DISPOSITION OF PEER REVIEW COMMENTS FOR TOXICOLOGICAL PROFILE FOR CHLOROMETHANE

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Agency for Toxic Substances and Disease Registry

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

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Comments provided by Peer Reviewer #1

ATSDR Charge Questions and Responses

Chapter 1. Relevance to Public Health

QUESTION: Do you agree with those effects known to occur in humans as reported in the text? If not, please explain why and provide a copy of additional references you would cite and indicate where (in the text) these references should be included.

COMMENT: Agree. Note that Fig. 1-2 title should describe whether circled values represent NOELs or LOELs (they appear to be LOELs)

RESPONSE: *ATSDR's Guidance for the Preparation of Toxicological Profiles dictates that there should be a subtitle for this figure that specifies that the values in the figure are LOAELs. The subtitle had been inadvertently removed; it has been added back into the figure in compliance with the Guidance document.*

QUESTION: 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: A recent comprehensive analysis of development toxicity in rats, mice and rabbits (Arts et al., Regul Toxicol Pharmacol 103: 274-281, 2019) concludes that the overall developmental toxicity data are not sufficient to justify an EU REACH classification of developmental toxicity. This study was available online in February 2019, which is the ending time period identified for the literature search supporting this draft. However, it is likely that this study was not captured due to the very immediate overlap of the ending search period and its publication.

RESPONSE: *It is standard ATSDR practice to only cite primary resources in chapter 2 of the profile. Arts et al. (2019) is a review paper which cites the two Wolkowski-Tyl 1983 papers. The 1985 John-Greene letter argues that the findings from Wolkowski-Tyl are due to the sectioning technique used. These studies and the letter to the editors are already summarized in the Profile. One new study is cited in Arts et al. (2019), Theuns-van Vliet, J.G., 2016. A Prenatal Development Study in New Zealand White Rabbits with Methyl Chloride by Inhalation Preceded by a Range Finding Study. Triskelion, Zeist, the Netherlands Unpublished report. After Peer Review, ATSDR received a copy of this study and given that it was unpublished, had it peer reviewed. The peer reviewers concluded the paper was well-conducted and therefore it has now been summarized in the profile. The inclusion of this paper resulted in a modification of the conclusions on the systematic review of developmental effects on chloromethane from moderate to not classifiable.*

Details on the study were added to section 2.3 (body weight) which reads "Further, no impact on body weight was observed in New Zealand white rabbits exposed to chloromethane to doses up to 1000 ppm 6 hours per day over the course of 22 days (Theuns-van Vliet et al. 2016)." In addition a summary of the paper is also included in section 2.17 (developmental) and reads "Theuns-van Vliet 2016, an unpublished study on pregnant New Zealand White rabbits and their fetuses exposed pregnant rabbits (n=22 with 163-178 fetuses per treatment group) to approximately 0, 265, 511 or 1,012 ppm chloromethane 6 hours per day on gestation days 6-28. On gestation day 29, the rabbits were sacrificed, and developmental parameters were measured. Although some developmental effects such as some fetal deaths and flexure of the forepaw were observed in some exposed fetuses, these observations were not considered treatment-related by the authors. With regard to potential heart effects, the author found no significant differences

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in papillary muscle, chordae tendineae (heart strings), or other heart malformations in the fetuses other than indentation of the apex of the heart in 4 exposed fetuses, which the author considered to be inter-animal variation (Theuns-van Vliet 2016). Therefore, it appears there are species differences as it relates to the developmental toxicity of chloromethane."

QUESTION: Have exposure conditions been adequately described? If you disagree, please explain

COMMENT: Release of CM from vinyl chloride plastics is described as "major" anthropogenic source, based on a single paper for which no data are provided. Thus, the current description does not support chloromethane (CM) residuals in vinyl chloride plastics as a "major" anthropogenic source.

RESPONSE: *Data on chloromethane emissions or releases from vinyl chloride production were not found in the literature, but studies on releases from burning plastic were identified. The summary in chapter 1 on the relationship between chloromethane and vinyl chloride production has been updated to reflect that production could be a source and is not a definite, major source. Instead of saying "A major anthropogenic source of chloromethane in the environment is the production of vinyl chloride because chloromethane is an impurity in vinyl chloride," chapter 1 now says, "Chloromethane is an impurity in vinyl chloride, and its production could be an anthropogenic source of chloromethane in the environment." Chapter 5 also clarifies that this is a potential source, saying "Chloromethane is an impurity in vinyl chloride when the vinyl chloride is produced from the thermal dehydrochlorination of 1,2-dichloroethane (Zaidman et al. 1991). Exposures to chloromethane could take place during the manufacture of vinyl chloride or when vinyl chloride wastes have been released to the environment or to waste sites. Information is lacking to make any firm estimates of such potential exposures. Of the 236 current or past NPL sites (ATSDR 2019) showing site contamination with chloromethane, 174 (about 74%) also showed site contamination related to vinyl chloride".*

Chapter 2. Health Effects

QUESTION: Do the health effect conclusions made in Chapter 2 adequately reflect the findings in the published literature? If not, please suggest appropriate changes.

COMMENT: See the comment above noting that the report of Arts et al. (2019) should be included in the health effects review in that it provides new data and analyses addressing development toxicity potential in rats, mice and rabbits.

RESPONSE: *It is standard ATSDR practice to only cite primary resources in chapter 2 of the profile. Arts et al. (2019) is a review paper which cites the two Wolkowski-Tyl 1983 papers. The 1985 John-Greene letter argues that the findings from Wolkowski-Tyl are due to the sectioning technique they used. These studies and the letter to the editors are already summarized in the Profile. One new study is cited in Arts et al. (2019), Theuns-van Vliet, J.G., 2016. A Prenatal Development Study in New Zealand White Rabbits with Methyl Chloride by Inhalation Preceded by a Range Finding Study. Triskelion, Zeist, the Netherlands Unpublished report. After Peer Review, ATSDR received a copy of this study and given that it was unpublished, had it peer reviewed. The peer reviewers concluded the paper was well-conducted and therefore it has now been summarized in the profile. The inclusion of this paper resulted in a modification of the conclusions on the systematic review of developmental effects on chloromethane from moderate to not classifiable.*

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QUESTION: 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)? Were the major study limitations sufficiently described in the text without going into lengthy discussions? If study limitations were not adequately addressed, please suggest appropriate changes.

COMMENT: All identified human studies were appropriately caveated relative to their lack of value for serving as the bases for MRLs.

RESPONSE: *No revisions were suggested.*

QUESTION: 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: This sections appropriately identifies the studies best suited for derivation of the MRLs.

RESPONSE: *No revisions were suggested.*

QUESTION: 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: Selection of the mouse as most appropriate animal species for the neurotoxicity endpoint is appropriate given suggestion of neurotoxicity in humans and likely common metabolism of CM to GSH-derived metabolite(s) which are postulated as the likely responsible for the mode of action of CM neurotoxicity in rats and mice.

RESPONSE: *No revisions were suggested.*

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

COMMENT: Agree. Human data were not selected due to appropriate concerns associated with the adequacy of the exposure data. The selected animal studies had adequate dose-response data for the critical neurotoxicity endpoint.

RESPONSE: *No revisions were suggested.*

QUESTION: Are you aware of any studies that are not included in the profile that 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: See comment on Arts et al. (2019) evaluating developmental toxicity potential.

RESPONSE: *It is standard ATSDR practice to only cite primary resources in chapter 2 of the profile. Arts et al. (2019) is a review paper which cites the two Wolkowski-Tyl 1983 papers. The 1985 John-Greene letter argues that the findings from Wolkowski-Tyl are due to the sectioning technique they used. These studies and the letter to the editors are already summarized in the Profile. One new study is cited in Arts et al. (2019), Theuns-van Vliet, J.G., 2016. A Prenatal Development Study in New Zealand White Rabbits with Methyl Chloride by Inhalation Preceded by a Range Finding Study. Triskelion, Zeist, the Netherlands Unpublished report. After Peer Review, ATSDR received a copy of this study and given that it was unpublished, had it peer reviewed. The peer reviewers concluded the paper was well-conducted and therefore it has now been summarized in the profile. The inclusion of this paper resulted in a modification of the conclusions on the systematic review of developmental effects on chloromethane from moderate to not classifiable.*

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QUESTION: Are you aware of any studies that are not included in the profile that may be relevant to deriving MRLs for any of the substance isomers? Please provide a copy if this is a new reference.

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COMMENT: Given the uncertainly of the heart developmental toxicity reported by Wolkowski-Tyl (1981, 1983), it is appropriate not to rely on those data as the basis for an MRL. Even if the effects were to be accepted, the selected MRLs based on neurotoxicity will be protective of that endpoint.

RESPONSE: *No revisions were suggested.*

QUESTION: Were all appropriate NOAELs and/or LOAELs identified for each study (both in the text and the Levels of Significant Exposure (LSE) tables and figures)? 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: For Table 2-2, study # 10 (Chellman et al., 1986a), the 5000 ppm exposure resulting in 1/5 deaths was for a 5 day 6hr/day exposure period, not 2 days as described. For study #11, 5000 ppm induced the "serious" effect of death.

Table 2-2 should also note the data in John-Greene etal in which heart malformations were not replicated.

Table 2-2 should also include the newly published rabbit developmental toxicity data (Arts et al., 2019).

Table 2-2 does not include Wolkowki-Tyl (1983) rat developmental toxicity study.

Table 2-2, study #42 (Mitchell et al., 1979) should caveat that ocular effect was not regarded as treatment related.

Table 2-2, study #44, should note the actual numbers of animals that were in this interim sacrifice examination, not the total number of animals in the study (for the pathology endpoints).

RESPONSE: *In regard to the Chellman studies, the peer reviewer is correct, and we have corrected Table 2-2 and the corresponding Figure to indicate the 1/5 deaths occurred in the 5 day study, not the two day study.*

In regard to the John-Greene study referenced by the peer reviewer, this study is not a peer reviewed publication, but instead a letter to the editor. Therefore, this paper was not added to Table 2-2. However, the findings and conclusions from this letter are discussed in Section 2.17 (Developmental).

In regard to Arts et al. 2019, given this study is not a primary publication, we do not include that citation directly in Table 2-2. However, Arts et al. (2019) summarizes data from an unpublished study report by Theuns-van Vliet (2016). ATSDR obtained this study report from the study authors, had the information peer reviewed, and has included the findings of this research in Table 2-2, Figure 2-2, and the narrative sections where appropriate. Specifically, in Table 2-2, a NOAEL of 1000 ppm has been listed for both developmental and body weight effects.

In regard to the comment that the Wolkowski-Tyl 1983 rat developmental toxicity study is missing from Table 2-2, this data was included in the Figure 2-2. It has the figure key number of 16. Therefore, no edits were made based on this portion of the comment.

In regard to the comment on the Mitchell et al. 1979 caveat on the ocular effect, the following text was added to Table 2-2: "The authors considered this to only potentially be chemically related."

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In regard to the comment on study #44 (CIIT 1981, 12 month study), the number of animals has been corrected to those that were sacrificed at an interim sacrifice as opposed to the total number of animals in the study.

QUESTION: Do you agree with the categorization of "less serious" or "serious" for the effects cited in the LSE tables? If not, please explain why and suggest appropriate changes.

COMMENT: Agree.

RESPONSE: *No revisions were suggested.*

QUESTION: Have all possible mechanisms of action been discussed within their relevant health effect section? If not, please explain. If citing a new reference, please provide a copy and indicate where (in the text) it should be included.

COMMENT: Agree. All postulated and studies modes of actions were discussed, and generally reflected the conclusions of the study investigators.

RESPONSE: *No revisions were suggested.*

QUESTION: 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: The conclusions regarding the overall toxicity and mode of action examinations are consistent with the database. However, the genotoxicity section should note that the in vitro direct acting genotoxicity of CM was limited to extremely high concentrations in bacterial (>50,000 ppm), rat spermatocytes (30,000-50,000 ppm) and human lymphoblasts (> 10,000 ppm) (reviewed in Chellman et al., 1986). All of these extremely high concentrations are not relevant to existing animal toxicity study exposures.

RESPONSE: *In response to the reviewer's comment, text was added indicating the in vitro results demonstrated genotoxicity at high concentrations of exposure. Specifically, in Section 2.2 (Genotoxicity), the sentence summarizing the in vitro studies now reads: "Nevertheless, the in vitro studies demonstrate the direct genotoxicity of chloromethane, albeit at high concentrations of exposure" (the underlined text is new in response to this comment).*

Chapter 3. Toxicokinetics, Susceptible Populations, Biomarkers, Chemical Interactions

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

COMMENT: This section does not describe study of Heck et al (Biomed Mass Spectrometry 9: 347-353. 1982) which reports that exposure to rats to 3000 ppm CM (6 hr/day, 4 days) resulted in significant

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elevations in formaldehyde in liver, testes and brain, indicating formaldehyde as an in vivo metabolites of CM.

RESPONSE: *In response to this comment, in Section 3.1.3 the following text was added: "In addition, Heck et al. (1982) observed a doubling of formaldehyde in the liver and testes of male F344 rats after 4 days of 6 hour exposure to 3000 ppm of chloromethane compared to the control rats. Further, in this same study there was a sevenfold increase in formaldehyde in the brain of exposed rats compared to controls."*

In addition, in section 3.1.4 (Interactions with Other Chemicals), the underlined text was added: "However, as demonstrated by Jager et al., 1988, but disputed by Heck et al. (1982), there is some debate on whether formaldehyde is a metabolite of chloromethane metabolism in vivo."

QUESTION: Have all available pharmacokinetic/pharmacodynamic models and supporting data been presented? If not, please explain.

COMMENT: Yes

RESPONSE: *No revisions were suggested.*

QUESTION: Is there adequate discussion of the differences in toxicokinetics between humans and animals? Is there adequate discussion of the relevance of animal toxicokinetic information for humans?

COMMENT: Yes

RESPONSE: *No revisions were suggested.*

QUESTION: Are there any data relevant to child health and developmental effects that have not been discussed in the profile and should be? Please provide any relevant references.

COMMENT: Yes, rabbit developmental toxicity data presented in Arts etal (2019) should be provided.

RESPONSE: *It is standard ATSDR practice to only cite primary resources in chapter 2 of the profile. Arts et al. (2019) is a review paper which cites the two Wolkowski-Tyl 1983 papers. The 1985 John-Greene letter argues that the findings from Wolkowski-Tyl are due to the sectioning technique they used. These studies and the letter to the editors are already summarized in the Profile. One new study is cited in Arts et al. (2019), Theuns-van Vliet, J.G., 2016. A Prenatal Development Study in New Zealand White Rabbits with Methyl Chloride by Inhalation Preceded by a Range Finding Study. Triskelion, Zeist, the Netherlands Unpublished report. After Peer Review, ATSDR received a copy of this study and given that it was unpublished, had it peer reviewed. The peer reviewers concluded the paper was well-conducted and therefore it has now been summarized in the profile. The inclusion of this paper resulted in a modification of the conclusions on the systematic review of developmental effects on chloromethane from moderate to not classifiable.*

A summary of the paper is also included in section 2.17 (developmental) and reads "Theuns-van Vliet 2016, an unpublished study on pregnant New Zealand White rabbits and their fetuses exposed pregnant rabbits (n=22 with 163-178 fetuses per treatment group) to approximately 0, 265, 511 or 1,012 ppm

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chloromethane 6 hours per day on gestation days 6-28. On gestation day 29, the rabbits were sacrificed, and developmental parameters were measured. Although some developmental effects such as some fetal deaths and flexure of the forepaw were observed in some exposed fetuses, these observations were not considered treatment-related by the authors. With regard to potential heart effects, the author found no significant differences in papillary muscle, chordae tendineae (heart strings), or other heart malformations in the fetuses other than indentation of the apex of the heart in 4 exposed fetuses, which the author considered to be inter-animal variation (Theuns-van Vliet 2016). Therefore, it appears there are species differences as it relates to the developmental toxicity of chloromethane."

QUESTION: Is there a discussion of populations at higher risk of susceptibility? Do you agree with the choice of populations? Please explain and provide any additional relevant references.

COMMENT: Descriptions of populations at risk are appropriate.

RESPONSE: *No revisions were suggested.*

QUESTION: Are the biomarkers of exposure specific for the substance? Please explain.

COMMENT: The conclusion that there are no adequately developed biomarkers of exposure is appropriate.

RESPONSE: *No revisions were suggested.*

QUESTION: Are the biomarkers of effect specific for the substance? Please explain.

COMMENT: The discussed metabolite biomarkers are not sufficient to quantitatively characterize exposures.

RESPONSE: *No revisions were suggested.*

QUESTION: Is there adequate discussion of the interactive effects with other substances? Does the discussion concentrate on those effects that might occur at hazardous waste sites? Please explain and provide any additional references.

COMMENT: Text at bottom of p.123 continuing to top of p.124 speculates a possible interaction between CM and formaldehyde. However, Heck et al (1982) cited above indicates that exposure to rats to 6 ppm formaldehyde for 6 hr/day for 10 days did not increase formaldehyde in nasal mucusa and thus is unlikely to interact in liver, testes and brain in which CM elevated tissue formaldehyde.

RESPONSE: *In response to the peer reviewers comment the following sentence has been added to section 3.4 (Interactions with Other Chemicals): "Additionally, a consideration of how each chemical is distributed through the body and how one is exposed to it would contribute to a potential interaction."*

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QUESTION: If interactive effects with other substances are known, does the text discuss the mechanisms of these interactions? Please explain and provide any additional references.

COMMENT: Other than previous comment, interaction potential is appropriate presented.

RESPONSE: *No revisions were suggested.*

Chapter 4. Chemical and Physical Information

QUESTION: Are any of the values or information provided in the chemical and physical properties tables wrong or missing? Please explain and provide any additional references.

COMMENT: No missing data.

RESPONSE: *No revisions were suggested.*

QUESTION: Is information provided on the various forms of the substance? Please explain.

COMMENT: Yes

RESPONSE: *No revisions were suggested.*

Chapter 5. Potential for Human Exposure

QUESTION: Is the information on production, import/export, use, and disposal of the substance complete? Please explain and provide any additional relevant references.

COMMENT: Yes

RESPONSE: *No revisions were suggested.*

QUESTION: 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: p.143 states that CM "has been identified in air samples collected at 23 of 236 NPL hazardous waste sites" (citing ATSDR, 2017), but does not provide actual air concentrations. Details of concentrations "identified" should be provided.

RESPONSE: *The geometric mean of maximum concentrations in air is provided in the dataset, and it has been added to the profile.*

QUESTION: 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.

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COMMENT: The middle paragraph on p.144 notes the very important data describing massive amounts of natural CM release to atmosphere compared to TRI emissions. Further discussion should be presented as to how these global natural emissions are likely to be distributed across the US, i.e., are atmospheric levels resulting from such releases likely to represent dominate air exposures to US general population?

RESPONSE: *Literature was not found discussing whether exposure to the US general population was more likely to come from natural or anthropogenic sources from Google Scholar, Science Direct, or PubMed. Some discussion was added on the global distribution of chloromethane from all sources and on the spatial distribution in the US of chloromethane from some anthropogenic sources. This distribution is now compared to the monitoring data from EPA in the paragraph below. These paragraphs were edited as follows:*

"Chloromethane is the most abundant halocarbon in the atmosphere, and its total atmospheric burden is between 4000 to 5000 Gg (8,818,490,487 to 11,023,113,109 pounds) (Keppler et al. 2005). Total releases to environmental media estimated from the 2018 TRI are around 955,937 pounds (~433,606 kg) (TRI17 2018). Thus, more than 99% of ambient air concentrations of chloromethane on a global scale appear to come from releases from natural sources rather than from manufacturing or other emissions from anthropogenic processes or uses . Releases associated with manufacturing and production processes in the United States would constitute less than 1% of the global budget. Gases contributed by industrial and other anthropogenic sources tend to result in higher concentrations in middle northern latitudes (Khalil and Rasmussen 1999). Khalil and Rasmussen (1999) estimate that there is more chloromethane in the atmosphere in the tropical latitudes than at higher latitudes, which may be a result of more chloromethane being emitted from natural sources. McCulloch et al. (1999) estimated the global distribution of chloromethane from coal and waste combustion and industrial processes. In the United States, it appears that these emissions were higher in the east, with emissions nearing 0.022 grams of equivalent chlorine emissions per square meter per year in the Northeast and Midwest.

Typical estimates for the natural background concentrations of chloromethane in ambient air are 0.58 ppm (1.2 µg/m3) (Woodruff et al. 1998) to 0.87 ppm (1.8 µg/m3) (Logue et al. 2012). Chloromethane concentrations are often in excess of rural background concentrations in the ambient air of cities in the United States (Singh et al. 1982; Singh et al. 1983) (see Section 5.5.1). The authors suggested that this elevation may be the result of manufacturing or other anthropogenic emission sources in the urban areas, over and beyond releases from combustion or other background sources that would determine the levels in more rural areas. However, concentrations of chloromethane in air monitored by EPA in 2018 show that mean concentrations were highest in Florida, Michigan, Arizona, Delaware, and Washington D.C. (EPA 2018l), while only Florida and Michigan are accounted for in TRI (TRI17 2018). This suggests that emissions from sources aside from manufacturing contribute to chloromethane in the air in many states. Other than data from the TRI or rough estimates based on global budgets, no studies were identified that attempt to make quantitative estimates for natural or anthropogenic releases of chloromethane to the air in the United States."

QUESTION: 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

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RESPONSE: *No revisions were suggested.*

QUESTION: 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: p.163 notes that "These populations include individuals living in proximity to sites where chloromethane was produced or disposed, and individuals living near one of the 236 NPL hazardous waste sites where chloromethane has been detected in environmental media (ATSDR 20179)." However, see earlier comments that air concentrations of CM detected at NPL sites are not provided, and thus it is impossible to ascertain if the detected air concentrations differed from general background ambient CM concentrations reported at other rural and urban sites.

RESPONSE: *More discussion has been added to the profile to support this claim. Sentences were added stating: "The geometric mean of maximum concentrations in air at the 23 sites where chloromethane was detected was 0.006 mg/m^3, or 0.0029 ppm. This is higher than estimates of background concentrations in ambient air, which are between 0.00058 and 0.00087 ppm (Woodruff et al. 1998; Logue et al. 2012)."*

Chapter 6. Adequacy of the Database

QUESTION: Do you know of other studies that may fill a data gap? Please provide any relevant references.

COMMENT: See request to include Arts et al. (2019) developmental toxicity study in rabbits.

RESPONSE: *As noted in the previous responses to comments related to Arts et al. (2019), the data from the original study report Theuns-van Vliet, J.G., 2016. A Prenatal Development Study in New Zealand White Rabbits with Methyl Chloride by Inhalation Preceded by a Range Finding Study. Triskelion, Zeist, the Netherlands Unpublished report, has been incorporated throughout the profile. Therefore, a paragraph text in section 6.2 (Identification of Data Needs), in the developmental subsection, now reads: "The teratogenicity of inhalation exposure to chloromethane has been studied in rats, mice, and rabbits (Wolkowski-Tyl et al. 1981a, 1983a, Wolkowski-Tyl et al. 1981b, 1983b; Theuns-Van Vliet et al., 2016). In rats, delayed fetal development was found at a concentration that also resulted in maternal toxicity. The same was not seen in mice. Mice demonstrated cardiac heart malformations after gestational exposure to chloromethane. However, neither rats nor rabbits have experienced these effects after chloromethane exposure. Therefore, additional studies are needed to further evaluate the relevance of the delayed fetal development and cardiac effects seen in rats and mice, respectively, to humans given no other species has demonstrated the same effects.*

QUESTION: Do you agree with the identified data needs? Please explain.

COMMENT: I do not agree with data needs proposed for health implications of oral and dermal exposures. This boilerplate text is repeated throughout this section and is entirely unwarranted given draft's repeated emphasis that the high volatility of CM essentially restricts its exposures of concern to inhalation only (as is also stated repeatedly throughout the draft). It would be a complete waste of

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experimental resources to attempt to conduct oral or dermal toxicity studies to allow for oral/dermal MRL derivations for a chemical with the physico-chemico properties of CM.

Also, again given the p-chem properties of CM, there is no need to collect BCF values organisms at various trophic levels to estimate human dietary intake.

RESPONSE: *In section 6.2 (Data Needs) the following edits were made.*

In the Acute-, Intermediate-, and Chronic-Duration MRL subsections, text was added that reads as indicated below:

"As discussed above, the potential for humans to be exposed to chloromethane is greater for the inhalation route than for the oral and dermal routes, and therefore these routes of exposure are not considered to be as relevant given the likely route of exposure is inhalation"

Additional text more explicitly calling for studies on oral and dermal exposure effects have been removed from these sections.

QUESTION: Are the data needs presented in a neutral, non-judgmental fashion? Please note any bias in the text.

COMMENT: Yes

RESPONSE: *No revisions were suggested.*

Chapter 7. Regulations and Guidelines

QUESTION: Are you aware of any additional regulations or guidelines that should be included? Please provide citations.

COMMENT: Yes

RESPONSE: *No revisions were suggested.*

QUESTION: Are there any that should be removed? Please explain.

COMMENT: No

RESPONSE: *No revisions were suggested.*

Minimum Risk Levels (MRLs)

QUESTION: If no MRLs have been derived, do you agree that the data do not support such a derivation? Please explain.

COMMENT: No intermediate MRL inhalation MRL was derived because it was concluded "…using a NOAEL of 224 ppm as the basis for a point of departure would result in an intermediate MRL which is higher than the acute duration MRL." Use of 224 ppm NOEL may result in a similar or slightly lower

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MRL compared to the acute MRL when this NOEL is adjusted for 6/24 hr/day and 5/7 day/week exposure (224 x 6/24 x 5/7 = 40 ppm POD. Using the same total uncertainty factor 90 = 0.44 ppm.

Agree with decision that data are not adequate to develop oral or dermal MRLs.

RESPONSE: *No revisions were suggested.*

QUESTION: If MRLs have been derived, do you agree with the proposed MRL values? Explain. If you disagree, please specify the MRL value that you would propose.

a. Do you agree/disagree with each component of the total uncertainty factor? Explain. If you disagree, please specify the uncertainty factor(s) that you propose.

COMMENT: Agree with the proposed acute and chronic MRLs. The neurotoxicity endpoints selected for both MRLs is consistent with the primary toxicity of CM reported in animals and suspected in humans. Agree with the selection of the total UF associated with the acute and chronic MRL. The chronic MRL of 0.03 ppm (30 ppb) is likely about 10-30-fold higher than generally measured CM concentrations at various locations around the US.

RESPONSE: *No revisions were suggested*

QUESTION: Please comment on any aspect of our MRL database assessment that you feel should be addressed.

COMMENT: Overall, the toxicity endpoint (neurotoxicity) selected for the MRLs is appropriate for the overall toxicity profile of CM.

RESPONSE: *No revisions were suggested.*

Appendices

QUESTION: Please provide any comments on the content, presentation, etc. of the included appendices.

COMMENT: The methodology details for derivation of the MRLs is clearly described and appropriate.

p. A-7: "Chloromethane can quickly deplete liver GSH, which may impede the ability of GSH to prevent hepatoxicity. Additionally, Dodd et al. 1982 demonstrated that GSH can quickly recover. Therefore, intermittent exposure to chloromethane, which would allow for the repletion of GSH, may not be as toxic as continuous exposure." This speculation is inconsistent with the available mode of action data indicate GSH conjugation is not a typical detoxification mechanism for CM, but rather is an a toxification mechanism (presented clearly in earlier sections of draft; see Chellman et al., 1986). In addition, the Chellman et al (1986) study addressing the hepatoprotective effect of the leukotriene synthesis inhibitor also suggests that continued GSH depletion, coupled with a 2 hr non-exposure recovery period per day, is also consistent with the enhanced toxicity associated with 22 hr/day exposures vs 6 hr/day.

RESPONSE: *ATSDR agrees with the reviewer and the referenced text has been removed from the profile.*

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Annotated Comments on the Profile

COMMENT: No annotated comments received

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Comments provided by Peer Reviewer #2

ATSDR Charge Questions and Responses

Reviewer #2 did not provide responses to charge questions but provided annotated comments in a standalone document.

Annotated Comments on the Profile

COMMENT: "The only available human data regarding hepatic effects is from case studies which demonstrated chloromethane's potential to affect the liver through associated diagnosis of disease such as cirrhosis (Wood 1951) and jaundice (Spevak 1976) (case studies are not included in the systematic review)."

This is awkward—suggest removing "diagnosis of" so the sentence reads "through associated disease such as cirrhosis…"

RESPONSE: *This comment refers to the hepatic effects paragraph in section 1.2 (Summary of Health Effects). The sentence was edited as suggested.*

COMMENT: The detailed overview descriptions at the beginning of this chapter are presented without references. In my opinion references would help the interested reader quickly locate needed documentation of specific kinds of effects.

RESPONSE: *This comment refers to the endpoint bullet points in section 2.1 (Introduction). Citations were added as suggested.*

COMMENT: The healthy worker effect caveat is welcome and very necessary when quoting raw epidemiological mortality rate findings such as this.

RESPONSE: *No revisions suggested.*

COMMENT: Figure 2.2 shows the literature findings in a more easily understandable form. Still, the reader needs a narrative walk-through to extract the most important findings.

RESPONSE: *The LSE tables (Tables 2-1 and 2-3) and Figure 2-2 and Figure 2-3 are data summaries required in ATSDR's Guidance for the Preparation of Toxicological Profiles document. A narrative walk-through of these studies and effects organized by endpoint can be found in sections 2.1 through 2.20 of the toxicological profile.*

COMMENT: Opisthotonos—needs definition in the document for this unfamiliar term. On line dictionary says "spasm of the muscles causing backward arching of the head, neck, and spine, as in severe tetanus, some kinds of meningitis, and strychnine poisoning."

RESPONSE: *This comment refers to the use of "opisthotonos in section 2.2 (Death) in the following sentence: "Severe neurological effects, such as paralysis, convulsions, and opisthotonos, developed*

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before death." A parenthetical definition was added here. The sentence was updated as follows: "Severe neurological effects, such as paralysis, convulsions, and opisthotonos (arching of the head, neck, and spinal cord due to muscle spasms), developed before death."

COMMENT: You should give the times of these observations after exposure and the durations of the exposure.

RESPONSE: *This comment refers to the following sentence in section 2.4 (Respiratory): "Although an increase in red foci of the lungs was reported for 4/10 male rats exposed to 150 ppm, compared to no foci observed in the control, 4 female mice were observed with red foci in the controls whereas no others were reported to have foci." The following sentence was added after: "Observations were made after 90 days of exposure and when the rats were sacrificed."*

COMMENT: Briefly say what these outcomes were, perhaps in a footnote.

RESPONSE: *This comment refers to the following sentence in section 2.5 (Cardiovascular): "For example, an epidemiological study evaluated exposure to chloromethane either occupationally or through environmental exposures and neither found an association with cardiovascular outcomes (Holmes et al. 1986)." The sentence was edited to say: "For example, an epidemiological study evaluated exposure to chloromethane either occupationally or through environmental exposures and neither found an association with deaths due to cardiovascular diseases (e.g. diseases classified as circulatory system diseases using ICD codes) (Holmes et al. 1986)."*

COMMENT: This seems quite dubious as a finding.

RESPONSE: *This comment refers to the findings of Mitchell et al. (1979) described in section 2.9 (Hepatic). The profile originally stated: "Mitchell et al. (1979) reported hepatic infarct in 1/10 mice and 1/10 rats exposed to 1,500 ppm which, despite low incidence, was considered compound-related due to its unexpected occurrence in both rats and mice." The sentence was adjusted to clarify that this was the authors' conclusion and that other liver effects were also observed. The profile now states: "Mitchell et al. (1979) reported hepatic infarct in 1/10 mice and 1/10 rats exposed to 1,500 ppm which, despite low incidence, the authors considered compound-related due to its unexpected occurrence in both rats and mice and the observed increases in liver weight."*

COMMENT: The acronym ALT needs to be defined for the reader

RESPONSE: *This comment refers to the use of ALT in the following sentence in section 2.9 (Hepatic): "The authors observed a 50-fold increase in ALT activity in mice exposed for 6 hours to 1,500 ppm chloromethane without pretreatment." ALT is alanine aminotransferase. This is defined earlier in this section, so it was not defined it again here. No changes were made.*

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COMMENT: "tinctorial" is a highly unusual word that should not be used because it will not be understood by many readers. The definition that I found for it is "relating to colouring, staining, or dyeing. 2. imbuing with colour." I suggest substituting "staining".

RESPONSE: *This comment refers to the use of tinctorial in the following sentence in section 2.9 (Hepatic): "The increase was accompanied by equivocal lesions (change in tinctorial properties of liver cells, possibly due to decreased vacuolization)." This change has been made and "tinctorial" was replaced with "staining".*

COMMENT: "tinctorial" is used here for the third time in two paragraphs. This word is not known to many people and just adds murkiness to the narrative. Eliminate it by substituting "staining".

RESPONSE: *This comment refers to the use of tinctorial in the following sentence in section 2.9 (Hepatic): "A few studies have also looked at changes to hepatocytes in animals. Burek et al (1981) reported a slight liver effect characterized as altered staining properties of hepatocytes in rats exposed to 500 ppm for 72 hours and sacrificed immediately." This change has been made and "tinctorial" was replaced with "staining".*

COMMENT: "ALT" and "AST" need to be difined

RESPONSE: *This comment refers to the use of tinctorial in the following sentence in section 2.9 (Hepatic): "When McKenna et al. (1981b) exposed Beagle dogs to 99.9% pure chloromethane there were no effects on ALT or AST, but hepatocytes were swollen in 2/4 dogs at 400 ppm, 1/4 dogs at 150 ppm, 2/4 dogs at 50 ppm, and 0/4 controls." ALT and AST were both defined earlier in the second paragraph in section 2.9 (Hepatic). No definition was added here.*

COMMENT: There is no reference that advances the theory that is apparently "disputed" here. I would delete the sentence.

RESPONSE: *This comment refers to the following sentence in section 2.10 (Renal): "After a single, 8 hour exposure to 1,000 ppm chloromethane in male or female mice, formaldehyde levels were not observed to increase in livers or kidneys (ex vivo), disputing the theory that chloromethane exposure would produce formaldehyde that might cause renal cancer." This sentence was deleted.*

COMMENT: "women" should be "woman" as only one person was involved

RESPONSE: *The peer reviewer suggests this change in the following sentence in section 2.12 (Ocular): One case report identified blindness in a women following the cleaning of a toilet with sodium hypochlorite and hydrochloric acid." This change was made (woman).*

COMMENT: I would delete this sentence as unneeded and unsupported speculation.

RESPONSE: *The peer reviewer suggests deleting the following sentence from the first paragraph of section 2.12 (Ocular): "Experimental mixing of these chemicals with urine produced chloromethane and*

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chloramine, and the authors hypothesized that chloramine exposure might inhibit enzymes required for chloromethane metabolism, thereby potentiating the effects of chloromethane exposure (Minimi et al. 1998)." This sentence has been deleted.

COMMENT: Since these lesions were not observed at greater frequency in exposed animals than controls, there seems no reason to confuse the reader by reporting them.

RESPONSE: *This comment refers to the following discussion of the CIIT 1981 study in section 2.12 (Ocular): "In CIIT (1981) male and female F344 rats and B6C3F1 mice were exposed to chloromethane at target concentrations of 0, 50, 225, or 1,000 ppm, 6 hours/day, 5 days/week. Ophthalmic exams were performed at baseline and at sacrifice. At 6 months, corneal cloudiness or opacity without conjunctivitis was noted in control rats (2 /10 male rats and 1/10 females), at 50 ppm (1/10 males), and at 225 ppm (1/10 females). The significance of this lesion is not clear because there was no dose-related incidence pattern at later sacrifices." The data is presented as it was in the study report and it is appropriately caveated, so no edits were made based on this comment.*

COMMENT: 3 significant figures are barely acceptable here. 4 significant figures are excessive.

RESPONSE: *The peer reviewer suggests changing the data in section 2.15 (Neurological) in the following sentence: "Ambient air concentrations of chloromethane ranged from 1.8 to 70 ppm between the plants, with means from each plant ranging from 8.46 to 58.72 ppm. The overall mean was 33.57 ppm. Mean concentration of chloromethane in breath by plant ranged from 10.81 to 24.19 ppm, with an overall mean of 13.32 ppm." These are measurements provided in Repko et al. 1976, a study conducted in conjunction with industry and submitted to NIOSH. We pulled these measurements from Table 4 on p.17 of the Repko study and left the numbers as they were reported by the study authors. No changes were made in response to this comment.*

COMMENT: "sacrificed for cause" seems odd. I think it is sufficient to say simply "sacrificed"

RESPONSE: *The peer reviewer suggests this change in section 2.15 (Neurological) in the following sentence: "All females in this group were sacrificed for cause on GD 11-14 prior to the completion of exposure to GD 17; two females died prior to necropsy (as early as GD 9, after only 4 days of exposure)." "For cause" was deleted in response to this comment.*

COMMENT: The authors should include in their description the duration of exposure that produced these effects.

RESPONSE: *This comment refers to the following sentence in section 2.15 (Neurological): "Exposure to 500 ppm chloromethane resulted in ataxia in 6/74 females by GD 18; exposure to 750 ppm resulted in hyperactivity, ataxia, piloerection, tremors and convulsions." The length of exposure in this study was measured in gestation days. The next sentence says: "The authors concluded that inhalation exposure to chloromethane during GD 6-17 resulted in maternal toxicity at 750 ppm; teratogenic effects were seen at 500 and 750 ppm." The sentence in question and the next sentence explain that exposure occurred from gestation day 6 to 17. Therefore, no changes were made to this sentence.*

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COMMENT: This paragraph seems very confused. It begins by saying "Two studies evaluated at the effects of inhaled chloromethane exposure on beagles and cats (McKenna et al. 1981a; McKenna et al. 1981b) with doses up to 500 ppm and did not observe an effect." But the presentation does not apparently go on to say what effects were found at what higher doses.

RESPONSE: *This comment refers to the second paragraph in section 2.16 (Reproductive): "Based on a systematic review of the literature, reproductive effects are a suspected health effect related to chloromethane exposure. Much of the evidence for chloromethane's reproductive toxicity has come from a variety of rodent studies. Two studies evaluated the effects of inhaled chloromethane exposure on beagles and cats (McKenna et al. 1981a; McKenna et al. 1981b), with doses up to 500 ppm and did not observe an effect. Rodent studies at doses greater than 400 ppm observed an association. Reproductive effects appear to be particularly pronounced in male rodents, with several studies reporting enzymatic mediation of lesions (Chapin et al. 1984), dose-dependent development of lesions (Burek et al. 1981; Hamm et al. 1985; Morgan et al. 1982; Working et al. 1985b), disrupted or incomplete spermatogenesis (Burek et al. 1981; Chapin et al. 1984; Chellman et al. 1987; Morgan et al. 1982; Working et al. 1985b), and obstruction of the epididymis (Burek et al. 1981), among other effects. Pre- and post-implantation loss in females was attributed to failure of fertilization rather than early embryonic death (Working and Bus 1986), and to decreased sperm quality in chloromethane-exposed males (Working et al. 1985a). Most studies found more pronounced effects at higher levels of chloromethane exposure." The third sentence ("Two studies evaluated… and did not observe an effect") was moved to the end of the paragraph for clarity.*

COMMENT: What was the daily duration of exposure here?

RESPONSE: *The peer reviewer suggests adding the duration of exposure from the Chapin et al. 1984 study to the following sentence in section 2.16 (Reproductive): "At a slightly higher exposure level of 3500 ppm chloromethane (Chapin et al., 1984), with an interim delay to improve the condition of animals surviving the first 5 days of exposure, testicular and epididymal lesions were visible after 9 days of exposure." The duration was 6 hours/day. This information was added to the sentence. The profile now states: "At a slightly higher exposure level of 3500 ppm chloromethane (Chapin et al., 1984), with an interim delay to improve the condition of animals surviving the first 5 days of exposure, testicular and epididymal lesions were visible after 9 days of exposure for 6 hours per day."*

COMMENT: The sentence begins with "Which" I would suggest changing this to "These abnormalities were…"

RESPONSE: *The peer reviewer suggests this change in section 2.16 (Reproductive). The sentence says: "Which were observed eighteen hours after their last exposure during necropsy (Morgan et al., 1982)." This change was made.*

COMMENT: Delete "these"

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RESPONSE: *The peer reviewer suggests this change in section 2.16 (Reproductive). The sentence says: "Across the male rodent studies these lesions were often associated with testicular degeneration and ineffective spermatogenesis." This change was made, and "these" was deleted.*

COMMENT: "sufficient concentration" implies a threshold in the dose response relationship for DNA damage. This is very likely to be incorrect and must be deleted, as DNA damage occurs with any concentration of a DNA reactive agent. You could say "detectable DNA damage".

RESPONSE: *This comment refers to the following sentence in section 2.16 (Reproductive): "The authors concluded that a cytotoxic rather than genotoxic mechanism may play a role in the observed preimplantation losses, and that chloromethane may not reach the testes in sufficient concentration to produce DNA damage." This change was made so the sentence now says: "The authors concluded that a cytotoxic rather than genotoxic mechanism may play a role in the observed preimplantation losses, and that chloromethane may not reach the testes in sufficient concentration to produce detectable DNA damage."*

COMMENT: "inanition" is another highly unusual word that will not be clear to many readers. The definition I found for it is "exhaustion caused by lack of nourishment" I think this word should be deleted or a substitute found to describe the author's experimental findings more clearly.

RESPONSE: *This comment refers to the following sentence in the second paragraph in section 2.18 (Other Noncancer): "There was a significant degree of inanition in the 200-C and 400-C ppm mice prior to necropsy with decreased carcass size, amount of abdominal fat, amount of ingesta in the gastrointestinal tract, and small, pale livers." This word was replaced with "fatigue (likely due to decreased food consumption)."*

COMMENT: This is nonsensical. I don't know of any previous case where a dominant lethal observation has been dismissed on this basis. I would suggest deleting this sentence. Other things being equal, an observation of a dominant lethal effect in a mammal should be regarded as a very significant finding of genetic damage. Dominant lethal effects are fairly rare findings that must be regarded as important evidence of the potential of the compound to cause adverse genetic effects, at least at high doses.

RESPONSE: *This comment refers to the following sentence in section 2.20 (Genotoxicity): "Experiments on the mechanism of the post implantation loss observed in the females mated to the exposed males indicated that the dominant lethal effect may be secondary to epididymal inflammation , rather than a direct genotoxic effect of chloromethane (Chellman et al. 1986c)." Given the reviewers comments and in keeping with the authors interpretation, we kept in the inflammation statement, but clarified it is possible both mechanisms are playing a role and one should not be dismissed over the other. The profile now states: "Experiments on the mechanism of the post implantation loss observed in the females mated to the exposed males indicated both a dominant lethal effect and epididymal inflammation potentially played a role in post implantation loss (Chellman et al. 1986c)."*

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COMMENT: It should be presumed that positive dominant lethal observations in animals are a strong indicator of genetic risk in people. The current document presents an unduly cautious statement of likely genetic risk, particularly in the light of the positive findings from the dominant lethal assay.

RESPONSE: *This comment refers to the following sentence in section 2.20 (Genotoxicity): "Although chloromethane produced genotoxic effects in human lymphocytes in culture, it is not known whether chloromethane could produce dominant lethal mutations or other genotoxic effects in humans exposed by any route." This sentence has been removed based on the reviewer's comment.*

COMMENT: Nonsense. Dominant lethal assays are just not subject to this kind of problem because the effects are observed in the offspring of the dams mated to exposed males. This appears to be a case of an author trying to write off his own results because they might be unfavorable to the sponsor of his/her research.

RESPONSE: *This comment refers to the following sentence in section 2.20 (Genotoxicity): "Since concurrent exposure of male rats to chloromethane and BW755C, an anti-inflammatory agent, did not result in post implantation loss, it was suggested that the dominant lethal mutation was probably due to chloromethane-induced epididymal inflammation, possibly by inflammatory cell production (Chellman et al. 1986c)." This sentence was edited as follows based on the reviewer's comment: "Since concurrent exposure of male rats to chloromethane and BW755C, an anti-inflammatory agent, did not result in post implantation loss, it was suggested that the dominant lethal mutation may be due to chloromethane-induced epididymal inflammation,. However, there was a positive response to an assessment of a dominant lethal effect, and this cannot be ruled out as a mechanism of toxicity (Chellman et al. 1986c)."*

COMMENT: As I have already commented, this alleged inflammation-related complication of dominant lethal mutagenic toxicity is unsupported by a plausible mechanistic theory and should be deleted as an industry-inspired self serving argument to avoid the conclusion that chloromethane has definite genetic toxicity. It has no place in an ATSDR analysis.

RESPONSE: *This comment refers to the following sentence in section 2.20 (Genotoxicity): "Since studies using ^{14}C-chloromethane indicated that the carbon atom from chloromethane becomes incorporated into normal macromolecules via the one-carbon pool rather than binding to macromolecules as an alkylating agent (Kornbrust and Bus 1983; Peter et al. 1985), and since the dominant lethal effect may be secondary to inflammation, it is possible that in vivo genotoxicity and carcinogenicity (see Section 2.19) may be secondary to other toxic effects of chloromethane." "And since the dominant lethal effect may be secondary to inflammation" has been removed from this sentence.*

COMMENT: 1st paragraph. These conclusions require references

RESPONSE: *This comment refers to the bullet points at the beginning of section 3.1 (Toxicokinetics). References have been added.*

COMMENT: This sentence is confusing because the different external concentrations should give rise to different blood levels. I suspect that something has been omitted in the final editing of this sentence

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RESPONSE: *This comment refers to the following sentence in section 3.1.1 (Absorption): "This proportionality was confirmed at 15,000 and 40,000 ppm chloromethane for which the respective blood concentrations in dogs peaked at 0.12 mmol/100 cc (von Oettingen et al. 1949)." Edits were made so that the sentence now says: "This proportionality was confirmed at 15,000 and 40,000 ppm chloromethane for which the respective blood concentrations in dogs peaked at 0.12 mmol/100 cc at the lower dose with proportional extrapolation to approximately 0.32 mmol/100 cc at the higher dose (von Oettingen et al. 1949)."*

COMMENT: There must be a qualification here for the time of observation following exposure.

RESPONSE: *This comment refers to the following sentence in section 3.1.3 (Metabolism): "Nolan et al. (1985) exposed human volunteers to either 10 or 50 ppm chloromethane and determined that 15% and 61% of the chloromethane was metabolized, respectively, by those who metabolized chloromethane slowly or more rapidly (termed slow and fast metabolizers)." The quantification of within 6 hours of exposure was added to the sentence, which now states: "Nolan et al. (1985) exposed human volunteers to either 10 or 50 ppm chloromethane and determined that 15% and 61% of the chloromethane was metabolized within 6 hours after exposure, respectively, by those who metabolized chloromethane slowly or more rapidly (termed slow and fast metabolizers)."*

COMMENT: I can see no toxicological importance for this observation. I would just delete the paragraph in full.

RESPONSE: *The peer reviewer suggests deleting the following paragraph in section 3.1.3 (Metabolism):*

"Delbanco et al (2001) evaluated the enzyme activities of subgroups of GST in cancers compared with normal tissue from the same patient (N=21). Chloromethane was one of five substrates used to assess enzyme activities in GST subgroups. Chloromethane is specific to one isozyme: GST θ. In general, a decrease in enzyme activity was reported in renal tumors compared with surrounding normal tissue. For chloromethane the decrease in enzyme activity was 69% in renal cancers compared to normal tissue. There was no correlation between GST activities in tumors and tumor stage or age or sex of the patient. These results suggest that a GST dependent initial bioactivation can occur in the kidney."

This paragraph has been deleted.

COMMENT: Here and elsewhere, the authors say that a reaction "reached equilibrium". This is a mistake because one never really "reaches" full equilibrium. Equilibrium is approached, and there will come a point where it is not possible to measure any residual departure from equilibrium, but technically it is better to say that equilibrium is closely approached but not actually "reached".

RESPONSE: *This comment refers to the following sentence in section 3.1.4 (Excretion): "Putz-Anderson et al. (1981a) exposed volunteers to 100 or 200 ppm chloromethane for 3 hours, and breath concentrations reached equilibrium within one hour at 36 ppm (SD 12 ppm) and 63 ppm (SD 23.6 ppm) respectively." We agree and the phrase "reached equilibrium" was replaced with "approached equilibrium" here and throughout the Profile.*

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COMMENT: It is highly unusual for a PBPK model to have different compartments for working muscle and resting muscle. Clearly the same muscle can be resting and working at different times.

RESPONSE: *This comment refers to the following sentence in section 3.1.5 (3.1.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models): "Jonsson et al. (2001) used the data from the GSTT1 deficient group from the Lof et al. (2000) study (See Section 3.1.3) to develop a standard PBPK model for chloromethane with six tissue compartments: lung, working muscle, resting muscle, well-perfused tissues, liver, and fat." According to Jonsson et al "The muscle compartment, which includes skin, was subdivided in two compartments of equal volume, named resting and working muscle…to account for the increased blood flow to leg muscle during ergometer bicycle exercise." Experimental data were created with eight subjects that were exposed to methyl chloride (10 ppm, 120 min) in an exposure chamber with light physical exercise (bike). Therefore, no changes were made based on this comment as it is accurate as stated.*

COMMENT: typically this is done by adjusting the value of a metabolism parameter. Was this the case here?

RESPONSE: *This comment refers to the following sentence in section 3.1.5 (3.1.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models) in reference to the Jonsson et al. 2001 PBPK model: "The model was fit to experimental data." The sentence was edited to clarify and now states: "The model was fit to the experimental data using a Bayesian approach and assumptions regarding parameters related to metabolism."*

COMMENT: Reference here to "a young guinea pig" indicates that conclusions are being drawn from observations of a single animal. If so, this is just too slender an observational database to be used.

RESPONSE: *This comment refers to the following sentence in section 3.2 (Children and Other Populations That Are Unusually Susceptible): "Also, the older animals were more likely to die from high exposure; 500 ppm chloromethane resulted in mortality of adults within 1 week while a young guinea pig survived 12 weeks of the same exposure and was still alive in a non-functional state 14 months later." Updated this to the citation of the other paper, which made this point more clearly. The sentence now states: "Also, the older animals were more likely to develop severe effects or die from high exposure (Smith and von Oettingen 1947a, 1947b); young mice, rats, guinea pigs, and dogs were found to have less severe effects compared to older animals exposed to the same amount of chloromethane, and in some cases survived exposure to high levels of chloromethane, while older animals died. 500 ppm chloromethane resulted in mortality of adults within 1 week, while a young guinea pig survived 12 weeks from the same exposure and was still alive in a non-functional state 14 months later."*

COMMENT: It is not just "anticipated". The genetics of adults are necessarily the same as the genetics of children. There can be no case where a polymorphism present in adults is not also present in children

RESPONSE: *This comment refers to the following sentence in section 3.2 (Children and Other Populations That Are Unusually Susceptible): "It is anticipated that children would have a polymorphism similar to the adult population, although no specific data have been collected to test this hypothesis." To address this comment, this sentence was deleted, and the following sentence was edited to say: "If a*

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polymorphism is present in children, then some children with the same polymorphism as adults (i.e., those with higher levels of glutathione-S-transferase) would be more susceptible to the toxic effects of chloromethane."

COMMENT: Nonsense. I don't care whether there is a reference to this absurdity (NRC 1993). This must be deleted.

RESPONSE: *This comment refers to the following sentence in section 3.2 (Children and Other Populations That Are Unusually Susceptible): "For example, the fact that infants breathe more air per kilogram of body weight than adults may be somewhat counterbalanced by their alveoli being less developed, so there is a disproportionately smaller surface area for absorption (NRC 1993)." This sentence was deleted.*

COMMENT: This appears to be another example of an attempt by industrial sponsors of research to minimize the potential significance of positive toxicity findings. It should not have the implicit endorsement of the ATSDR.

RESPONSE: *This comment refers to the following sentence in section 3.2 (Children and Other Populations That Are Unusually Susceptible): "Studies on the mechanism of chloromethane-induced testicular effects suggested that preimplantation loss was due to cytotoxicity of chloromethane to sperm in the testes at the time of exposure, rather than to a genotoxic effect on the sperm (Chellman et al. 1986c, Chellman et al. 1987; Working and Bus 1986; Working et al. 1985a, Working et al. 1985b)." The text was edited to address this comment, but the inflammation text was kept. The following changes were made: "Studies on the mechanism of chloromethane-induced testicular effects suggested that preimplantation loss was potentially due to cytotoxicity of chloromethane to sperm in the testes at the time of exposure (Chellman et al. 1986c, Chellman et al. 1987; Working and Bus 1986; Working et al. 1985a, Working et al. 1985b). However, these findings do not negate the possibility of a dominant lethal mutation leading to post-implantation loss. Both mechanisms are plausible."*

COMMENT: This presumes a mechanism of distortion of dominant lethal results that, to my knowledge, as not been established in prior literature. I think it should be removed or highly qualified as a possible industry-sponsored attempt to minimize the implications of toxicity/mutagenicity findings for marketing their products.

RESPONSE: *This comment refers to the following sentence in section 3.2 (Children and Other Populations That Are Unusually Susceptible): "Since concurrent exposure of male rats to chloromethane and BW755C, an anti-inflammatory agent, greatly reduced the amount of post implantation loss, the dominant lethal mutations probably resulted secondary to the epididymal inflammatory response (Chellman et al. 1986c; Working and Chellman 1989)." Given the reviewers comments and in keeping with the authors interpretation, we kept the inflammation statement but made clarifications. The profile now states: "Since concurrent exposure of male rats to chloromethane and BW755C, an anti-inflammatory agent, greatly reduced the amount of post implantation loss, it is possible both dominant lethal and an epididymal inflammatory response (Chellman et al. 1986c; Working and Chellman 1989) can lead to post implantation loss."*

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COMMENT: I would change "female" to "male and female" as biomarkers of sperm parameters should also be included.

RESPONSE: *This comment refers to the boilerplate language in section 3.3 (Biomarkers of Exposure, Effect, and Susceptibility). The commenter suggests these changes to the following sentence: "This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity." This is boilerplate language from ATSDR's Guidance for the Preparation of Toxicological Profiles document, so while the reviewer makes a good point regarding examples of biomarkers of effect, this introduction is not meant to be exhaustive. No changes were made in keeping with the Guidance document and other recently published Profiles.*

COMMENT: This is a remarkable claimed increase—more than ten fold! This seems very doubtful. I think the numbers here should be double-checked.

RESPONSE: *This comment refers to the following sentence in section 5.2.2 (Import/Export): "U.S. imports of chloromethane increased from 228,303 kg in 2014 to 3,246,844 kg in 2018 (USITC 2019)." The USITC data have been double checked and confirmed. Other sources on the amount of chloromethane imports and exports were not located. One website shows chloromethane and chloroethane imports (in dollar units) increasing at a similar rate: https://www.flexport.com/data/hs-code/290311-chloromethane-and-chloroethane. Therefore, no changes were made in response to this comment.*

COMMENT: These two estimates show a relatively wide spread. It would be helpful for the reader if the authors would briefly give the reason for the relatively large difference between the two estimates.

RESPONSE: *This comment refers to the following sentence in the water paragraph in section 5.4.2 (Transport and Partitioning): "Using the embedded scenarios for a typical pond and lake developed by the Athens Environmental Research Laboratory of the EPA, half-lives for volatilization were calculated to be 2.5 hours and 18 days, respectively." This information is from the report "Environmental Pathways of Selected Chemicals in Freshwater Systems Part 1 Background and Experimental Procedures". The report provides background information on EXAMS and the environmental assessment used to assess the rates of removal in different freshwater systems. These sentences were added: "The rate of disappearance of chemicals in the model is assumed to be driven by transformation and transport processes and by hydraulic and hydrological processes in the water bodies (Smith et al. 1977). For different water bodies, data on physical, chemical, and biological processes are integrated by the model, resulting in different half-lives for volatilization."*

COMMENT: The geometric standard deviations of eight or nine thousand in this table seem highly suspect. The geometric standard deviation can be calculated by first calculating the logs of the individual parameter values, calculating the standard deviation of these logs, and then doing the antilog of the result. For example, if logs to base 10 are used, then the geometric standard deviation = 10^(Standard deviation

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of base 10 logs). Additionally, the median air level of "0.002140767" contains an impossibly large number of significant figures—7. The value presented should be shortened to no more than 3 significant figures—0.00214.

RESPONSE: *This comment refers to table 5-6 in section 5.5 (Levels in the Environment), which shows the concentrations of chloromethane in soil, water, and air at NPL sites. In response to this comment, all of the concentrations in the table were updated to be three significant figures. The values were also checked, and some were updated. The geometric standard deviations were previously inappropriately converted to 8192 and 9092 for water and soil, respectively; these have been corrected and are now 8.19 and 9.09. The values for air were not converted from mg/L to ppb using appropriate conversion factors prior to this draft, so these have also been corrected to 1.04 (median) and 3.29 ppb (geometric mean).*

COMMENT: The connection here is necessarily indirect because cellulose does not have chlorine atoms needed for the formation of chloromethane.

RESPONSE: *This comment refers to the following sentence in section 5.5.4 (Other Media). "Palmer (1976) suggested that 1 cm^3 of chloromethane gas (2.2 mg) was produced for each gram of cellulose burned (glowing combustion)." In response to this comment more context from the paper was added to explain how chloromethane is produced by heating chlorine compounds in contact with cellulose. This section now states: "When chlorine compounds are heated in contact with cellulose, gaseous chlorine compounds are produced by reactions involving the hydroxyl groups or the water formed in situ by dehydration (Palmer 1976). Wood pulp and other cellulosic materials can release methane when burned which is converted to chloromethane by the chlorine in the material, producing 1 cm^3 of chloromethane gas (2.2 mg) for each gram of cellulose burned in glowing combustion (Palmer 1976)."*

COMMENT: I think this should be deleted. Without actual measurements it is not necessary to include this speculative suggestion. A full model-based assessment of the difference in exposures to children vs adults would require taking into account the mixing of air within residences and other buildings, ventilation rates, and numerous other considerations.

RESPONSE: *The commenter suggests deleting the following sentence from section 5.6 (General Population Exposure): "Chloromethane vapors are heavier than air and since young children are closer to the ground or floor because of their height, they may be exposed to more chloromethane than nearby adults during accidental exposures." This has been deleted.*

COMMENT: The reference to that one study should be explicitly included here.

RESPONSE: *The commenter suggests adding a citation to the following sentence in section 6.1 (Existing Information on Health Effects): "A number of studies have evaluated the health effects of chloromethane exposure in animals for the inhalation route, although only a single comprehensive chronic study in rats and mice has been performed." A reference to CIIT 1981 was added here.*

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COMMENT: I would delete this as this mechanism of interference with dominant lethal results has not, to my knowledge, been documented elsewhere in the literature. I believe it is likely an attempt by industrial sponsors of the research to downplay the likely significant genetic hazard of chloromethane.

RESPONSE: *The commenter suggests deleting the following sentence in the Genotoxicity health effects paragraph in section 6.2 (Identification of Data Needs): "Studies of the mechanism of dominant lethal mutations in rat sperm resulting from inhalation exposure of male rats to chloromethane suggest that the dominant lethal effects may be secondary to inflammation of the epididymis (Chellman et al. 1986c)." This section was edited based on the reviewer's comments as follows: "According to the study authors, dominant lethal mutations in rat sperm resulting from inhalation exposure of male rats to chloromethane suggest that the dominant lethal effects may be secondary to inflammation of the epididymis (Chellman et al. 1986c). However, this is not known, and dominant lethal effects are still a concern."*

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Comments provided by Peer Reviewer #3

ATSDR Charge Questions and Responses

Chapter 1. Relevance to Public Health

QUESTION: Do you agree with those effects known to occur in humans as reported in the text? If not, please explain why and provide a copy of additional references you would cite and indicate where (in the text) these references should be included.

COMMENT: Yes, but data re few

RESPONSE: *No revisions were suggested.*

QUESTION: 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: Maybe, this is an age-old problem of cross-species generalizability.

RESPONSE: *No revisions were suggested.*

QUESTION: Have exposure conditions been adequately described? If you disagree, please explain

COMMENT: Yes

RESPONSE: *No revisions were suggested.*

Chapter 2. Health Effects

QUESTION: Do the health effect conclusions made in Chapter 2 adequately reflect the findings in the published literature? If not, please suggest appropriate changes.

COMMENT: Yes, although details were lacking on human cancer studies.

RESPONSE: *Reviewer #3 provided annotated comments on the cancer section to address this concern. These have been responded to as appropriate and are describe below in the annotated comments section.*

QUESTION: 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)? Were the major study limitations sufficiently described in the text without going into lengthy discussions? If study limitations were not adequately addressed, please suggest appropriate changes.

COMMENT: Yes

RESPONSE: *No revisions were suggested.*

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QUESTION: 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: Yes

RESPONSE: *No revisions were suggested.*

QUESTION: 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: Yes

RESPONSE: *No revisions were suggested.*

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

COMMENT: Yes

RESPONSE: *No revisions were suggested.*

QUESTION: Are you aware of any studies that are not included in the profile that 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

RESPONSE: *No revisions were suggested.*

QUESTION: Are you aware of any studies that are not included in the profile that may be relevant to deriving MRLs for any of the substance isomers? Please provide a copy if this is a new reference.

COMMENT: No

RESPONSE: *No revisions were suggested.*

QUESTION: Were all appropriate NOAELs and/or LOAELs identified for each study (both in the text and the Levels of Significant Exposure (LSE) tables and figures)? 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: Yes

RESPONSE: *No revisions were suggested.*

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QUESTION: Do you agree with the categorization of "less serious" or "serious" for the effects cited in the LSE tables? If not, please explain why and suggest appropriate changes.

COMMENT: Yes

RESPONSE: *No revisions were suggested.*

QUESTION: Have all possible mechanisms of action been discussed within their relevant health effect section? If not, please explain. If citing a new reference, please provide a copy and indicate where (in the text) it should be included.

COMMENT: Yes

RESPONSE: *No revisions were suggested.*

QUESTION: 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, but the database is not adequate regarding chronic effects. This is partly because exposure beyond background ambient air/water exposure, which are uniformly low, is primarily occupational and there are few studies

RESPONSE: *As noted by the peer reviewer, the database for chronic-duration exposure is limited. There is one inhalation study, CIIT 1981, and no oral exposure studies of chronic duration. However, the CIIT 1981 study is a full toxicological evaluation of chloromethane in both rats and mice evaluating multiple durations of exposure. In addition, the main effects observed in this study (e.g., neurological) were supported by shorter-duration studies. Therefore, ATSDR believes the database is adequate to inform a chronic duration inhalation MRL. However, ATSDR does agree the data is inadequate for an oral MRL and have concluded this in the Profile. No changes have been made to the profile in response to this comment.*

Chapter 3. Toxicokinetics, Susceptible Populations, Biomarkers, Chemical Interactions

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

COMMENT: I am an epidemiologist and not competent to comment on details of toxicokinetics

RESPONSE: *No revisions were suggested.*

QUESTION: Have all available pharmacokinetic/pharmacodynamic models and supporting data been presented? If not, please explain.

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COMMENT: I am an epidemiologist and not competent to comment on details of toxicokinetics

RESPONSE: *No revisions were suggested.*

QUESTION: Is there adequate discussion of the differences in toxicokinetics between humans and animals? Is there adequate discussion of the relevance of animal toxicokinetic information for humans?

COMMENT: I am an epidemiologist and not competent to comment on details of toxicokinetics

RESPONSE: *No revisions were suggested.*

QUESTION: Are there any data relevant to child health and developmental effects that have not been discussed in the profile and should be? Please provide any relevant references.

COMMENT: Not that I know of

RESPONSE: *No revisions were suggested.*

QUESTION: Is there a discussion of populations at higher risk of susceptibility? Do you agree with the choice of populations? Please explain and provide any additional relevant references.

COMMENT: Yes, it seems so. Don't know of other data.

RESPONSE: *No revisions were suggested.*

QUESTION: Are the biomarkers of exposure specific for the substance? Please explain.

COMMENT: There are no good biomarkers of exposure

RESPONSE: *No revisions were suggested.*

QUESTION: Are the biomarkers of effect specific for the substance? Please explain.

COMMENT:

RESPONSE: *No revisions were suggested.*

QUESTION: Is there adequate discussion of the interactive effects with other substances? Does the discussion concentrate on those effects that might occur at hazardous waste sites? Please explain and provide any additional references.

COMMENT: This discussion seems adequate. It seems there is little literature.

RESPONSE: *No revisions were suggested.*

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QUESTION: If interactive effects with other substances are known, does the text discuss the mechanisms of these interactions? Please explain and provide any additional references.

COMMENT: I don't know of any other literature

RESPONSE: *No revisions were suggested.*

Chapter 4. Chemical and Physical Information

QUESTION: Are any of the values or information provided in the chemical and physical properties tables wrong or missing? Please explain and provide any additional references.

COMMENT: I am an epidemiologist and cannot comment on this section.

RESPONSE: *No revisions were suggested.*

QUESTION: Is information provided on the various forms of the substance? Please explain.

COMMENT: I am an epidemiologist and cannot comment on this section.

RESPONSE: *No revisions were suggested.*

Chapter 5. Potential for Human Exposure

QUESTION: Is the information on production, import/export, use, and disposal of the substance complete? Please explain and provide any additional relevant references.

COMMENT: Yes, very good.

RESPONSE: *No revisions were suggested.*

QUESTION: 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 revisions were suggested.*

QUESTION: 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: This seems to be an adequate discussion.

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RESPONSE: *No revisions were suggested.*

QUESTION: 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 although it would be good to always translate ppm to ug/m3 when giving information on levels, as the units differ at different points in the text.

RESPONSE: *As dictated by ATSDR's Guidance for the Preparation of Toxicological Profiles air concentrations should use the same units as those presented in the inhalation LSE table. The LSE table uses ppm, so all units in Chapter 5 pertaining to air have been updated to ppm, units for water are presented as g/L, and g/kg for soil.*

QUESTION: 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 revisions were suggested.*

Chapter 6. Adequacy of the Database

QUESTION: Do you know of other studies that may fill a data gap? Please provide any relevant references.

COMMENT: No

RESPONSE: *No revisions were suggested.*

QUESTION: Do you agree with the identified data needs? Please explain.

COMMENT: Yes (there are few data)

RESPONSE: *No revisions were suggested.*

QUESTION: Are the data needs presented in a neutral, non-judgmental fashion? Please note any bias in the text.

COMMENT: Yes

RESPONSE: *No revisions were suggested.*

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Chapter 7. Regulations and Guidelines

QUESTION: Are you aware of any additional regulations or guidelines that should be included? Please provide citations.

COMMENT: No

RESPONSE: *No revisions were suggested.*

QUESTION: Are there any that should be removed? Please explain.

COMMENT: No

RESPONSE: *No revisions were suggested.*

Minimum Risk Levels (MRLs)

QUESTION: If no MRLs have been derived, do you agree that the data do not support such a derivation? Please explain.

COMMENT: I am not a toxicologist and cannot comment here, as MRLs here have derived largely from animal data. There are few human data beyond high dose experimental data, so human data cannot be used for MRLs in general.

RESPONSE: *No revisions were suggested.*

QUESTION: If MRLs have been derived, do you agree with the proposed MRL values? Explain. If you disagree, please specify the MRL value that you would propose.

a. Do you agree/disagree with each component of the total uncertainty factor? Explain. If you disagree, please specify the uncertainty factor(s) that you propose.

COMMENT: I am not a toxicologist and cannot comment here, as MRLs here have derived largely from animal data. There are few human data beyond high dose experimental data, so human data cannot be used for MRLs in general.

RESPONSE: *No revisions were suggested.*

QUESTION: Please comment on any aspect of our MRL database assessment that you feel should be addressed.

COMMENT: I am not a toxicologist and cannot comment here, as MRLs here have derived largely from animal data. There are few human data beyond high dose experimental data, so human data cannot be used for MRLs in general.

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RESPONSE: *No revisions were suggested.*

Appendices

QUESTION: Please provide any comments on the content, presentation, etc. of the included appendices.

COMMENT: No comments received

RESPONSE: *No revisions were suggested.*

Annotated Comments on the Profile

COMMENT: Sounds like just confounding, not residual confounding.

RESPONSE: *This comment refers to the following sentence in the cardiovascular effects paragraph in section 1.2 (Summary of Health Effects). "This lack of information on residual confounding increases the risk of bias of these studies (Rafnsson and Gudmundsson 1997; Rafnsson and Kristbjornsdottir 2014)." The word "residual" has been removed from the sentence.*

COMMENT: Case control study? Control here seems to me non exposed.

RESPONSE: *This comment refers to the Repko et al. 1976 entry in Table 2-1. The Reference and Study Population information states: "Case-control study of 122 workers (8 female, 114 male) aged 18-61 and 49 unexposed control workers (3 female, 46 male) aged 20-59 from 7 different locations of the same company in 6 U.S. states who were or were not occupationally exposed to chloromethane." This commenter is correct that the controls are unexposed. Case-control was specified as the study type in order to provide methodological information. This section was adjusted for clarity. It now says "Case-control: Study of 122 unexposed workers (8 female, 114 male) aged 18-61 compared to 49 unexposed workers (3 female, 46 male) aged 20-59 from 7 different locations of the same company in 6 U.S. states who were or were not occupationally exposed to chloromethane."*

COMMENT: What was the outcome?

RESPONSE: *This comment refers to the Stewart et al. 1980 entry in Table 2-1. Specifically, it refers to the outcome of the study, which states: "No significant effects of chloromethane exposure were identified, but some subjects exhibited higher breath and blood levels than their peers." More information was added to the description of the study outcome. However, most of these data are presented in figures instead of tables, so the values available to provide here were limited to what the authors stated in the text. The outcome now states: "No significant effects of chloromethane exposure were identified, but some subjects exhibited higher breath and blood levels than their peers. Four participants had 60 to 110% higher mean chloromethane concentrations in their breath at the beginning of exposure and three to six times the mean chloromethane concentrations 1 hour post exposure. The blood concentrations of chloromethane in these four participants were also elevated compared to the other participants. The authors interpreted these results to mean that higher levels of chloromethane in breath result from higher levels of chloromethane in blood."*

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COMMENT: What is evidence of exposure?

RESPONSE: *This comment refers to the following sentences in section 2.2 (Death): "Conversely, no excess mortality was observed in a mortality study on workers who manufactured butyl rubber and were exposed to chloromethane for many years with long-term follow-up (Holmes et al. 1986). However, when evaluating results from occupational cohort studies consideration of the healthy worker effect (i.e., individuals that are occupied and working are healthier than their non-working counterparts) is necessary." The commenter suggests adding more information on the evidence of chloromethane exposure for the workers in the Holmes et al. 1986 study. Chloromethane is used in the butyl rubber manufacturing process. The preceding sentence was adjusted to clarify this relationship. The sentences now say: "Conversely, no excess mortality was observed in a mortality study on workers who used chloromethane to manufacture butyl rubber and were exposed to chloromethane for many years with long-term follow-up (Holmes et al. 1986). However, when evaluating results from occupational cohort studies consideration of the healthy worker effect (i.e., working individuals tend to be healthier on a population group level compared to their non-working counterparts) is necessary."*

COMMENT: Probably should be called 'non exposed' rather than 'controls'

RESPONSE: *The commenter suggests this edit for the following sentence, which refers to the Rafnsson and Gudmundsson 1997 study of men who lived on a fishing trawler with a leaking refrigerator, in section 2.5 (Cardiovascular): "The controls were matched on age and occupation." "Unexposed" was added here to clarify, but "controls" was left in given the matched case control methodology of the study. The sentence now says: "The unexposed controls were matched on age and occupation."*

COMMENT: How many deaths from cardo disease?

RESPONSE: *The commenter suggests clarifying how many men in the exposed population and how many of the referents from the Rafnsson and Gudmundsson 1997 study died from cardiovascular disease. The sentence the commenter refers to is in section 2.5 (Cardiovascular). The sentence was updated from: "The authors reported excess mortality from cardiovascular disease (M-H=2.1, 95% CI= 1.2-3.8) in the exposed population compared to the referents." It now says: "The authors reported excess mortality from cardiovascular disease (M-H=2.1, 95% CI= 1.2-3.8) in the exposed population (5 cardiovascular deaths out of 18 deckhands and 3 cardiovascular deaths out of 6 officers) compared to the referents (20 cardiovascular deaths out of 120 unexposed referents)."*

COMMENT: Number of deaths?

RESPONSE: *The commenter suggests clarifying how many crewmembers from the Rafnsson and Kristbjornsdottir 2014 study died from cardiovascular disease. The sentence the commenter refers to is in section 2.5 (Cardiovascular). The sentence was updated from: "Rafnsson and Kristbjornsdottir (2014) found that with increased follow up time (follow up to 2010) the association between chloromethane and deaths from cardiovascular disease was confirmed (HR=2.06, 95% CI= 1.02-4)." It now says "Rafnsson and Kristbjornsdottir (2014) found that with increased follow up time (follow up to 2010) the association between chloromethane and deaths from cardiovascular disease was confirmed (HR=2.06, 95% CI=*

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1.02-4.15 based on 10 cardiovascular deaths out of 27 crewmembers compared to 41 cardiovascular deaths out of 135 unexposed referents).”

COMMENT: Number deaths?

RESPONSE: *The commenter suggests clarifying how many crewmembers from the Rafnsson and Kristbjornsdottir 2014 study died from acute coronary heart disease and from cerebrovascular disease. The commenter refers to the following sentence in section 2.5 (Cardiovascular): “They subdivided this category into acute coronary heart disease deaths (HR=3.12, 95% CI= 1.11-8.78), and cerebrovascular disease deaths (HR=5.35, 95% CI= 1.18-24.35), both of which were increased in exposed crew members compared to the referents.” It was updated to say: “They subdivided this category into acute coronary heart disease deaths (HR=3.12, 95% CI= 1.11-8.78; 5 crew deaths compared to 15 referent deaths), and cerebrovascular disease deaths (HR=5.35, 95% CI= 1.18-24.35; 3 crew deaths compared to 4 referent deaths), both of which showed increased hazard of death in exposed crew members compared to the referents.”*

COMMENT: Clarify that these workers were currently exposed.

I would make note that this is the only epi study of possibly longterm effects. Provide more information on mean years exposed.

RESPONSE: *The peer reviewer is referring to the discussion of the Repko et al. 1976 study in section 2.15 (Neurological). The section originally said: “Repko et al. (1976) performed a study on the effects of chloromethane from exposures to workers. Seventy-three behavioral measures of task performance, four indices of exposure, eight indicators of neurological function, and a clinical EEG were obtained. The study population was derived from several fabricating plants operated by the same company. Exposed workers (n=122) used chloromethane in the manufacture of foam products, while controls (n=49) had not ever knowingly worked with chloromethane.” The paragraph was edited to clarify the study methodology and exposure. Edits were not made to state that this epi study is the only study of long term effects because other studies such as the Rafnsson studies also evaluated long term health effects. The section now says: “Repko et al. (1976) performed a study on the neurological effects of occupational exposure to chloromethane. The study population was derived from several fabricating plants operated by the same company. Exposed workers (n=122) used chloromethane in the manufacture of foam products, while controls (n=49) had not ever knowingly worked with chloromethane. The amount of time study participants worked at the plants ranged from 1 to 311 months for exposed workers and 11 to 194 months for controls, depending on the plant. Seventy-three behavioral measures of task performance, four indices of exposure, eight indicators of neurological function, and a clinical EEG were obtained.”*

COMMENT: Confusing, this sentence was there were behavioral effects, but on line 21 it says there were no significant differences (between who?) and neurologic tests. Are cognitive tests in line 22 not neurological tests?

And what does it mean in line 22 that cognitive effects were found, but the pattern of correlation coefficients indicated that chloromethane in breath is not a sensitive indicator of performance deficit?

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That seems to mean that in fact no cognitive effects related to breath concentrations were found, but effects were found related to air concentrations

RESPONSE: *This comment refers to the paragraph discussing the Repko et al. 1976 study in section 2.15 (Neurological). The comment refers to the following sentences: "There were no significant differences in neurological tests or EEGs. In the behavioral battery, effects on cognitive time-sharing and finger tremor were found, but the pattern of correlation coefficients indicated that chloromethane in breath is not a sensitive indicator of performance deficit." As described in the beginning of this paragraph, neurological effects were tested by 8 indicators and a clinical EEG was obtained. These measures are separate from the 73 behavioral measures of task performance. "Battery" was replaced with "task performance tests" for clarity.*

Exhaled chloromethane was measured, but the concentrations found in breath were not predictive of task performance while levels of chloromethane in the air were. This likely has to do with individuals' metabolism and excretion of chloromethane and shows that exposure level is more indicative of an effect than level of excretion in the breath. The description in this paragraph is accurate and was not changed.

COMMENT: What was evidence of exposure to chloromethane in this plant?

RESPONSE: *The peer reviewer is referring to the second paragraph in section 2.19 (Cancer). The reviewer suggests clarifying the following sentence: "Specifically, cohorts include workers from a butyl rubber manufacturing plant , Icelandic fisherman accidentally exposed due to a refrigerant leak and various occupational populations exposed to chlorinated solvents in the workplace (Barry et al. 2011; Dosemeci et al. 1999; Holmes et al. 1986; Jiao et al. 2012; Kernan et al. 1999; Rafnsson and Gudmundsson 1997; Rafnsson and Kristbjornsdottir 2014)." Chloromethane is used in the manufacturing process. This sentence has been adjusted to clarify this relationship and was edited to say: "Specifically, cohorts include workers from a butyl rubber manufacturing plant that used chloromethane as a diluent , Icelandic fisherman accidentally exposed due to a refrigerant leak and various occupational populations exposed to chlorinated solvents in the workplace (Barry et al. 2011; Dosemeci et al. 1999; Holmes et al. 1986; Jiao et al. 2012; Kernan et al. 1999; Rafnsson and Gudmundsson 1997; Rafnsson and Kristbjornsdottir 2014)."*

COMMENT: # deaths?

RESPONSE: *This comment refers to the deaths from lung cancer and renal cancer in the following sentence in section 2.19 (Cancer): "The cohort of Icelandic fisherman was also used to assess potential association between chloromethane and death from lung cancer (Rafnsson and Gudmundsson 1997) and death from renal cancer (Rafnsson and Kristbjornsdottir 2014)." Given the small sample size, the number of deaths is not very informative. Therefore, the hazard ratios were added here: "The cohort of Icelandic fisherman was also used to assess potential association between chloromethane and death from lung cancer (Rafnsson and Gudmundsson 1997) and death from renal cancer (HR = 9.35; 95% CI: 1.28-68.24) (Rafnsson and Kristbjornsdottir 2014)."*

COMMENT: Number of women? Percent with TT?

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RESPONSE: *This comment refers to the following sentence in section 2.19 (Cancer):* "*Barry et al. (2011) found an association between chloromethane exposure and the risk of non-Hodgkin's lymphoma only among women with the TT (but not TA or AA) genotype of the CYP2E1 rs2070673 gene." Text was added to say: "Barry et al. (2011) found an association between chloromethane exposure (never versus ever exposed) and the risk of non-Hodgkin's lymphoma only among women with the TT (but not TA or AA) genotype of the CYP2E1 rs2070673 gene. This was based on an analysis of 648 women, of which 29 were TT +, had exposure to chloromethane, and had non-Hodgkin's lymphoma."*

COMMENT: What was the definition/evidence of exposure in these studies? Provide percentage of cases and controls exposed. Give ORs. Make reference to Table 2.-1 In general these studies seem under-discussed as they are really the only human studies outside of the small Icelandic fishermen study, -who had acute exposure

RESPONSE: *This comment refers to the fourth paragraph in section 2.19 (Cancer) that discusses case-control studies that assessed potential carcinogenicity. Clarifying data was added to the paragraph (see above comment response for edits). A reference to Table 2-1 was added at the end of the paragraph: "Additional information on these studies can be found in Table 2-1."*

COMMENT: Maybe note that Dosemeci found no renal cancer effects in his case control study

RESPONSE: *The commenter suggests adding this to the fifth paragraph in section 2.19 (Cancer) after the following sentence: "A high incidence of renal tumors was found in male mice that were exposed primarily to approximately 1,000 ppm chloromethane and died or were killed at 12 months or later (primarily between 18 and 24 months) in a 2-year oncogenicity study (CIIT 1981)." The format of the Toxicological Profiles splits the animal and human studies into separate paragraphs. The results from Dosemeci et al. 1999 are discussed in the previous paragraph in the sentence that says "Dosemeci et al. (1999) did not find any association between chloromethane and renal cell carcinoma and Kernan et al. (1999) found unclear associations with pancreatic cancer that were not dose-, gender-, or race-specific."*

COMMENT: Might note here positive association with NHL in Barry et al. human study

RESPONSE: *This comment refers to the following sentence in section 2.20 (Genotoxicity): "Although chloromethane produced genotoxic effects in human lymphocytes in culture, it is not known whether chloromethane could produce dominant lethal mutations or other genotoxic effects in humans exposed by any route." This sentence is accurate. Although the Barry et al. study found increased odds of NHL associated with exposure to chloromethane, the study data were from a case-control study looking at exposure and genetic variation in metabolic genes. Genotoxicity as a result of exposure to chloromethane were not measured or discussed. However, this sentence has been deleted in response to another peer reviewer's comment.*

COMMENT: Cancer in blood cells?

RESPONSE: *This question refers to the following sentence in section 6.1 (Existing Information on Health Effects): "The organs or systems adversely affected in humans after exposure to chloromethane*

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include the liver, kidney, neurological system (including behavioral alterations,) and potentially the cardiovascular system." The health effects in this sentence refer to those that were most supported by the results of the literature review. Given no government entity has concluded chloromethane is potentially carcinogenic we did not add anything in response to this comment.

COMMENT: Again, how common is the TT genotype? I note that for all genotypes combined there were significant effects, implying that the TT type is common

RESPONSE: *This question refers to the following sentence in section 6.1 (Existing Information on Health Effects): "One found an association with increased risk of death from renal cancer (Rafnsson and Kristbjornsdottir 2014), while another found an increased risk with non-Hodgkin's lymphoma for those individuals with one genetic phenotype whose functional significance is unclear (Barry et al. 2011)." Given this sentence is a summary to explain the adequacy of the existing information on chloromethane, We have not made edits in this sentence. However, in response to a previous comment, text was added on the information on genotypes in section 2.19 (Cancer) as recommended. The following sentence was added in section 2.19 (Cancer): "Barry et al. (2011) found an association between chloromethane exposure (never versus ever exposed) and the risk of non-Hodgkin's lymphoma only among women with the TT (but not TA or AA) genotype of the CYP2E1 rs2070673 gene. This was based on an analysis of 648 women, of which 29 were TT +, had exposure to chloromethane and had non-Hodgkin's lymphoma."*

COMMENT: This sort of information should have been discussed on page 117.

RESPONSE: *The commenter suggests adding information to Chapter 3 similar to this sentence in section 6.1 (Existing Information on Health Effects): "No information was available regarding immunological, developmental, reproductive, or genotoxic effects in humans exposed to chloromethane by any route." This information was presented in each of the relevant sections of chapter 2. It does not belong in chapter 3 because chapter 3 discusses toxicokinetics, not the health effects associated with absorption, distribution, metabolism, and excretion.*

COMMENT: Not sure why this section is here, it repeats earlier text in 6.1 and 2.1

RESPONSE: *This comment refers to the health effects paragraph in section 6.2 (Identification of Data Needs). Given the length of the Toxicological Profiles, each chapter is written so that it can be read on its own. The full Profile as well as individual PDFs of each chapter will be available on the ATSDR website. Therefore, some information is briefly summarized here for the reader's benefit. Section 6.1 summarizes existing data and Section 6.2 puts these data in the context of data needs for the chemical.*

COMMENT: See earlier comments

RESPONSE: *This comment refers to the following sentence in the cancer paragraph in section 6.2 (Identification of Data Needs): "Additional research is needed to validate whether chloromethane exposure is associated with non-Hodgkin's lymphoma." As noted above in response to a previous comment, text was added on the information on genotypes in section 2.19 (Cancer) as recommended. The following sentence was added in section 2.19 (Cancer): "Barry et al. (2011) found an association*

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between chloromethane exposure (never versus ever exposed) and the risk of non-Hodgkin's lymphoma only among women with the TT (but not TA or AA) genotype of the CYP2E1 rs2070673 gene. This was based on an analysis of 648 women, of which 29 were TT +, had exposure to chloromethane and had non-Hodgkin's lymphoma."

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