DISPOSITION OF PEER REVIEW COMMENTS FOR TOXICOLOGICAL PROFILE FOR BROMOMETHANE

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

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Comments provided by Peer Reviewer #1

General Comments

COMMENT: It is not entirely clear to me what prompted this document, as methyl bromide is less and less present in ambient air, as its use has been phased out in the US – and presumably other countries (can this be clarified?) – due to its ozone-depleting ability. In general, even before this phase-out ambient air levels were low, and it was a relatively rare occupational exposure. Perhaps something might be said about the motivation for this document.

RESPONSE: *As mandated by the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), ATSDR develops profiles on substances identified on the Substance Priority List (SPL); bromomethane is ranked at 439 on the SPL (https://www.atsdr.cdc.gov/spl/resources/index.html). ATSDR is also mandated to update the profiles.*

COMMENT: As a relative newcomer to these Tox Profiles (this is the first I have read in detail, from end to end), I found several things confusing. It appears that there are two goals, one to assess the occurence and likely health effects of methyl bromide, and second, to establish MRLs. This might be stated clearly at the beginning. The section on MRLs was particularly confusing because of the use of the passive voice. For example, on page 35 line 7, one finds that 'an MRL of 0.02 ppm has been derived'. My first thought was, well, who derived it? Only gradually did I come to the view that in fact the ATSDR has derived it in this Tox Profile. Why not define clearly what an MRL is, how it is derived, and then proceed to derive it? This would be clearer. The details in the Appendix don't provide an overview of the method. I suppose there are established rules on how to write these documents, but for a 'layman' things could be clearer.

RESPONSE: *The focus of the profile is discussed in the Foreword. ATSDR disagrees with the Reviewer that the profile does not define an MRL. The definition of an MRL is discussed in the introduction to Section 2.3 and the introduction to Appendix A. The text in Section 2.3 has been revised to indicate that ATSDR derived the MRLs. ATSDR has recently revised the format of the toxicological profile; the revised MRL Worksheets provide a better overview on how MRLs are derived.*

COMMENT: I also note, as a general impression, that many sections appear to be repetitive with other sections. This is probably inevitable given the division of health effects between routes of exposure, the separate discussions of biomarkers, genotoxicity, toxic mechanism, susceptible populations, the separate discussion health effects for different durations of exposure, etc.

RESPONSE: *ATSDR has recently revised the format of the toxicological profile; the revised format eliminates some of the repetitiveness of the old format.*

COMMENT: While the human data on the health effects of methyl bromide are not extensive, I do get the feeling that they are a bit under-emphasized here relative to the animal data; see specific comments below.

RESPONSE: *See responses to specific comments.*

Specific Comments

COMMENT (page 25, line 21): "there are not reliable studies available in human that evaluated whether bromomethance can cause cancer". This hardly seems accurate, although it depends what you mean by 'reliable'. The NCI study by Barry et al. (2012) strikes me as 'reliable'. Retrospective exposure assessment in the Ag Health Study, while always difficult, is some of the best that is around, and the findings of a strong and significant positive trend of stomach cancer with increased exposure (albeit based on small numbers) seems reliable to me.

On line 22, animal data is dismissed due to negative inhalation studies. But IARC's monograph in 1991 says that bromomethane has 'limited' evidence of animal carcinogenicity, based on mixed results on studies in rats and mice, although it is true that the NTP 1992 negative animal study was not considered by IARC. Seemingly however there was some positive evidence in IARC's view.

There are other supporting animal data for potentially carcinogenic effects of methyl bromide cited in Barry et al. (2012), including DNA adducts in the forestomach and other areas, and data on increased mutation, SCEs, and micronuclei, and also some supporting human data for these effects in one study (Calvert et al. 1998, in Mutation Research), which seems to have been missed, it is not cited at all in this document. There is also no citation of Ganswendt et al. 1991 (Foor Chem Tox) with the data on DNA adducts. Also, not mentioned are three other epi studies of cancer (Mills et al. 2003, Cockburn et al. 2011, Mills et al. 2007) – see Barry et al. 2012 for discussion of these studies. These findings have some positive findings for gastric cancer and for prostate cancer. Note that the Barry et al. (2012) did not support earlier associations found for prostate cancer (Alvanja et al. 2003, Cockburn et al. 2011, Mills et al. 2003). There is a discussion of possible reasons why in the Discussion section of Barry et al. (2012). All this seems to have been missed by ATSDR.

In sum, although the data are sparse and the animal data not consistent, I think this summary of the cancer literature is not entirely accurate/balanced.

RESPONSE: *The Reviewer is referring to the statement in the How Can Bromomethane Affect My Health section of the Public Health Statement (Chapter 1) regarding the results of available carcinogenicity data in humans and animals. The intent of this paragraph is to very briefly present the results of available epidemiology and experimental cancer studies and to list available cancer classifications from HHS (NTP), EPA, and IARC. A more in-depth discussion of carcinogenicity data is presented in Chapter 3 (Section 3.2.1.7 for inhalation exposure and Section 3.2.2.7 for oral exposure). Please note that the statement that there are no reliable studies in humans was revised to indicate that there is limited information of bromomethane carcinogenicity in humans.*

The profile was revised to add the Mills and Yang (2003, 2007) and the Cockburn et al. (2011) studies to discussion of carcinogenicity in Section 3.2.1.7, and the Calvert et al. (1998b) and Gansewendt et al. (1991) studies were added to the discussion of genotoxicity in Section 3.3.

COMMENT (page 27, line 15): Ambient levels are quite low, but some higher occupational exposures still occur due to pesticide use. I am confused by this summary of recommendations and limits. The cited OSHA limit of 20 ppm for workers is a 'ceiling' limit, but I believe the 8-hour recommended limit is 5 ppm, as indeed is cited on page 118. It might also be noted that Cal OSHA has a 1 ppm limit, while AGCIH likewise recommends a 1 ppm limit. As for EPA, I am a little confused. I read in the MMWR article July 15, 2011, regarding case reports of occupational over-exposure and health effects, in footnote

page 923, that EPA has a recommended 8-hour limit for intermediate/long duration exposure of 0.15 ppm in air. But nothing is mentioned here about an EPA recommended air limit.

RESPONSE: *Regarding the Reviewer's comment in Chapter 1, What Recommendations Has the Federal Government Made to Protect Human Health section, OSHA does not have a ceiling limit for bromomethane; 20 ppm is the PEL value, as reported in OSHA (2015). The value reported on page 118 of the profile is outdated and has been deleted. Regarding the comment on an EPA-recommended air limit, the Reviewer is referring to a footnote in the O'Malley et al. (2011) paper, which notes that "short- and intermediate-term (1 day to 6 months) exposures to MeBr concentrations of 0.15 ppm for an 8-hour time-weighted average are of concern," which is cited to the EPA re-registration document. ATSDR was unable to locate this information in the EPA document. In the document, it is noted that if exposures to chloropicrin (which is added to bromomethane products as a warning agent) exceed 0.15 ppm, then handlers should use respirators. EPA has established a Health Effects Division Human Equivalent Concentration (HED HEC) of 1 ppm for short- and intermediate-term ambient exposure to bromomethane. ATSDR does not typically cite these divisional values; EPA's reference doses (RfDs) and reference concentrations (RfCs) reported in IRIS assessments are the preferred source of toxicity information used by EPA.*

COMMENT (page 32, Figure 2-1): The title says health effects in humans and animals, but in the body of the figure we see lonely 'effects in animals', which is confusing.

RESPONSE: *The figure title was corrected.*

COMMENT (page 35, lines 10-15): As noted earlier, the document would be clearer there were some prior general discussion of how MRLs are derived. Only line 14 an uncertainty factor of 90 is cited, 9 for LOAEL, 3 for animal-human extrapolation, 10 for human variability, which would seem to lead to a factor of 9*3*10=270, rather than 90. It does appear that 90 was used in the calculation (1.8/90=-0.02).

RESPONSE: *The typographical error in the uncertainty factor for use of a minimal LOAEL was corrected from the value of 9 to the value of 3.*

COMMENT (page 45): The comments on the Anger et al. study are perhaps overly critical. The lack of measured exposure is not a fatal flaw, many occupational studies don't have measurement, but are based on job. Furthermore, there are supporting measurements taken of other fumigators doing similar work to the fumigators kin the study. These workers were clearly exposed occupationally, and the exposure groupings seem reasonable. It seems clear that structural fumigators have had higher exposures than other fumigators. The fact that different exposure groups differed on some demographic factors does not in itself suggest confounding unless these factors are known to be related to worse performance on neurobehavioral tests. Furthermore, these factors were controlled in some analysis. More to the point is that this positive study is counter-balanced by the negative study by Calvert et al. in 1998 (Am J Pub Hlth). However, Calvert et al note that the workers in Anger et al. were probably exposed to higher levels of methyl bromide than those in Anger et al. A more balanced discussion of these two studies – the only two human studies for neurotoxicity, would be desirable.

RESPONSE: *The profile discusses a number of human studies examining neurological end points including Deschamps and Turpin (1996), Johnstone (1945), Watrous (1942), Calvert et al. (1998), and Anger et al. (1986), as well as a large number of case reports. ATSDR does not consider the lack of accurate monitoring data in the Anger et al. (1986) as a "fatal flaw." However, the Agency has low*

confidence that the exposure levels reported in the paper that are for another group of workers should be used to quantify the neurological effects reported in the Anger et al. (1986) paper. Although statistical adjustments were made for some of the potential confounding variables, others remained that may have influenced the results, which is why they are noted in the profile. The following note was added to Section 3.2.1.4 regarding these statistical adjustments: It is noted that the study accounted for potential confounders by dividing workers into separate groups based on the percentage of time they used bromomethane or sulfuryls fluoride and statistical adjustments were made for some variables including age, alcohol consumption, and race..

COMMENT (page 49, Cancer section): As noted earlier, the cancer section overly discounts the value of the human epidemiology (admittedly not extensive), in relation to the Barry et al. study (2012), and omits on study by Calvert et al. regarding mutations/micronuclei, as well as the two studies by Mills et al, and one by Cockburn et al., as noted earlier. The Barry et al. study, the strongest epidemiologic study, is discounted in the last sentence on this page, in which it is said that "the applicators in this cohort were likely exposed to multiple pesticides, and these studies are inadequate for establishing bromomethane causality". While technically true, no epidemiologic studies 'establish causality', outside of randomized trials which cannot be conducted for suspected human toxins. Pesticide applicators are exposed typically to many pesticides. Only 14% of subjects reported use of methyl bromide, and investigators were able to classify these into high and low intensity, and high and low duration, and a dose response was found for both high and low intensity, and intensity-weight duration – while controlling for these other pesticides to which these workers were exposed. Hence this epidemiologic evidence should be considered as somewhere between moderate to relatively strong evidence of an association with stomach cancer, weaker because there is only one study and stomach cancers are rare.

RESPONSE: *The Mills and Yang (2003, 2007) and Cockburn et al. (2011) studies were added to Section 3.2.1.7 Inhalation, Cancer and the Calvert et al. (1989b) and Gansewendt et al. (1991) studies were added to Section 3.3 Genotoxicity. ATSDR disagrees with the Reviewer that the available epidemiological data provide moderate to relatively strong evidence of an association with cancer; these studies provide suggestive evidence. The sentence referenced by the Reviewer regarding the limitations of the epidemiology cancer studies was revised to indicate that the available studies provide some suggestive evidence of carcinogenicity but that the studies cannot establish causality; none of the studies measured bromomethane exposure levels and workers were likely exposed to multiple pesticides.*

COMMENT (page 56, line 26): The human study Calvert et al. (1998, Mutation Res) is omitted here, as noted earlier. This section on Genotoxicity omits the study in rates of DNA adducts by Ganswendt et al, as noted earlier.

RESPONSE: *The Calvert et al. (1998) and Gansewendt et al. (1991) studies were added to the genotoxicity section (Section 3.3).*

COMMENT (page 77): Figure 3.4 indicates no human cancer data, which ignores the existing data noted earlier (Barry et al.) and indicates no data on genotoxicity, ignoring Calvert et al. 1998 (Mut Res), as noted earlier.

RESPONSE: *The figure has been revised to indicate that there are human genotoxicity and carcinogenicity data.*

COMMENT (page 81, lines 20-22): See earlier comments. Being exposed to multiple compounds is not a fatal flaw in epi studies, due to being able to control for other pesticide exposures in the regression model. Furthermore, one is able to know who was exposed to high vs low levels of methyl bromide, so that among the multiple exposures one can identify a key one with high exposure. Again, there is a lot of repetition here; intermediate and chronic duration is not a definable or probably useful distinction for studies of humans.

RESPONSE: *Regarding the Reviewer's comment in Cancer subsection of Section 3.12.2—Although several studies have investigated the carcinogenicity of bromomethane in workers (Alavanja et al. 2003; Barry et al. 2012; Wong et al. 1984), the studies have limited use in establishing the carcinogenic potential of bromomethane because the workers were exposed to numerous compounds—ATSDR notes that most of the available epidemiology studies for bromomethane did not control for potential exposure to other pesticides, although categorizing workers based on estimated exposure does decrease the uncertainty. The referenced statement was revised to indicate that some studies have found cancer associations but interpretation of the data is limited by the lack of information on bromomethane exposure levels and possible exposure to other pesticides. In several places in the profile, ATSDR has defined intermediate and chronic exposure durations; the duration categories are used to assess potential health risks associated with a particular exposure length.*

COMMENT (page 101, Table 6-2): Might be useful to indicate which sources are anthropogenic, which appears to be 1 and 2, and 4 and 5. Maybe group them together.

RESPONSE: *It is difficult to separate out the anthropogenic and natural sources of bromomethane because some natural sources serve as sinks of anthropogenically produced bromomethane and the amount produced by some plants is high due to increased production of food and biofuel crops.*

COMMENT (page 111, Table 6-4): It is curious that the median levels are going down, as expected till 2014, when they increase, and still increased in 2015. Any reason for this?

RESPONSE: *ATSDR does not have an authoritative source to explain the increase in bromomethane levels in 2014 and 2015.*

COMMENT (page 115, Table 6-6): You might mention that these are all occupational exposures. Also, there are some places where ppm is used, others were ppmv is used. Might be best to be consistent.

RESPONSE: *Table 6-6 does not list occupational exposure levels; these are air monitoring levels following fumigation. Revisions were made to consistently use ppmv throughout this section of the profile.*

COMMENT (page 117, line 30): See earlier comment, this seems to contradict text on page 27.

RESPONSE: *The statement on page 117 (Section 6.5)—Exposure levels inside factories are regulated by OSHA, and the 8-hour average concentration is not permitted to exceed 5 ppmv (OSHA 1989)—was deleted from the profile.*

COMMENT (page 117, Section 6.5): It seems to me that a summary table of observed occupational air levels should be presented here or in section 6.7. It is not clear why there are separate section for high exposure and occupational exposure, as they are generally the same.

RESPONSE: *As noted in the text of this section, occupational exposure levels are highly variable depending on the conditions and use of respirators, which makes it difficult to present the data in a table. Exposure levels are reported in the text.*

COMMENT (page 118, lines 7-17): There are air levels reported by Yamano et al. 2011, which should also be mentioned here.

RESPONSE: *The air concentrations were added.*

COMMENT (page 132): See earlier comment regarding MRLs.

RESPONSE: *See responses to these specific comments.*

COMMENT (page 133, Table 8-1): See earlier comment p. 27. This table might be separated into ambient air recommendations vs occupational ones.

RESPONSE: *In the revised format of the toxicological profile, ambient air recommendations are separated from occupational values.*

Comments provided by Peer Reviewer #2:

General Comments

COMMENT: Overall document reads well and keep the neutral tone. I also mostly agree with the authors interpretation of the data presented.

RESPONSE: *No specific revisions were suggested.*

Specific Comments

COMMENT (page 25, line 33): Consider revising language "It is not known whether children are more susceptible than adults to the effects of bromomethane" to "There is limited data on the toxicity of bromomethane in children". In general, children exposed to the same levels of bromomethane as adults may receive larger doses because their physiology i.e., greater lung surface area, body weight ratio, and increased minute volumes.

RESPONSE: *Regarding the Reviewer's comment in the subsection How Can Bromomethane Affect Children? in Chapter 1, ATSDR notes that the suggested text is beyond the scope of the public health statement. A statement was added referring the reader to Section 3.7 for more information; Section 3.7 includes a discussion of physiological differences between children and adults.*

COMMENT (page 43, line 28): There is no mention of human studies about body weight after inhalation. Here is a suggested reference - https://ehp.niehs.nih.gov/1205682/

RESPONSE: *The Gemmell et al. (2013) study was added to the discussion of developmental effects in Section 3.2.1.6 since the study evaluated birth weight.*

COMMENT (page 54, line 8): Page 54, Line 8: Consider adding information about prostate cancer study. A direct link has been shown between methyl bromide exposure and prostate cancer in farmworkers. Ref: https://academic.oup.com/aje/article/157/9/800/97345/Use-of-Agricultural-Pesticides-and-Prostate-Cancer https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2822396/

RESPONSE: *The Reviewer referenced two papers: Alavanja et al. (2003) and Prins (2008). The Alavanja et al. (2003) study is cited in the profile in Section 3.2.17. The Prins (2008) paper is a review that discusses the Alavanja et al. (2003) study; this review was not added to the profile.*

Annotated Comments

COMMENT (page ix): Consider adding this explanation to show AAPCC is one central body that works with local centers to provide poisoning support to all states; reference http://www.aapcc.org/.

RESPONSE: *The text was revised to state that AAPCC provides support to poison control centers.*

COMMENT (Table of Contents): Please check the page numbers. E.g., contributors are listed on page xi but listed as x. Also, 3.2.2.3 is on page 56 but missing in the table of content.

RESPONSE: *The Table of Contents has been corrected.*

COMMENT (page 23): Consider adding year to show that phase out is not recent; Ref.- https://www.epa.gov/ods-phaseout/phaseout-class-i-ozone-depleting-substances .

RESPONSE: *The date of the EPA phase-out—2005—was added to the What is Bromomethane section of Chapter 1..*

COMMENT (page 23, line 33): change "is" to "in"

RESPONSE: *The suggested revision was made in the What Happens to Bromomethane When It Enters the Environment section of Chapter 1.*

COMMENT (page 24, line 3): Change "with" to "will"

RESPONSE: *The suggested revision was made in the What Happens to Bromomethane When It Enters the Environment section of Chapter 1.*

COMMENT (page 24, line 11): Correct term is "parts per billion" as used in rest of the document.

RESPONSE: *The suggested revision was made in the How Might I Be Exposed to Bromomethane section of Chapter 1.*

COMMENT (page 25, line 5): Consider using term "patients" or "individuals" instead of "cases". A case means different to different people e.g., a case to epidemiologists means an individual who met a case definition.

RESPONSE: *The term "less serious cases" was revised to "individuals with less serious effects" in the How Can Bromomethane Affect My Health section of Chapter 1*

COMMENT (page 25, line 33): Consider revising language "It is not known whether children are more susceptible than adults to the effects of bromomethane" to "There is limited data on the toxicity of bromomethane in children". In general, children exposed to the same levels of bromomethane as adults may receive larger doses because their physiology i.e., greater lung surface area, body weight ratio, and increased minute volumes.

RESPONSE: *As noted previously, a statement—More information on the susceptibility of children can be found in Section 3.7 of the toxicological profile—was added to the How Can Bromomethane Affect Children section of Chapter 1; Section 3.7 includes a discussion of physiological differences between children and adults.*

COMMENT (page 25, line 34): Change “in” to “an”.

RESPONSE: *The suggested revision was made to the How Can Bromomethane Affect Children section of Chapter 1.*

COMMENT (page 31, line 2): Do you mean minor variation as stated on page no. 49 line 7? Currently it sounds like fused vertebrae is a minor health effect. Also, you may add “decrease weight” here as well.

RESPONSE: *The text in Section 2.2 was revised to indicate that fused vertebrae was a minor variation and decreased fetal weight was added.*

COMMENT (page 31, line 18): Referring to the callout for Figures 2-1 and 2-2, what is the source of this information? Sorry, if I missed it.

RESPONSE: *The data for these figures come from the LSE tables in Chapter 3.*

COMMENT (page 32, Figure 2-1): Both table 2-1 and 2-2 labeled as “Effects in Animals”. Consider changing title accordingly.

RESPONSE: *There is no Table 2-1 in the profile; ATSDR is assuming that the Reviewer is referring to Figures 2-1 and 2-2. The title of these figures was revised to “Health Effects in Animals Following …Exposure to Bromomethane”.*

COMMENT (page 35, line 14): Change the uncertainty factor for minimal LOAEL from 9 to 3.

RESPONSE: *In Section 2.3, the uncertainty factor used to adjustment for the use of a minimal LOAEL in the intermediate-duration inhalation MRL was corrected from 9 to 3.*

COMMENT (page 40, line 14): Change “regeneration” to “degeneration”.

RESPONSE: *Regarding the comment in Section 3.2.1.2—Respiratory Effects, ATSDR verified that regeneration of the olfactory epithelium is correct and the suggested revision was not made.*

COMMENT (page 40, line 33): Is this 110 or 11.0?

RESPONSE: *Regarding the comment in Section 3.2.1.2—Respiratory Effects,the correct dose is 11.0 for the study reported by EPA (2001b).*

COMMENT (page 43, line 28): There is no mention of human studies about body weight after inhalation. Here is a suggested reference - https://ehp.niehs.nih.gov/1205682/.

RESPONSE: *As noted previously, the Gemmill et al. (2013) study was added to the discussion of developmental effects in Section 3.2.1.6.*

COMMENT (page 51, line 23): Change "wer" to "were"

RESPONSE: *Regarding the comment in Section 3.2.1.2—Gastrointestinal Effects, the suggested revision was made.*

COMMENT (page 54, line 8): A direct link has been shown between methyl bromide exposure and prostate cancer in farmworkers. Ref: https://academic.oup.com/aje/article/157/9/800/97345/Use-of-Agricultural-Pesticides-and-Prostate-Cancer https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2822396/

RESPONSE: *The Alavanja et al. (2003) study is discussed in the profile in Section 3.2.1.7.*

COMMENT (page 59, line 7): Change "55.4 and 52.1%" to 55.4% and 52.1%"

RESPONSE: *The suggested revision was made in Section 3.4.1.1.*

COMMENT (page 61, line 1): Change "blood:brain" to "blood-brain"

RESPONSE: *The suggested revision was made in Section 3.4.2.1.*

COMMENT (page 116, line 12): Add a space between "1971" and "to".

RESPONSE: *The suggested revision was made in Section 6.4.2.*

COMMENT (page 122, lines 22-23): Consider replacing "began over a decade ago" with "on January 1, 2005"

RESPONSE: *The date (2005) was added to Section 6.8.1.*

Comments provided by Peer Reviewer #3

General Comments

COMMENT: Overall, the toxicological profile for bromomethane document is appropriately complete and presents a succinct summary of key literature with pertinent information for the target audience. The following provides a more detailed assessment organized by major sections in the profile.

RESPONSE: *No revisions were suggested.*

Chapters 1 and 2. Public Health Statement and Relevance to Public Health

COMMENT: The effects known to occur in humans have been adequately reported in the text. A range of data was reported over a series of studies in multiple animal models and from human exposure events. Although one of the objectives of this section was to address exposure conditions for humans around hazardous waste sites, it is unclear what the likelihood of those exposures are. The authors mention that few NPL sites have been evaluated for bromomethane which may account for the limited data reported. More information could be summarized relative to identified locations where populations are more likely to be exposed.

RESPONSE: *Areas where higher than background levels could be found are discussed in Chapter 1 in the "How Might I Be Exposed to Bromomethane" section. A more detailed discussion is presented in Section 6.7.*

COMMENT: Given the absence of data specifically in humans, animal effects are appropriate to consider as likely to be of concern in humans with additional uncertainty factors incorporated. The information as presented in this document appears to be complete and appropriate.

RESPONSE: *No revisions were suggested.*

COMMENT: In terms of routes of exposure to the body and effects, exposure conditions have been adequately described but not in terms of environmental sites where exposures are most likely to occur. Additional information is needed relative to the total number of NPL sites evaluated/yet to be evaluated for bromomethane and the exposure routes and estimated populations exposed. This information, however, may not be clearly available to the profile authors.

RESPONSE: *Information on sites to be evaluated for bromomethane is not readily available.*

COMMENT: The derived inhalation MRLs are justifiable with conservative estimates from animal studies and substantial uncertainty factors. Please check text on Page 35, lines 13-14 for what may be an error in reporting a UF of 9 for the use of a minimal LOAEL (should it be 3?).

RESPONSE: *The correct uncertainty factor for the use of a LOAEL should be 3; the typographical error in Section 2.3 was corrected.*

COMMENT: Animal data is less suitable for an MRL derivation for oral exposure. The literature supports that oral exposure routes are not likely for humans and that current animal data is not adequate to justify establishing an MRL for this route of exposure.

RESPONSE: *No revisions were suggested.*

Specific Comments

COMMENT (page 23, line 33): Typo- "in"

RESPONSE: *The suggested revision was made in the What Happens to Bromomethane When It Enters the Environment section of Chapter 1.*

COMMENT (page 24, lines 1 and 24): Explain if "other chemicals" are less harmful

RESPONSE: *Regarding the statement—In the environment, bromomethane breaks down to other chemicals—in the What Happens to Bromomethane When It Enters the Environment section of Chapter 1 (Line 1), the text was revised to—Bromomethane is broken down in the environment. Regarding the statement—Most bromomethane in your body is broken down into other chemicals…—in the How Can Bromomethane Enter and Leave My Body section of Chapter 1 (Line 24), it is beyond the scope of the profile to include a discussion of the toxicity of the metabolites methanol and bromide ion (based on currently available data) and the toxicity of the metabolite break down products.*

COMMENT (page 26, lines 11-13): What is meant by do not enter areas too soon? Define time context for avoiding areas.

RESPONSE: *The amount of time before entering the areas would be dependent on the application. The profile (How Can Families Reduce the Risk of Exposure to Bromomethane section in Chapter 1) was revised to state that you should not enter the area sooner than permitted.*

COMMENT (page 29, line 8): Although detailed later, consider briefly stating the two use exemptions here.

RESPONSE: *The two use exemptions—to eliminate quarantine pests and for agricultural use where there are no technically or financially feasible alternatives—was added to the discussion Section 2.1 of EPA's phase-out of bromomethane production and use.*

Chapter 3. Health Effects

Section 3.1 Introduction

COMMENT: No additional comments. This section provides standard overview statements for the following subsections.

RESPONSE: *No revisions were suggested.*

Section 3.2 Information on Health Effects

COMMENT: The review has fulfilled the stated purpose of this section, "to specify the health effects that are associated with the substance and the degree of certainty attached to that association." Toxicological effects have been clearly organized by the category of health effect with a well-supported summary of comparative data presented in the LSE tables.

RESPONSE: *No revisions were suggested.*

Specific Comments

COMMENT (page 38, line 19): Consider defining "ordinary temperature" and providing a range of standard conditions where bromomethane exists as a gas.

RESPONSE: *The sentence in Section 3.2.1 was revised to state that bromomethane is a gas.*

COMMENT (page 41, line 17): Typo "cases of"

RESPONSE: *The suggested revision was made in Section 3.2.1.2—Cardiovascular Effects.*

COMMENT (page 44, line 2): Typo "decrease"

RESPONSE: *The suggested revision was made in Section 3.2.1.2—Body Weight Effects.*

COMMENT (page 48, line 8): Consider explaining what is meant by "a shift in quality perception"

RESPONSE: *An explanation of the shift in odor quality perception was added to Section 3.2.1.4.*

COMMENT (page 50, line 7): Consider defining "ordinary conditions"

RESPONSE: *The text in Section 3.2.2 was revised to "at room temperature"*

COMMENT (page 51, line 23): Typo "were"

RESPONSE: *The suggested revision in Section 3.2.1.2—Gastrointestinal Effects was made.*

Toxicity – Quality of Human Studies

COMMENT: The authors report that there are many reports of human death following exposure to bromomethane. Those selected for this review appear to be representative of the breadth of human exposure data which is primarily characterized by acute, accidental events with high concentration levels

of the contaminant and serious health effects relative to workplace settings. Studies reporting respiratory effects do not provide known exposure levels. Human study limitations were adequately identified which include a lack of low dose, chronic exposure data, confounding from multiple chemical exposures and uncertain concentration levels. These limitations were adequately, and succinctly, described in the text.

RESPONSE: *No revisions were suggested.*

COMMENT: Author conclusions appear appropriate and complete for the available data. Study limitations were identified where discovered and a complete and complex dataset was broken down effectively in concise summaries both in the text and with the use of Table/Figure 3-1. Species and sex differences were noted along with reports of several conflicting studies where the same adverse effects were not always found to be significant. Experimental design (i.e., exposure concentration, frequency, duration) was not always identical in comparative studies which may account, in part, for variable results. Experiments where carcinogenic effects were uncertain and minimal in several animal studies were adequately justified.

RESPONSE: *No revisions were suggested.*

COMMENT: NOAELs and LOAELs were appropriately identified in the text narrative and in Table 3-1. Statistical methods were not detailed, however, indications of low statistical power and reports of significant or not significant results are mentioned which aid in the assessment of study results. I am not aware of other key studies for inclusion in this section and find the current review to be extremely thorough.

RESPONSE: *No revisions were suggested.*

Health Effects in Humans Exposed Tables

COMMENT: Epidemiological studies in humans are limited to a few acute, high concentration exposure events and 1-2-week occupational exposure. These events have been adequately described.

RESPONSE: *No revisions were suggested.*

Toxicity – Quality of Animal Studies

COMMENT: Animal studies included a wide range of exposure concentrations, durations, frequencies, and endpoint evaluations with suitable numbers and types of animals collectively. Animal species were highly varied and appropriate with considerations of age, sex, species, exposure route and more. In general, experimental design appears to be appropriate and limitations in design, hazard delivery route, and endpoint interpretation were transparently described in the text.

RESPONSE: *No revisions were suggested.*

COMMENT: Conclusions drawn by the authors relative to animal studies and the assumptions of human health effects were appropriate and supported by referenced studies. The authors were careful to provide information on study limitations where existing. Appropriate NOAELs and LOAELs were

identified for each study. Where available, observed values of no or low effect were summarized in easy-to-interpret tables

RESPONSE: *No revisions were suggested.*

COMMENT: A discussion of other toxic forms of bromomethane was generally not presented, although in later sections indications are that volatilization and degradation is rapid and additional toxicological effects are not significant.

RESPONSE: *No revisions were suggested.*

COMMENT: Statistical methods from various studies were not detailed in this section, however, indications of low statistical power and reports of significant or not significant results are mentioned which aid in the assessment of study results. I am not aware of additional studies that were not included in this review that would be important to consider.

RESPONSE: *No revisions were suggested.*

Levels of Significant Exposure (LSE) Tables and Figures

COMMENT: The LSE tables are complete and self-explanatory. They are an appropriate accompaniment to the narrative and summarize well the various key studies. Tables lack description of cancer effects in humans and animals as none have been consistently identified. The table key indicates carcinogenic effects were considered but not identified as a notable effect. For other effects, categorization of less serious and serious endpoints in the LSE tables appear appropriately interpreted.

RESPONSE: *No revisions were suggested.*

Evaluation of Text

COMMENT: Major study limitations have been adequately discussed. Evaluations from animal studies were used to estimate human exposure limits with appropriate uncertainty factors and conservative estimates. The relevance of the endpoints for human health was adequately discussed and summarized in bottom-line statements throughout the text. Numerous studies were summarized and adequately addressed with varying dose/response data. Conclusions are conservative and appropriate given the available database.

RESPONSE: *No revisions were suggested.*

COMMENT: Animal data was used to provide a conservative estimate of possible human health effects with appropriate uncertainty factors. This information will be useful to community and healthcare stakeholders.

RESPONSE: *No revisions were suggested.*

Mechanisms of Action

COMMENT: Action mechanisms were adequately discussed and highlighted where uncertainties were noted or recovery occurred.

RESPONSE: *No revisions were suggested.*

Hazard Identification/Systematic Review Information

COMMENT: Based on the thoroughness of the current review, I agree that the selection of endpoints is appropriate and that the list of endpoints provided in Appendix B is an adequate standard list.

RESPONSE: *No revisions were suggested.*

COMMENT: Although a guidance on the development and necessary components of the toxicological review is given, the eight step ATSDR SR protocol is not clearly defined in Appendix B. The standard protocol could be better described for clarity. For example, the SR framework as presented in Appendix B provides useful guidance on categories of inclusion and standard format but in a review where not all studies need to be exhaustively included it would be useful to have standard criteria on the process of eliminating studies. Based on what criteria would documents be excluded?

RESPONSE: *The charge question regarding systematic review (which is typically presented in Appendix B) is not relevant to the bromomethane profile, since this profile did not undergo a systematic review. The Systematic Review appendix does include a discussion on inclusion criteria.*

Section 3.4 Toxicokinetics

COMMENT: Discussion of absorption, distribution, metabolism and excretion are adequate relative to what is known about bromomethane. Information on the potentially harmful effects (or lack thereof) or relative toxicity of bromomethane metabolites would be of interest. In addition, a variety of organs and tissues have been evaluated relative to bromomethane storage and are adequately described. Metabolic parameters were adequately described, however, there are no PBPK models for bromomethane identified which is another gap identified in the current literature.

RESPONSE: *No revisions were suggested.*

COMMENT: Dose response differences were evaluated and noted between animal studies and there are no reliable dose response data sets for humans leading to the assumption that humans are as sensitive as animals to bromomethane's neurological and respiratory toxicity. However, given a more precautionary and conservative approach in risk assessment, it is appropriate to make such assumptions in the absence of definitive data.

RESPONSE: *No revisions were suggested.*

COMMENT: The authors provided an adequate discussion of the relevance of animal toxicokinetic information for humans and the assumption of human susceptibility relative to adverse effects in animals.

A general statement of whether or not bromomethane metabolites are a potential concern for animal or human health should be added if known or assumed.

RESPONSE: *Based on available mechanistic data, the causative agent (parent compound or metabolite) is not known for most effects. Section 3.5.2 does include a note that several bromomethane metabolites, including methanethiol and formaldehyde, are highly reactive compounds capable of inhibiting cellular respiration.*

Sections 3.7 and 3.10 Children and Other Populations That Are Unusually Susceptible

COMMENT: Standard language in the report acknowledges that children may vary in their susceptibility to environmental hazards. However, the authors report there is limited data on bromomethane toxicity in children except for a single case where an infant was accidentally exposed and died from pneumonia due to aspiration. Additional issues relative to child health and bromomethane toxicity do not appear to be specifically known and animal studies with offspring of rabbits and rats have not reported developmental effects following inhalation or oral exposures.

RESPONSE: *No revisions were suggested.*

COMMENT: No studies have been identified where specific human subpopulations (i.e., elderly, chronically ill, immunocompromised, etc.) are known to be more susceptible to bromomethane. However, differences in animal sex and species correlated with differences in sensitivity to bromomethane. To date, these differences have not been confirmed in humans.

RESPONSE: *No revisions were suggested.*

Section 3.8 Biomarkers of Exposure and Effect

COMMENT: The authors appropriately summarize the presence of blood or serum bromide levels as moderately useful biomarkers for exposure to bromomethane. Such assessments are complicated by the rapid and variable half-life of the contaminant. Urine metabolites are potential targets but are also short-lived. Increased levels may be from confounding exposure to bromide in the diet or medicinal treatments, requiring the use of combined methods for increased occurrence of bromomethane exposure (measuring bromide and methylation increases). The authors reviewed studies from 1983 to 2008 and highlight data gaps in the literature in terms of identification of useful biomarkers. Statements are consistent and appear to be supported by the literature.

RESPONSE: *No revisions were suggested.*

Section 3.9 Interactions with Other Chemicals

COMMENT: The authors point out that no studies have been published regarding bromomethane's interactions with other chemicals. However, studies have shown a protective effect from cellular glutathione indicating that chemicals effecting glutathione levels might increase bromomethane toxicity. The authors further speculate that bromomethane may have additive or synergistic interactions with other alkylating agents but neither of these interactive effects have been studied or reported in the literature.

RESPONSE: *No revisions were suggested.*

COMMENT: Figure 3-4 could be improved by adding symbols indicating if currently blank cells are not studied or if there were no identified effects.

RESPONSE: *There is a figure legend stating that the dots indicate existing studies.*

Section 3.12.2 Identification of Data Needs

COMMENT: This section provides an excellent summary of exposure effects in humans and animals and the most sensitive targets of toxicity with acknowledged limitations. This section also provides context relevant to exposures from waste sites, which is the most likely exposure risk for most humans. The authors further state that threshold exposures for acute, intermediate and chronic inhalation exposures are known for humans and that ongoing long-term epidemiological studies are underway examining health effects of pesticide applicators in agricultural settings. Where threshold values are mentioned, the authors should list the quantitative values in the narrative or refer to the appropriate table/section in the profile and indicate whether these are occupational exposure thresholds or other known exposure scenarios.

RESPONSE: *The intent of Section 3.12.2 is to provide a high-level review of the existing data so as to support the identification of data needs. Details, such as threshold levels, are not included in this section of the profile.*

Specific Comments

COMMENT (page 84, line 31): Insert "data"

RESPONSE: *The sentence in Section 3.12.2—Children's Susceptibility was corrected—There are limited data on the toxicity of bromomethane in children…*

Chapter 4. Chemical and Physical Information

COMMENT: This chapter appropriately contains very little text. The authors present adequate tables describing the chemical identity of bromomethane and the physical and chemical properties of the chemical. The information appears to be complete.

RESPONSE: *No revisions were suggested.*

Chapter 5. Production, Import/Export, Use, and Disposal

COMMENT: Information in this section appears to be complete and current relative to available databases on facilities reporting. The authors caution that only certain types of industrial facilities are

required to report to the TRI database and that more manufacturers may be contributing to the production or use of bromomethane.

RESPONSE: *No revisions were suggested.*

COMMENT: Also described are the use exemptions for strawberry farmers and dry cure pork producers. In addition, uses related to QPS are listed under a Clean Air Act exemption. (QPS should be added to the list of abbreviations).

RESPONSE: *QPS was added to the list of acronyms in Appendix C.*

Chapter 6. Potential for Human Exposure

COMMENT: The overview statement is a little confusing where bromomethane has been identified in 94/1832 hazardous waste sites proposed for the NPL. Previously (P. 23, line 9-10) the authors state that 12/1177 of current or former NPL sites are indicated as bromomethane sites. Are both the former and latter represented in the 94 site count? In the identified sites, is there more information that can be shared on concentration, storage conditions, potential half-life expectancy, containment or treatment? Are drinking water wells impacted or exposures limited to air/inhalation? The potential pathway from the waste sites to humans is not described but may not be known. If more information is known, please add details here since a particular focus of this profile is on human exposures from waste sites and little has been reported on this specific scenario.

RESPONSE: *The number of NPL sites in which bromomethane has been detected is 94; the text in Chapter 1 was corrected. Additional information regarding these sites is not readily available.*

COMMENT: Estimated releases from known manufacturing and processing facilities have been described as well as fate, transport, and degradation information but this information is not supplied in the context of waste sites- either known or unknown, although this information may be highly speculative and not appropriate to describe in this report.

RESPONSE: *Estimated releases of bromomethane from waste sites is not known.*

COMMENT: Section 6.4 describes detection of bromomethane in air, water and soil in natural environments and at NPL sites. Areas where the chemical is being used as a fumigant create the greatest opportunity for air exposures. These would include primarily populations who use bromomethane in occupational settings. In this section, detected concentrations should be put in the context of MRLs or threshold levels for the reader.

RESPONSE: *A statement to this effect is more appropriate to the Relevance to Public Health discussion (Chapter 2). Recent air monitoring data were added Section 2.1 and a statement was added to Section 2.2 that the concentrations associated with adverse effects are much higher than those found in ambient air.*

COMMENT (page 116, lines 18-20): Consider providing context with numerators and denominators for the 3.2% and 0.8% values. Consider a similar action on P. 117, lines 12-13.

RESPONSE: *Regarding the Reviewer's comment on the percentage of bromomethane detected in groundwater wells in Section 6.4.2, ATSDR notes that Plumb (1992) (the source of the information on page 116) and EFSA (2015) (the source of information on page 117) do not provide this information.*

COMMENT: The authors list several data needs and also topics where bromomethane information is incomplete but where additional data would not be essential to understanding fate, transport and health risks. Their assessment appears to be neutral and non-bias, supported by information in the literature and a practical assessment of priority data needed.

RESPONSE: *No revisions were suggested.*

COMMENT: Persons living in areas where bromomethane is being used as a soil fumigant or who are near a waste site containing bromomethane are also at risk but information on their exposures appears to be unknown. Identifying locations where use or production is permitted would help to alert physicians and concerned citizens of potential risks and possibly enable area avoidance as previously recommended. The authors point out that an exposure assessment for the general population would be helpful. Their assessment is justifiable. However, no studies of populations near waste sites have been conducted or are pending.

RESPONSE: *Because the location of permitted use can change yearly depending on whether EPA grants a critical use exemption, this information was not added to the profile.*

Chapter 7. Analytical Methods

COMMENT: I agree with the authors that an additional data need is the development of sensitive and specific assays or biomarkers to evaluate exposure levels in humans and that these methods should be used to monitor populations living in higher exposure regions. A research priority should be rapid diagnostic/assessment tools for field based monitoring or real-time, long term environmental/air monitoring studies.

RESPONSE: *ATSDR does not discuss field-based monitoring tools in the toxicological profile; thus, a data need was not added. The need for additional air monitoring studies is discussed in Section 6.8.1.*

Chapter 8. Regulations and Guidelines

COMMENT: Regulations and guidelines presented appropriately detail a narrative of how MRLs were determined for intermediate duration and chronic inhalation exposures. The narrative is accompanied by tables with relevant international and national guidelines relative to various exposure factors and agencies.

RESPONSE: *No revisions were suggested.*

Chapter 9. References

COMMENT: The list of references appears to be reasonably complete, citing government and industry reports as well as academic research. References are appropriately coded with an asterisk indicating they were cited in the test. The majority of references were, in fact, cited in the text.

RESPONSE: *No revisions were suggested.*