E1-catalyzed production of cytotoxic metabolites. Lower reduced GSH levels in mice may also play a role in increased sensitivity to cellular injury.

RESPONSE: *The comment refers to Section 3.10, POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE. Text suggested by the Reviewer was added.*

COMMENT: p. 78, lines 20 & 21: There is substantial evidence that CYP2E1-catalyzed oxidation contributes to 1-BP induced spermatoxicity and hepatotoxicity (Garner et al., 2006, 2007; Liu et al., 2009). The putative cytotoxic oxidative metabolites have not been identified, but CYP2E1 inhibition should be protective. The trick would be to administer the CYP2E1 inhibitor quickly enough following 1-BP exposure. The antidote might have to be given concurrently with 1-BP, as 1-BP is very rapidly absorbed, distributed to tissues, and metabolically activated.

An alternative therapeutic approach would be to administer antioxidants to inhibit lipoperoxidation. N-acetycysteine or another agent that will significantly enhance levels of reduced glutathione may also be beneficial.

RESPONSE: *Some of the text from the Reviewer's comment was added to the profile.*

COMMENT: p. 79, lines 34 & 35: It may be difficult to obtain approval from an Internal Review Board, even for a short-term, low-level human study of 1-BP, since DHHS has classified the chemical as reasonably anticipated to be a human carcinogen.

RESPONSE: *The comment refers to the sentence: "Controlled exposure experiments in humans would help to determine exposure concentrations that lead to minor neurological and/or respiratory complaints" that appears in the Data Needs section. The sentence was deleted.*

COMMENT: p. 81, lines 1-4: Garner et al. (2007) exposed wild-type and CYP2E1-null mice to 1-BP in a closed inhalation chamber for 6 hours. The initial chamber vapor concentration of 800 ppm diminished over the next 6 hours at a carefully monitored rate. Only the wild-type mice exhibited sperm injury. Thus, the LOAEL over the 6 hours was lower than the 800 ppm that caused morphological changes in the medulla oblongata and posterior tibial nerve in rats (Wang et al., 2002).

RESPONSE: *The information provided by the reviewer was incorporated into Chapter 2, the Rationale Statement, the section on reproductive effects in Chapter 3, the Data Needs section, and the LSE table.*

COMMENT: p. 81, line 18: Substitute the word "neurotoxicological" for "toxicological."

RESPONSE*: The change was made as suggested.*

COMMENT: It would also be highly advisable to conduct studies to establish a LOAEL and a NOAEL for spermatotoxicity in both mice and rats, although mice are the more sensitive species. Liu et al. (2009) conducted a 28-day inhalation toxicology study in 3 strains of mice. The lowest vapor level (50 ppm) was spermatotoxic in all 3 strains, so additional experiments should be performed to more precisely identify LOAELs and NOAELs.

RESPONSE: *NOAELs for spermatotoxicity were established in both mice and rats in the NTP (2011) 14-week studies and were 250 and 500 ppm 1-bromopropane, respectively. In addition, the comprehensive 2-generation reproductive study sponsored by the Bromine Solvent Consortium (BSOC 2001) also established a NOAEL of 250 ppm 1-bromopropane for F0 and F1 males. It may be a good idea to try to replicate the results from Liu et al. (2009) since the reported LOAEL of 50 ppm in the 3 strains of mice tested is 5-fold lower than the NOAEL reported by NTP (2011). Text to this effect was added the section on Reproductive Toxicity.*

COMMENT: p. 82, line 5: Additional neurological investigations may also identify an oral LOAEL lower than 200 mg/kg.

RESPONSE: *Text was added to the Neurotoxicity section indicating that additional studies may be conducted to identify an acute-duration oral NOAEL for neurotoxicity, but consideration should be given to the fact that the oral route of exposure is not an exposure route of concern.*

COMMENT: p. 83, lines 3-6: Smith et al. (2011) expressed a number of concerns about the Li et al. (2010) investigation that are not included in the text of the document. In light of the types of close-contact operations the workers were engaged in, I find it hard to believe that their exposure to the VOC was so low (i.e., 1.28 ppm). The current document's authors should do a better job supporting their "determination" that the report by Li et al. was "adequate" to use as a basis for derivation of the chronic inhalation MRL.

RESPONSE: *An extended discussion of the limitations of the Li et al. (2010) study is now presented in the revised MRL Rationale Statement document. Some of this discussion has also been incorporated into Appendix A.*

COMMENT: p. 83, lines 16 & 17: Again, it would be worthwhile to more precisely identify NOAELs for adverse male reproductive effects in mice and/or rats. These end points may well be of greater toxicologic importance and irreversibility that decreased grip strength or increased spontaneous locomotor activity.

RESPONSE: *As mentioned above, NOAELs have been identified in studies by NTP (2011) and BSOC 2001). Text was added to the section on Reproductive Toxicity suggesting research that could explain the apparent inconsistencies between the results from these studies and those reported by Liu et al. (2009).*

COMMENT: p. 85, lines 28 & 29: Objective, quantitative measures of other neurological or neuromuscular parameters would also be important to include in a human study protocol.

RESPONSE: *Text was added indicating that evaluation of other neurophysiological parameters also would be on interest.*

COMMENT: p. 87, lines 117-19: It seems clear that mice are more susceptible to 1-BP-induced hepatotoxicity and gonadal toxicity, because mice metabolically activate more 1-BP by CYP2E1-mediated oxidation and conjugate more of the chemical due to higher GST activity.

RESPONSE: *Lines 117-119 state almost the same that Garner et al. (2015) identified as a data need.*

COMMENT: p. 87, lines 21-24: See newly published PBPK model by Garner et al. (2015).

RESPONSE: *The model developed by Garner et al. (2015) is discussed in Section 3.4.5 of the profile.*

COMMENT: p. 87, lines 31 & 32: See previous suggestions to assess the efficacy of antioxidants and compounds to augment GSH levels.

RESPONSE: *A sentence was added indicating that further research the efficacy of antioxidants and compounds that increase GSH levels would be valuable.*

COMMENT: p. 97, line 26 & 27 and p. 98, line 4 & 5: Can pertinent references be included here?

RESPONSE: *References have been added to the text as suggested.*

COMMENT: p. 101, lines 7 & 8: What is the difference between the abbreviations "ppmv" and "ppm"?

RESPONSE: *The abbreviation ppmv refers to parts per million by volume; a definition was added at first occurrence.*

COMMENT: The comments refer to text that includes **An MRL**… or **An LC_{50}**… The Reviewer suggests deleting the letter **n** in the word **An** so that the text would be **A MRL**… or **A LC_{50}**…

RESPONSE: *According to The ACS Style Guide: Choose the articles "a" and "an" according to the pronunciation of the words or abbreviations they precede: a nuclear magnetic resonance spectrometer; an NMR spectrometer.*

According to the AMA Manual of Style: Abbreviations and acronyms are preceded by a or an according to the sound following: a UN resolution; an HMO plan; a WMA report; an NIH grant. No change was made.

CORPORATE STUDIES

COMMENT: I do not see that citing the three reports by ELF Atochem, or the report by Albemarle (1997) and that by the Brominated Solvents Consortium are problematic. Each study appears to be conducted according to GLP requirements. The studies' findings add modestly to our knowledge at 1-BP's toxicological properties, but do not significantly impact the Tox Profile's findings or conclusions.

RESPONSE: *No response is necessary.*

COMMENT: ADDITIONAL REFERENCES

Banu S, Ichihara S, Huang F, et al. 2007. Reversibility of the adverse effects of 1-bromopropane exposure in rats. Toxicol Sci 100:504-512.

Bruckner JV, Anand SS, Warren DA. 2013. Toxic effects of solvents and vapors. In: Klaassen, CD, ed. Casarette and Doull's Toxicology-The Basic Science of Poisons. 8th Edition, New York, NY: McGraw-Hill, 1036-1044.

Bruckner JV, Mackenzie WF, Ramanathan R, et al. 1989. Oral toxicity of 1, 2-dichloropropane: Acute, short-term, and long-term studies in rats. Fundam Appl Toxicol 12:713-730.

Bruckner JV. 2000. Differences in sensitivity of children and adults to chemical toxicity: The NAS panel report. Regul Toxicol Pharmacol 31:280-285.

Dallas CE, Ramanathan R, Muralidhara S, et al. 1989. The uptake and elimination of 1,1,1-trichloroethane during and following inhalation exposures in rats. Toxicol Appl Pharmacol 98:385-397.

Easley CA, Bradner JM, Moser A, et al. 2015. Assessing reproductive toxicity of two environmental toxicants with a novel in vitro human spermatogenic model. Stem Cell Res 14:347-355.

Garner CE, Liang S, Yin L, et al. 2015. Physiologically-based pharmacokinetic modeling for 1-bromopropane in F344 rats using as uptake inhalation experiments. Toxicol Sci 145:23-36.

Hines RN. 2007. Ontogeny of human hepatic cytochromes P450. J Biochem Mol Toxicol 21:169-175.

Lag M, Soderlund EJ, Omichinski JG, et al. 1991. Effect of bromine and chlorine positioning in the induction of renal and testicular toxicity by halogenated propanes. Chem Res Toxicol 4:528-534.

RESPONSE: *References have been reviewed and added to the text as appropriate.*