Disposition of Peer Review Comments for Toxicological Profile for 1,1,1-Trichloroethane

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

December 2022

Peer reviewers for the third pre-public draft of the Toxicological Profile for 1,1,1-Trichloroethane were:

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NOTE: Peer reviewer comments are written next to "COMMENTS:" in unformatted text. Any italicized text following the comment is added for clarification purposes. Any page and line numbers that were added by the Reviewers have been kept, but often will not align with the appropriate text.

COMMENTS PROVIDED BY PEER REVIEWER #1

ATSDR Charge Questions and Responses

Peer Reviewer #1 did not provide responses to the charge questions. However, general comments on the profile were provided which have been pasted below the charge questions. Annotated comments on the profile have been incorporated.

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. Pertinent details are provided. No change is suggested.

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: Yes. Especially significant are those where relevant routes of human exposures are used at reasonable doses.

RESPONSE: *No revisions were suggested.*

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

COMMENT: Yes. They have been adequately described.

RESPONSE: *No revisions were suggested.*

Minimal 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: Not applicable.

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.

COMMENT: No response was provided by the reviewer.

RESPONSE: *No revisions were suggested.*

QUESTION (Subset of preceding question): 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 uncertainty factors used in this study.

RESPONSE: *No revisions were suggested.*

QUESTION (Subset of preceding question): Please comment on any aspect of our MRL database assessment that you feel should be addressed.

COMMENT: None.

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.

RESPONSE: *No revisions were suggested.*

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: No changes are suggested as the studies are adequately described.

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: 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.*

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.

RESPONSE: *No revisions were suggested.*

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: Yes. No improvement is needed.

RESPONSE: *No revisions were suggested.*

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: No.

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: No.

RESPONSE: *No revisions were suggested.*

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

COMMENT: No.

RESPONSE: *No revisions were suggested.*

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

COMMENT: No.

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: Yes.

RESPONSE: *No revisions were suggested.*

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: Yes.

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.

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: Yes. Nothing to add.

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: Yes. Nothing to add.

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. Nothing to add.

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: Yes. Nothing to add.

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.

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. No bias is apparent in the writeup.

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: No.

RESPONSE: *No revisions were suggested.*

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

COMMENT: No.

RESPONSE: *No revisions were suggested.*

Additional References from Reviewer*

**These are references cited within the reviewer's individual comments. Responses to the reviewer's comments specify the disposition of these references within the toxicological profile.*

Appendices

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

COMMENT: None.

RESPONSE: *No revisions were suggested.*

Unpublished Studies

QUESTION: Did the study use an adequate number of animals and practice good animal care?

COMMENT: Not applicable.

RESPONSE: *No revisions were suggested.*

QUESTION: Did the study account for competing causes of death?

COMMENT: Not applicable.

RESPONSE: *No revisions were suggested.*

QUESTION: Did the study include a sufficient number of dose groups, and sufficient magnitude of dose levels?

COMMENT: Not applicable.

RESPONSE: *No revisions were suggested.*

QUESTION: If you think the study was not adequately designed or reported, does that negate the utility of the of the study. Please explain.

COMMENT: Not applicable.

RESPONSE: *No revisions were suggested.*

QUESTION: Do you agree with the conclusions of the author? If not, please explain.

COMMENT: Not applicable.

RESPONSE: *No revisions were suggested.*

Annotated Comments on the Profile

COMMENT: Either should be completed or deleted.

***RESPONSE**: This comment refers to the following sentence in section 2.2 (Death – Inhalation): "The LC50 values in rats and the LOAEL values resulting in mortality in each species are recorded in Error! Reference source not found and plotted in Error! Reference source not found." The links to Table 2-3 and Figure 2-2 have been fixed and the sentence now reads: "The LC50 values in rats and the LOAEL values resulting in mortality in each species are recorded in Table 2-3 and plotted in Figure 2-2."*

COMMENT: Middle bracket symbol should be deleted.

***RESPONSE**: This comment refers to the following sentence in section 2.3 (Body Weight - Inhalation): "Body weight remained unaffected in most intermediate-duration studies across animal species at concentrations up to 2,210 ppm (MacEwen and Vernot 1974; Prendergast et al. 1967; Rosengren et al. 1985; Toftgard et al. 1981; Torkelson et al. 1958; Truffert et al. 1977})." The change has been made and the bracket symbol at the end of the sentence was deleted.*

COMMENT: Missing period should be added after 6 days.

***RESPONSE**: This comment refers to the following sentence in section 2.3 (Body Weight - Inhalation): "Jones et al. (1996) showed an 18% decrease in litter weight for CD-1 mice exposed to 2,000 ppm 17 hours per day for 6 days" The change has been made and a period has been added to the end of the sentence.*

COMMENT: Small bracket symbol at the near end of line should be deleted.

***RESPONSE**: This comment refers to the following sentence in section 3.1.1 (Absorption): "Absorption is expected to be relatively low after steady state is reached, because the initial extensive absorption of 1,1,1-trichloroethane is the result of blood and tissue loading (which in turn are affected by respective blood:air and tissue:blood partition coefficients (PCs)), tissue volumes and blood flows, and low metabolism (Johns et al. 2006; Reitz et al. 1988)." The parentheses have been deleted and commas have been added. The sentence now reads: "Absorption is expected to be relatively low after steady state is reached because the initial extensive absorption of 1,1,1-trichloroethane is the result of blood and tissue loading, which in turn are affected by respective blood:air and tissue:blood partition coefficients (PCs), tissue volumes and blood flows, and low metabolism (Johns et al. 2006; Reitz et al. 1988)."*

COMMENT: Refence of L You and CE Dallas 2000 is incomplete and needs proper format.

***RESPONSE**: This comment refers to the following sentence in section 3.1.1 (Absorption): "Animal experiments provide supporting evidence that inhaled 1,1,1-trichloroethane is rapidly and extensively absorbed and that the absorption, during short-term exposures, is influenced by ventilation rate (Schumann et al. 1982; Gargas et al. 1986; Dallas et al. 1989; Warren et al. 1998; You and Dallas 2000)." Reference has been formatted throughout the text.*

COMMENT: "Trichloroacetic Acid" and "Urine" are very far apart. These two should be brought together in the middle.

RESPONSE*: This comment refers to Figure 3-1 (Metabolic Scheme for 1,1,1-Trichloroethane) and the figure has been edited as suggested by the reviewer.*

COMMENT: Ideally free radical symbol(.) should be on carbon of CH2 not on hydrogen as depicted.

RESPONSE*: This comment refers to the following sentence in section 5.4.2 (Transformation and Degradation – Air): "1,1,1-Trichloroethane is degraded via H-atom abstraction to CCl3CH2· and reacts with O2 to yield the peroxy radical (CCl3CH2O2) (DeMore 1992; Spence and Hanst 1978)." The free radical has been moved from the hydrogen to the carbon of CH2 and the sentence now reads: "1,1,1-Trichloroethane is degraded via H-atom abstraction to CCl3·CH2 and reacts with O2 to yield the peroxy radical (CCl3CH2O2) (DeMore 1992; Spence and Hanst 1978)."*

COMMENT: Free radical should be on O not at H as depicted.

RESPONSE*: This comment refers to the following sentence in section 5.4.2 (Transformation and Degradation – Air): "Using an estimated atmospheric hydroxyl (OH·) radical concentration of 5.0x105 mol/cm3 (Atkinson 1985), the more recent rate constants translate to a calculated lifetime or residence time of ≈6 years." The free radical has been moved from the H to the O and the sentence now reads: "Using an estimated atmospheric hydroxyl (·OH) radical concentration of 5.0x105 mol/cm3 (Atkinson 1985), the more recent rate constants translate to a calculated lifetime or residence time of ≈6 years."*

COMMENT: OH should be spell out as 'hydroxyl'

RESPONSE*: This comment refers to the following sentence in section 5.4.2 (Transformation and Degradation – Air): "This indicates that the predominant tropospheric sink of 1,1,1-trichloroethane is through its reaction with OH radicals." The 'OH' has been replaced with 'hydroxyl' and the sentence now reads: "This indicates that the predominant tropospheric sink of 1,1,1-trichloroethane is through its reaction with hydroxyl radicals."*

COMMENT: Attention is needed to this section which is often used by the users to get the details described in the given reference. In this respect several deficiencies are noted. Often reference details are missing. Such as Page 200 line 47; page 203 line 36; page 205, line 35 etc. Proper abbreviations should be used for all references.

Open Veterinary Journal --> Open Vet J.

Cancer Research --> Cancer Res

Delete the issue numbers in parentheses

Details are missing from Baker & Bonin 1981

Details are missing from Daniel & Dehnel 1981

Details are missing from Fey et al. 1981

***RESPONSE**: Updated these references in Chapter 8 as the comment pertains to the References in Chapter 8. The issue numbers in parentheses were not deleted because this is in accordance with ATSDR guidelines in ATSDR's "Guidance for the Preparation of Toxicological Profiles".*

COMMENTS PROVIDED BY PEER REVIEWER #2

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, I agree with the known human effects. This chemical was the subject of study over several decades.

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: The animal studies are at substantially higher concentrations. Since 1,1,1-trichloroethane is used less in the US it is unlikely that excessive inhalation exposures occur. Animal studies were conducted in the hundreds of ppm range. Other than the dose issue, the animal data are generally suggestive of potential human effects.

RESPONSE: *Even though the animal studies are being conducted at higher concentrations, similar health effects are observed in humans at lower doses as well. Neurological effects are observed in both humans and animals after inhalation exposure with dose ranges of 175-10,000 ppm and 100 – 22,250 ppm, respectively.*

Numerous inhalation studies in laboratory animals and a few human studies strongly support neurological effects following exposure to 1,1,1-trichloroethane. Observed health effects in controlled human exposure studies include impaired manual dexterity, eye-hand coordination, perceptual speed, and reaction time, as well as increased tiredness and disturbances of equilibrium and coordination (Gamberale and Hultengren 1973; Mackay et al. 1987; Savolainen et al. 1981; Muttray et al. 2000; Stewart et al. 1961; Torkelson et al. 1958). Dornette and Jones (1960) also found that administering 1,1,1-trichloroethane at high concentrations induced general anesthesia in hospital patients. The principal neurological effects observed in animals exposed to 1,1,1-trichloroethane are signs of central nervous system depression, such as impaired performance in behavioral tests, ataxia, and unconsciousness, and are similar to those seen in humans (Geller et al. 1982; Kjellstrand et al. 1985; Torkelson et al. 1958; Bowen and Balster 1996; Mullin and Krivanek 1982; Ohnishi et al. 2013; Bowen and Balster 1998; Hougaard et al. 1984; Balster et al. 1982).

This suggests that even though the animals are exposed to higher levels of 111-TCE similar effects are observed in humans at comparable doses. This is indicative of the fact that the underlying mechanism of toxicity could potentially be similar eliciting similar health effects in both animals and humans. No changes were made in response to this comment.

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

COMMENT: Yes, this chemical is a legacy chemical that now has limited use in the US. The exposures were adequately described.

RESPONSE: *No revisions were suggested.*

Minimal 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: Based on policy I agree with the logic provided. Dermal exposure and MRL methods remain an issue. I am not certain why. Is the uncertainty too great?

RESPONSE: *ATSDR guidelines in ATSDR's "Guidance for the Preparation of Toxicological Profiles" does not provide guidance for developing an MRL for dermal exposure, therefore ATSDR does not develop MRL's for dermal exposure.*

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.

COMMENT: The use of a human PBPK for the acute-duration MRL is a valuable contribution. As a PBPK modeler I did need to review the Yang et al. 2006 document closely to better understand how the time adjustment (24 hours) was carried out. I believe the methodology is ok for the intended purpose.

RESPONSE: *No revisions were suggested.*

QUESTION (Subset of preceding question): 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 agree, the use of the UFs is protective of human health.

RESPONSE: *No revisions were suggested.*

QUESTION (Subset of preceding question): Please comment on any aspect of our MRL database assessment that you feel should be addressed.

COMMENT: To me it seems likely that no chronic animal studies will be undertaken with this chemical in the future. The data that exist are it. Do you expect the database to be expanded?

RESPONSE: *In our current literature search we did not identify any ongoing studies that examine the effects of 111 TCE after chronic-duration exposure. Future updates of this profile will include any additional studies that examine the health of effects of chronic-duration exposure to 111 TCE in animals.*

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: The conclusions are summarized in Chapter 1and Chapter 2. Much literature that was reviewed. The text reflects the literature, that is, the exposures and effects are reported. Large tables report human studies and animal studies. Text is provided. Very extensive.

RESPONSE: *No revisions were suggested.*

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: For humans, limitations are listed for each study in the Tables. Yes, but one would need to retrieve the paper to get details.

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: My bias is that GLP studies would preside over other reported toxicity studies, if available. It is hard to imagine that academic studies would be on par with the NTP 2000 study because it would be almost impossible to do. To extrapolate from oral to inhalation, route-to-route modeling could be accomplished. This would be for systemic toxicity only, not portal of entry toxicity. The results of the route-to-route extrapolation could be compared directly to non-GLP toxicity studies to decide a path forward. However, the methodology shown in the report is adequate and in not flawed!

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: Based on apparent ATSDR methods, yes. Many animal studies were described, with adequate detail. See comment above. I feel that people who are interested enough to know the details of a study would seek out the paper.

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, in terms of determining a NOAEL and less serious and serious LOAEL values. A huge effort has been invested on dose-response.

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: I am unaware of any recent toxicity studies.

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, I am not aware, for the isomer, 1,1,2-trichloroethane.

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: This is a daunting task without the papers in hand to ensure appropriate concentrations were used. I scanned text and tables looking for errors. My eyes did not find any issues. Benchmark dose software was also used.

RESPONSE: *No revisions were suggested.*

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: It took me awhile to understand these designations. I see this has been a huge undertaking. For users, this information could be very important. I agree with the designations as I scan many studies. There must be a bright line for each species in terms of body weight gain decreases. I assume the designation of Less Serious and Serious for the animals is meant for only animal interpretation (not human). For human studies, a designation of less serious is given across inhalation studies. But in the right situation, such as for pilots, or military in confined spaces such as tanks any problem with cognition is a potential threat. I am not aware of this chemical as a contaminate for these occupations.

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: I was hopeful that new exciting mechanistic studies were undertaken, but I did not find anything for this chemical. Citing the possible involvement of trichloroethanol is appropriate. This does bring up a future issue of using reading across for other solvents, where occupational studies continue looking at CNS effects using modern toxicology methods. This may have some impact on how you keep the document relevant in the future.

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, at the beginning of the Chapter, the information is synthesized to provide the most sensitive endpoints across several studies, CNS and liver. I agree.

RESPONSE: *No revisions were suggested.*

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: For the purposes of this profile, the text is ok. Someday providing a database of manuscripts (that can be downloaded) would be a huge benefit to many people and if data are digitized that would be useful as well. For me, reading this is taking me back in time. I used to be familiar with many of the papers and still know some of the authors. The pharmacokinetics of 1,1,1-trichloroethane suggesting first pass metabolism of 40% is most likely wrong (Mortuza et al. 2018, page 178). The chemical is weakly metabolized. This is usually referred to as systemic bioavailability.

"As the duration of inhalation exposure increases, the percentage of absorption decreases because steady-state levels are approached in the blood and tissues, and 1,1,1-trichloroethane is metabolized at a low rate." page 168. This is an advanced topic and provides little helpful information, especially relative to waste sites. Reaching steady-state for this chemical would be difficult to do.

RESPONSE: *The study by Mortuza et al. 2018 was reviewed and it was clarified that approximately 14.8% of 1,1,1 -TCE was exhaled through the first pass. This correction has been made to the text. It is now corrected to "Approximately 14.8% of the chemical in venous blood was eliminated during its first pass through the liver and lungs, respectively, after oral administration of 10 mg 1,1,1-trichloroethane/kg in rats."*

This update to the profile was developed based on the extensive literature search conducted from January 2004 to October 2020. This section includes information for all identified and pertinent peer-reviewed studies.

This sentence has been deleted "As the duration of inhalation exposure increases, the percentage of absorption decreases because steady-state levels are approached in the blood and tissues, and 1,1,1-trichloroethane is metabolized at a low rate.".

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

COMMENT: I believe so. I am familiar with many of the models and the authors.

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 doubt if people know that excretion by exhalation is (can be) described in PBPK models as: Excretion= (Concentration of chemical in plasma (mg/L) divided by the blood/air partition coefficient)x breathing rate (L/hr)= mg/hr of chemical exhaled. The greater the value of the blood/air partition coefficient, the less chemical is exhaled in breath. So, this last statement may be worth including because of differences in the blood/air partition coefficient across species.

There is discussion about animal and human PK. I think a clear statement about how and why animal PK is extrapolated to humans would be helpful. For example, animal toxicokinetic information can be extrapolated to humans, moving away from administered dose to internal dose. This provides a tool to compare internal doses that are equivalent in animal and human, which is more useful than external dose. This section could be strengthened.

RESPONSE: *Added the statement suggested by the reviewer "Animal toxicokinetic information can be extrapolated to humans as this provides a method to compare internal doses that are equivalent in animal and human, which is more useful than external dose. The greater the value of the blood/air partition coefficient, the less the chemical is exhaled in breath. The blood/air partition coefficients are listed in Table 3-1."*

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: I do not know of any studies with this chemical. The hay day for research on this chemical was long ago from my perspective.

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: There is a modest discussion about sensitive populations. Documented health issues for a community population do not exist. Speculation is provided about special populations. Yes.

RESPONSE: *No revisions were suggested.*

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

COMMENT: Only the parent chemical (breath) unless, 1,1,1-trichloroethane is the only known exposure. The two most common metabolites of 1,1,1-trichloroethane are also common metabolites of other solvents.

RESPONSE: *No revisions were suggested.*

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

COMMENT: I do not think so. Many solvents can affect the CNS system.

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: Yes, this is literature from the 1980s. While the discussion is about the literature (which is not specific to hazardous waste sites), interpretations about the relevance of interactions are offered. This is good. I recall many of these studies at the time they were published. Since this solvent is weakly metabolized, its interactions are limited in this regard. Thus, metabolism and hepatotoxicity influencing other solvents or this substance when co-exposed is of minimal concern at hazardous waste sites.

RESPONSE: *No revisions were suggested.*

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: To the degree possible at the time when the research was conducted, mechanisms are mentioned and explained. With the advent of molecular biology methods, the information is somewhat dated.

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 believe the values are ok.

RESPONSE: *No revisions were suggested.*

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

COMMENT: Because this chemical exists as a vapor, there is no concern for different forms of this chemical.

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: It appears that the information is complete as can be. I think statements about stopping production of 1,1,1-trichloroethane (Montreal Protocol), when it is not true, should be changed. Production continues, less than before the Montreal Protocol, but it still continues. The Montreal Protocol reduced the production of 1,1,1-trichloroethane. I think rewording these statements is important and provides a justification why this document is still important, especially for occupationally exposed individuals.

RESPONSE: *Clarification has been made throughout Chapter 5 to indicate that the Montreal Protocol reduced the production of 1,1,1-trichloroethane, but some production continues.*

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, well done. Yes, extensive analyses. No. Very impressive compilation of information.

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: Yes. No. This section is exceptional, covering much information. I am unaware of any other relevant information. Very impressive.

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, there are tables and text. Extensive information. The units are ok, but the units are not the same across tables, such as ug/L and mg/L, pptv in air, etc. It is easier to grasp limits of detection and measured media if the units are the same Yes, this is ok. I think so. No.

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: Yes, a job well done. Yes, no doubt that occupational exposure is the concern. Occupational exposures of pregnant or lactating women were not discussed. It probably happens.

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: I have no animal studies to recommend.

RESPONSE: *No revisions were suggested.*

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

COMMENT: I am surprised that ATSDR is not considering modern methods such as transcriptomics and other measures of toxicity in cells. The NTP program has shifted away (with limited exceptions) from whole animal toxicity studies, FDA/NCTR has greatly reduced the number of whole animal toxicity studies, and WPAFB (AF) no longer does toxicity testing in whole animals. The future view of whole animal toxicity testing suggests that whole animal toxicity testing for chemicals will be the exception, and not the norm. Even for drugs, in FDA, there are limited efforts ongoing to use cells for safety assessments, with some in use now. I am not enthusiastic about the recommendations for more animal studies for this chemical. I do understand and recognize the logic and reasoning for the recommendations. The bar will be very high for conducting whole animal toxicity studies via NTP. I suggest that ATSDR start reporting in vitro toxicity or in vitro PK studies, like genotoxicity. If these data are not used, state this.

RESPONSE: *The data needs section is identifying areas to improve risk assessment. It does not specify research methods as this would be up to the entities conducting the research. ATSDR would certainly support the shift away from animal testing when data could be garnered through alternative methods. The content and development of the data needs section is in accordance with ATSDR guidelines as listed in ATSDR's "Guidance for the Preparation of Toxicological Profiles".*

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

COMMENT: I think that Tox21 is not recognized as a viable methodology for the future. The tools for safety assessment are changing. I believe it is time to start reporting in vitro studies that maybe relevant to toxicity, MOA, or pharmacokinetics. If there are none, state this. This does not mean that you use the data.

RESPONSE: *The data needs in this profile are developed based on the ATSDR guidelines listed in ATSDR's Guidance for the Preparation of Toxicological Profiles" .*

Chapter 7. Regulations and Guidelines

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

COMMENT: No, unless you go to the state level, perhaps?

RESPONSE: *No revisions were suggested.*

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

COMMENT: I think it would be helpful to add the apical endpoints used for deriving the guideline exposure values. Footnotes describe this information for some of the exposure guideline values.

RESPONSE: *The data in Chapter 7 of this profile are developed based on the ATSDR guidelines listed in ATSDR's "Guidance for the Preparation of Toxicological Profiles" .*

Additional References from Reviewer*

***These are references cited within the reviewer's individual comments. Responses to the reviewer's comments specify the disposition of these references within the toxicological profile.*

No studies were listed.

Appendices

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

COMMENT:

A. Important for many. How you came up with the MRL values, very well described.

B. Good for some who want to do searches.

C. Massive, complex, almost needs a 'how to do it' guide.

D. I like it. Useful for people new to the tox profile.

E. Ok. Should be useful to some.

F. Good to have definitions.

G. Good to have a list of acronyms.

RESPONSE: *No revisions were suggested.*

Unpublished Studies (If Applicable to Review)

No studies were reviewed.

Annotated Comments on the Profile

COMMENT: If this is the case, then is the concern solely for individuals who have been exposed in the past? Suggest that this sentence be re-worded. "You are not likely to be exposed to large enough amounts of 1,1,1-trichloroethane to cause adverse health effects."

RESPONSE*: The sentence was edited to "Health effects are observed when there is an exposure to large amounts of 1,1,1- TCE."*

COMMENT: Then what is the basis for concern about the compound? "However, since 2012, 1,1,1-trichloroethane is not expected to be commonly used, and therefore, the likelihood of being exposed to it is remote"

RESPONSE*: The sentence was edited to "Since 2012, 1,1,1-trichloroethane is not used as frequently and the ambient levels are steadily declining."*

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: Chapter 1 concisely describes the key effects of 1,1,1-trichloroethane (111-TCE) and lists the primary effects as neurological (known health effect) and hepatic (presumed health effect). Figures 1-1, 1-2, and 1-3 illustrates the array of observed effects in humans and animals from acute, intermediate, and chronic exposure by the oral and inhalation routes according to dose, ranging from 7-100 ppm to > 10,000 ppm. The body of data support the conclusion, and the scientific community has a consensus, that these two effects – neurological and hepatic – are the most important for humans.

A major concern I have with the entire document is that numerous effects that occur from exposures to thousands of ppm 111-TCE are not put into any context. For example, exposures in environmental settings, such as from contaminated water or soil, are certainly at much lower levels. Even most occupational exposures will be at much lower levels than many of the effects shown in the upper half of these figures. Thus, the relevance of many of the exposures described in this chapter and throughout the document should be made clearer. While the document does an excellent job of delineating all the available studies, what is missing is a thorough evaluation of the quality, significance, and human health relevance of these data.

RESPONSE: *Data with respect to human health and health effects are presented throughout the text in the profile, where appropriate. The derivation of minimal risk levels is a key example of taking exposure levels into consideration. The studies that were used at higher levels of exposure were not used to derive the MRLs. The MRLs were based on lower concentrations/doses of exposures which provide a protective effect. In every section in Chapter 2 there is a detailed description of human health effects. Appendix C: Framework For ATSDR's Systematic Review Of Health Effects Data For 1,1,1-Trichloroethane provides a detailed evaluation of quality and significance of both human and animal studies.*

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: The selective observation of certain effects only in animals is not made especially clear in this chapter. While it is clearly stated, for example, that hepatic effects have been observed in animals but not in humans, making the liver a "presumed" target for humans, this point is not made clearly for many of the other observed effects that occur at higher exposure doses. The situation with reproductive and renal effects seems especially pertinent and are important examples of target systems that often show species-dependent differences.

RESPONSE: *Evaluating hepatic effects seen in animal studies as potential targets in humans is based on the systematic review conducted in Appendix C: Framework For ATSDR's Systematic Review Of Health Effects Data For 1,1,1-Trichloroethane. Based on ATSDR's "Guidance for the Preparation of Toxicological Profiles" (these reviews are conducted based on published peer-reviewed literature). While both reproductive and renal effects are pertinent health effects that show species-dependent differences, there are minimal published peer-reviewed literature that demonstrate these effects thus precluding reproductive and renal endpoints from being evaluated for hazard identification by the formal systematic review process.*

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

COMMENT: Exposure routes are clearly explained. There are essentially three exposure routes, dermal, inhalation, and oral. The document clearly explains the forms, situations, and frequency in which exposure by each route occurs.

RESPONSE: *No revisions were suggested.*

Minimal 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: The document clearly explains how MRLs are calculated and the rationale for when sufficient data are unavailable to prevent calculation of these values. This issue is very clear and straightforward.

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. 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: While the calculation of MRLs is explained, the basis for the composite uncertainty factor in each case is not clearly explained. Typically, one sees a breakdown of uncertainly factors based on whether a LOAEL or NOAEL is available, whether acute, subchronic, or chronic toxicity studies are available in animals and/or humans, and whether the database available is sufficiently robust. None of this information is presented in Chapter 1, only the composite UF values of 100 are given. The MRL Worksheets in Appendix A do provide much of this information. However, clear reference to this needs to be given in Chapter 1, which serves as an Executive Summary.

RESPONSE: *Table 1-1 has been developed based on ATSDR's "Guidance for the Preparation of Toxicological Profiles" . Table 1-1 in Chapter 1 provides the summary of effects and MRLs and does not present the breakdown of these uncertainty factors. These uncertainty factor breakdowns are detailed in Appendix A. ATSDR Minimal Risk Level Worksheets.*

QUESTION (Subset of preceding question): Please comment on any aspect of our MRL database assessment that you feel should be addressed.

COMMENT: The decision to use composite UFs of 100 for MRL calculations should be better explained in both Chapter 1 and in the Worksheets in Appendix A. Specifically, each component of the UF should be explained and separately highlighted so that it is clear where the uncertainties and datagaps exist.

RESPONSE: *Table 1-1 has been developed based on ATSDR's "Guidance for the Preparation of Toxicological Profiles" . Table 1-1 in Chapter 1 provides the summary of effects and MRLs and does not present the breakdown of these uncertainty factors. These breakdowns are detailed in Appendix A. ATSDR Minimal Risk Level Worksheets. Appendix A also has been developed based on the guidance provided by ATSDR where each component for uncertainty factors are listed as detailed in the guidance. For each MRL the uncertainty factors are detailed as follows "An MRL derivation for acute-duration inhalation exposure resulted in an adjusted LOAEL of 119 ppm, which was then divided by a total uncertainty factor of 100 (10 for the use of a LOAEL and 10 for human variability). An MRL derivation for intermediate-duration inhalation exposure is based on a NOAEL of 70 ppm divided by a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability). A provisional intermediate-duration oral MRL was derived for 1,1,1-trichloroethane based on a decrease in body weight gain in mice given diets containing encapsulated 1,1,1-trichloroethane. The MRL is based on a BMDL10 of 208 mg/kg/day divided by a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability)."*

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: The most significant, overriding issue that I have, which I also expressed in response to Charge Questions related to Chapter 1, is whether these health effects occur at doses or concentrations of 111-TCE that are relevant to environmental or occupational exposure levels. Numerous studies, especially the animal studies, are described in which animals are exposed to 111-TCE at doses of >1,000 ppm to > 10,000 ppm. While these studies represent valid data, their relevance to potential human exposures needs to be clearly discussed and emphasized.

RESPONSE: *Chapter 2 consists of endpoint-specific discussions of available epidemiological and toxicological health effects data involving inhalation, oral, or dermal exposure to the profiled substance.*

Even though the animal studies are being conducted at higher concentrations, similar health effects are observed in humans at lower doses. Neurological effects are observed in both humans and animals after inhalation exposure with dose ranges being 175-10,000 ppm and 100 – 22,250 ppm , respectively. Numerous inhalation studies in laboratory animals and a few human studies strongly support neurological effects following exposure to 1,1,1-trichloroethane. Observed health effects in controlled human exposure studies include impaired manual dexterity, eye-hand coordination, perceptual speed, and reaction time, as well as increased tiredness and disturbances of equilibrium and coordination (Gamberale and Hultengren 1973; Mackay et al. 1987; Savolainen et al. 1981; Muttray et al. 2000; Stewart et al. 1961; Torkelson et al. 1958). Dornette and Jones (1960) also found that administering 1,1,1-trichloroethane at high concentrations induced general anesthesia in hospital patients. The principal neurological effects observed in animals exposed to 1,1,1-trichloroethane are signs of central

nervous system depression, such as impaired performance in behavioral tests, ataxia, and unconsciousness, and are similar to those seen in humans (Geller et al. 1982; Kjellstrand et al. 1985; Torkelson et al. 1958; Bowen and Balster 1996; Mullin and Krivanek 1982; Ohnishi et al. 2013; Bowen and Balster 1998; Hougaard et al. 1984; Balster et al. 1982). This suggests that even though the animals are exposed to higher levels of 111-TCE, similar effects are observed in humans at comparable doses. This is indicative of the fact that the underlying mechanism of toxicity could potentially be similar eliciting similar health effects in both animals and humans. Additionally, the potential for human exposures are discussed in detail in Chapter 5.

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: The limited number of human studies that focus on adverse health effects of 111-TCE are appropriately identified. Tables list the available studies according to time of administration or exposure (i.e., acute, intermediate, chronic) and endpoint. I do not see any discussion of key limitations, however, which would include the following factors: 1) Dose relevance; 2) sample size; 3) characterization of exposure; 4) study design; and 5) confounding factors. In most cases, exposure information is provided. In some cases, exposure is mentioned but dose is not provided.

RESPONSE: *Table 2-1 lists the sample size, study type, and exposure by health effects for the epidemiological studies listed in the ToxProfile.*

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: As one would expect, many more studies in experimental animals are available than in humans. Animal numbers are provided in the tables in Chapter 2. In a few cases where the findings summarized in these tables are discussed, adequacy of or adherence to standard experimental design principles are noted. For most of the studies, however, adequacy of animal subject numbers is not clearly addressed. As far as the number of doses administered, again this information is provided in the tables in Chapter 2.

RESPONSE: *All the animal studies listed in the text of Chapter 2 are also included in the LSE tables 2-3, 2-4, 2-5. Systematic review was conducted for neurological and hepatic endpoints which also includes the studies in Chapter 2, LSE tables 2-3 and 2-4.*

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: Most studies have been conducted in rats and mice, although a smaller number of studies have also been conducted in rabbit, dog, guinea pig, and monkey. The studies are appropriate with regard

to species and endpoints measured. Again, however, the issue of dose appropriateness is not adequately addressed. While the figures and tables clearly list the doses administered in. each study, there is no apparent discussion of the appropriateness or sufficiency of the doses. Moreover, as noted previously and repeatedly, the relevance of the doses for human exposures is also not considered.

RESPONSE: *Discussion of appropriateness or how sufficiency of doses pertains to the study design in these peer-reviewed studies is beyond the scope of this Tox Profile. Relevance of the doses for human exposures is discussed in Chapter 2 in each end point specific section.*

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

COMMENT: Identification of dose-response relationships is critical. In many cases, responses are noted but it is also stated that a dose-response was not observed. This raises important questions that are not really addressed. For example, in some cases a response may only be observed at the very highest exposure dose. In other cases, however, multiple exposure doses are used but effects are only observed at a middle dose or do not show a progression of severity with increasing dose. While these observations are noted, their significance in terms of the quality of the study or the potential for unaccounted for confounding factors are not discussed. Thus, when the lack of a dose-response for a given effect exists in a study, some evaluation or discussion of what this means, especially in terms of the strength of the study, should be provided.

RESPONSE: *Based on the guidelines provided by ATSDR to develop this ToxProfile, after examining a given study for the lack of a dose-response for a health effect, the absence of it is detailed in the corresponding section pertaining to that endpoint. Appendix C includes dose-response effect as a criteria to determine the confidence in a study in the systematic review.*

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, I am not aware of additional animal studies that have not been included in the document.

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, I am not aware of additional animal studies that would be useful in deriving MRL values.

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, appropriate NOAELs and LOAELs have been identified. The text clearly explains the values that were used.

RESPONSE: *No revisions were suggested.*

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: The categorization of effects as “less serious” or “serious” seems to be scientifically correct and aligns with the observed dose responses. By LSE tables, I assume the Charge Questions are referring to the tables in Appendix D.

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: All potential mechanisms of action have been discussed. There is a relative paucity of mechanistic information related to adverse effects of 111-TCE.

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: All conclusions are generally appropriate. However, there are some errors in how some aspects of the data are presented.

RESPONSE: *The identified errors have been incorporated into the Annotated Comments section. No revisions needed here.*

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

Toxicokinetics:

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

COMMENT: No. Unfortunately, the document omits a large number of human studies relating to ADME of 111-TCE. The following is text that I prepared on human data relating to this topic for the recently held IARC Workshop (October 2021) for Volume 130 of the IARC Monograph series. All the work described in this section are human studies.

Human 1,1,1-TCE ADME Studies:

4.1.1 Humans

(a) Absorption

There are a fairly large number of studies published in humans on the absorption of 1,1,1-trichloroethane (1,1,1-TCE) by either the dermal or inhalation route of exposure. In general, all studies demonstrate rapid absorption, with many of these, especially the more recent studies, relating absorption to some measurement of either 1,1,1-TCE or one of its metabolites in either urine or blood. Dermal or percutaneous absorption is assessed by either direct application of 1,1,1-TCE to the skin or by assessing dermal penetration of 1,1,1-TCE vapours. Studies involving dermal absorption showed rapid absorption related to the type or condition of skin exposed, duration of exposure, and exposure concentration (Stewart and Dodd (1964); Aitio et al. (1984); Poet et al. (2000)). Several studies have been conducted on the percutaneous absorption of solvent vapours (Riihimäki & Pfäffli (1978); Wallace et al. (1989); Giardino et al. (1999)). Absorption was shown to be rapid for the vapor from several halogenated solvents, including 1,1,1-TCE, with differences noted according to solvent lipid solubility, skin condition, and activity level of the subject. With volatile solvents such as 1,1,1-TCE, absorption by the dermal route is very small as compared to inhalation in the absence of respiratory protection use by the subjects (Giardino et al. (1999)). Dermal absorption of 1,1,1-TCE is considerably slower than that of other organic solvents. Such as trichloroethylene, perchloroethylene, toluene, or xylene (Kezic et al. (2000, 2001)).

Another focus of several human studies on 1,1,1-TCE absorption from inhalation exposures has been to use measurements of either exhaled breath, blood, or urine as surrogates for estimating the exposure dose. Droz et al. (1988) exposed volunteers were by inhalation to 200 ppm 1,1,1-TCE during 6 hours and detected 1,1,1-TCE in breath for up to15 hours post exposure. Nagatoshi et al. (1994) used urinary excretion of various organic solvents, including 1,1,1-TCE, to conclude that worker exposure was extremely small in factories that exercised proper control over toxic materials. [The Working Group noted that the nature of the controls, specifically whether both inhalation and dermal exposures were considered, is unclear.] Nolan et al. (1984) used both blood and expired air concentrations of 1,1,1-TCE to validate inhalation exposure. They found that both measurements were proportional to exposures and suggested that 25% of the 1,1,1-TCE during the 6-hour exposure was absorbed. Tay et al. (1995) similarly found a good correlation between concentrations of 1,1,1-TCE in end-of-shift expired air ($r = 0.81$) and venous blood samples ($r = 0.88$). Gill et al. (1991), Hajimiragha et al. (1986), and Monster & Houtkooper (1979) all found blood concentrations of 1,1,1-TCE to provide an accurate assessment of inhalation exposure and absorbance. Monster & Houtkooper (1979) directly compared the accuracy of measurements in blood, urine, and exhaled air to indicate inhalation exposures to 1,1,1-TCE, trichloroethylene, or perchloroethylene. For all three solvents, concentrations of the parent compound in blood gave the best estimates of exposure, although the advantages of using blood were very small compared to exhaled air measurements. Simultaneously measuring solvent in urine and exhaled air did not significantly improve exposure estimates.

(b) Distribution

Much of absorbed 1,1,1-TCE in humans is rapidly excreted in exhaled air as the unmetabolized parent compounds (Gamberale & Hultengren, 1973; Caplan et al., 1976). Caplan et al. (1976) analysed the tissue distribution of 1,1,1-TCE in an otherwise healthy, 40-year-old female who had been poisoned by 1,1,1-TCE. The woman was found in a closed and poorly ventilated room in which paint, paint thinner, and towels soaked in those materials were found. There were paint stains on areas of the skin, suggesting that exposure was both by inhalation and the dermal route. By far the highest concentration of 1,1,1-TCE was found in the brain (36 mg/100 mL), with markedly lower concentrations found in the kidneys, liver, lung, blood and bile (12, 5, 1, 2, and < 1 mg/100 mL, respectively).

Hajimiragha et al. (1986) concluded that their data on human exposures to volatile halogenated hydrocarbons agreed with those of Monster (1979) in that blood levels of 1,1,1-TCE are determined by a complex equilibrium involving uptake, exhalation, and tissue storage, especially in adipose tissue. This is then followed by redistribution from tissues into blood and from blood into alveolar air or biotransformation. These authors also noted that tissue depletion occurs quickly, with the exception of adipose tissue, which begins once blood concentrations decrease below a certain level and is determined by the fat:blood partition coefficient of 1,1,1-TCE. Consistent with the conclusion that 1,1,1-TCE is stored and gradually released after repeated exposures, Seki et al. (1975) found that in printing factory workers exposed solely to 1,1,1-TCE at levels of up to 53 ppm, there was a linear relationship between total trichloro-compounds in urine and environmental vapour concentrations. Towards the end of the work week, however, increased levels of urinary metabolites were generally noted, consistent with potential accumulation of 1,1,1-TCE over the course of the work week. [The variability of such measurements of urinary metabolites, such as in the study of Monster & Houtkooper (1979), suggest some caution is needed in making conclusions about accumulation of 1,1,1-TCE.] The rapid, initial distribution of 1,1,1-TCE into tissues from blood and subsequent elimination, however, result in a weak correlation between clinical toxicity and blood levels (Meredith et al., 1989).

(c) Metabolism

The metabolites of 1,1,1-TCE are not unique to 1,1,1-TCE exposure and are also formed after exposure to trichloroethene and tetrachloroethene, though in different fractions. Only a small fraction (< 10%) of the absorbed 1,1,1-TCE is metabolized (Fernández et al., 1977). Of the 10% of 1,1,1-TCE that is absorbed, 2–5% is eliminated as trichloroethanol (half-life of 10–27 hours) and 1–2% as trichloroacetic acid (half-life of 70–85 hours) in urine, representing a minor elimination pathway (Humbert & Fernández, 1976; Monster, 1986). Nevertheless, that they are well correlated with airborne exposures indicating a possibly useful biomarker of current exposure (trichloroethanol) and weekly average exposure (trichloroacetic acid), in the absence of other chlorinated solvents (Imbriani et al., 1988).

As most of the pharmacokinetics data in humans for 1,1,1-TCE show that only a limited amount of absorbed compound is metabolized (i.e., < 10%) (Monster, 1979), there is not an extensive amount of data available on rates of metabolism. Nonetheless, several studies in humans have demonstrated that trichloroethanol (TCOH) and trichloroacetic acid (TCA) are the primary metabolites, with TCOH being the more abundant one of the two (Nolan et al., 1984; Berode et al., 1990; Kawai et al., 1991; Pedrozo & Siqueira, 1996; Tomicic et al., 2011).

Based on similarities with the more widely studied solvent trichloroethylene and on experimental data from rodent studies, Guengerich et al. (1991) concluded that metabolism of 1,1,1-TCE to TCOH occurs primarily by human cytochrome P450 2E1 (CYP2E1). To support this suggestion for humans, there are two studies (Berode et al., 1990; Johns et al., 2006) that provide indirect evidence for the function of various CYP enzymes in 1,1,1-TCE oxidation. These studies correlated metabolism of 1,1,1-TCE with that of other CYP2E1 substrates and showed that metabolism of 1,1,1-TCE is increased by ethanol consumption.

1,1,1-TCE is oxidized by one of several CYP enzymes to form TCOH, which subsequently undergoes either oxidation to TCA or glucuronidation to form the corresponding glucuronide conjugate TCOG. Both metabolites are recovered in urine, with the majority being TCOH Most of the metabolic flux is to TCOH rather than TCA (Kawai et al., 1991). Other minor metabolites, including carbon dioxide and acetylene excreted in the exhaled air, have also been described (Tomicic et al., 2011). The potential implications of formation of acetylene from 1,1,1-TCE are discussed in Section 4.2. Acetylene has been proposed to be formed from 1,1,1-TCE via multiple steps of reductive dehalogenation that involve CYP enzymes as well. Similar studies in experimental animal models that could provide additional support for this pathway are not available.

(d) Excretion

Excretion of 1,1,1-TCE absorbed by either the dermal or inhalation route occurs by one of two mechanisms, exhalation of unmetabolized 1,1,1-TCE or urinary excretion of either 1,1,1-TCE or its metabolites. For the latter, the urinary metabolites are primarily TCOH and TCA, with the former being the predominant form. Human studies on workers exposed to 1,1,1-TCE have focused for many years on validating measures that can be sensitive indicators or biomarkers of exposure. For example, Stewart et al. (1961) performed controlled human exposures to 1,1,1-TCE vapour and showed an exponential decay curve for the concentration of 1,1,1-TCE in expired air. Similar studies, such as those by Seki et al. (1975), Abe & Wakui (1984), Nolan et al. (1984); Hajimiragha et al. (1986), Imbriani et al. (1988), Gill et al. (1991), Kawai et al. (1991), Laparé et al. (1995), Mizunuma et al. (1995), Tay et al. (1995), and Tomicic et al. (2011) have all shown the predominance of exhalation of unmetabolized 1,1,1-TCE in the excretion of inhaled or absorbed 1,1,1-TCE. Moreover, several of these studies (Nolan et al., 1984; Laparé et al., 1995) concluded that measurement of 1,1,1-TCE concentration in expired air is the most reliable indicator of exposure and that measurement of urinary metabolites is subject to error and the potential for significant individual variation. If urine is selected for monitoring exposure, parent chemical or total trichloro-compounds rather than specific metabolites is recommended by most of these studies.

References:

Abe, T., and Wakui, C. (1984) Necessity for total trichloride compound measurement in screening tests for workers exposed to trichloroethylene or 1,1,1-trichloroethane. Jpn. J. Indus. Health 26, 492-499.

Aitio et al. (1984) Skin absorption as a source of error in biological monitoring. Scand. J. Work Environ. Health 10(5), 317-320.

Berode et al. (1990) Demethylation pathways in caffeine metabolism as indicators of variability in 1,1,1-trichloroethane oxidation in man. Pharmacology & Toxicology 67, 41-46.

Caplan (1976) 1,1,1-Trichloroethane: Report of a fatal intoxication. Clin. Toxicol. 9, 69-74.

Droz et al. (1988) A Direct Reading Method for Chlorinated Hydrocarbons in Breath. Am. Indus. Hygiene Assoc. J. 49(7), 319-324.

Fernández et al. (1977) Trichloroethylene exposure. Simulation of uptake, excretion, and metabolism using a mathematical model. Br. J. Ind. Med. 34(1), 43-55.

Gamberale (1973) Methylchloroform exposure II. Psychological functions. Work-environm. Health 10, 82-92.

Giardino et al. (1999) Real-time breath analysis of vapor phase uptake of 1,1,1 trichloroethane through the forearm: Implications for daily absorbed dose of volatile organic compounds at work. Appl. Occupat. Environ. Hygiene 14(11), 719-727.

Gill et al. (1991) The response of evidential breath alcohol testing instruments with subjects exposed to organic solvents and gases I. Toluene, 1,1,1-trichloroethane and butane. Med. Sci. Law 31, 187-200.

Guengerich, F. P., Kim, D.-H., and Iwasaki, M. (1991). Role of human cytochrome P-450 IIE1 in the oxidation of many low molecular weight cancer suspects. Chem. Res. Toxicol. 4, 168-179.

Hajimiragha et al. (1986) Human exposure to volatile halogenated hydrocarbons from the general environment. Int. Arch. Occup. Environ. Health 58, 141-150.

Humbert and Fernández (1976) Simultaneous determination of trichloroacetic acid and trichloroethanol by gas chromatography. Int. Arch. Occup. Environ. Health 36(4), 235-41.

Imbriani et al. (1988) 1,1,1-Trichloroethane (methyl chloroform) in urine as biological index of exposure. Am. J. Indus. Med. 13, 211-222.

Johns et al. (2006) Ethanol-induced increase in the metabolic clearance of 1,1,1-trichloroethane in human volunteers. Toxicol. Sci. 92, 61-70.

Kawai et al. (1991) Exposure of 1,1,1-trichloroethane and dose-related excretion of metabolites in urine of printing workers. Toxicol. Lett. 55, 39-45.

Kezic et al. (2000) Skin absorption of some vaporous solvents in volunteers. Int. Arch. Environ. Health 73, 115-122.

Kezic et al. (2001) Dermal absorption of neat liquid solvents on brief exposures in volunteers. Am. Indus. Hygiene Assoc. 62(1), 12-18.

Laparé et al. (1995) Effect of various exposure scenarios on the biological monitoring of organic solvents in alveolar air II. 1,1,1-Trichloroethane and trichloroethylene. Int. Arch. Occup. Environ. Health 67, 375-394.

Meredith et al. (1989) Diagnosis and treatment of acute poisoning with volatile substances. Hum. Exp. Toxicol. 8, 277-286.

Mizunuma et al. (1995) Urinary methylchloroform rather than urinary metabolites as an indicator of occupational exposure to methylchloroform. Int. Arch. Occup. Environ. Health 67, 19-25.

Monster, A.C. (1979) Difference in uptake, elimination and metabolism in exposure to trichloroethylene, 1,1,1-trichloroethane and tetrachloroethylene. Int. Arch. Occup. Environ. Health 42, 311-317.

Monster and Houtkooper (1979) Estimation of individual uptake of trichloroethylene, 1,1,1 -trichloroethane and tetrachloroethylene from biological parameters. Int. Arch. Occup. Environ. Health 42, 319-323.

Nagatoshi et al. (1994) Determination of urinary metabolites of organic solvents among chemical industry workers. Jpn. J. Ind. Hlth. 36, 106-113.

Nolan et al. (1984) Kinetics and metabolism of inhaled methyl chloroform (1,1,1 -trichloroethane) in male volunteers. Fund. Appl. Toxicol. 4, 654-662.

Pedrozo and Siqueira (1996) [Spectrophotometric and gas chromatographic analysis of trichloroacetic acid in urine]. Rev. Saude Publica. 30(3), 261-6. https://doi.org/10.1590/S0034-89101996000300009. PMID: 9110472.

Riihimaki and Pfaffli (1978) Percutaneous absorption of solvent vapors in man. Scand. J. Work Environ, Health 4(1), 73-85.

Seki et al. (1975) Trichloro-compounds in the urine of humans exposed to methyl chloroform at sub-threshold levels. Int. Arch. Arbeitsmed. 34, 39-49.

Stewart and Dodd (1964) Absorption of carbon tetrachloride, trichloroethylene, tetrachloroethylene, methylene chloride, and 1,1, 1-trichloroethane through the human skin. Am. Indus. Hygiene Assoc. J. 25, 439-446.

Stewart et al. (1961) Human exposure to 1,1,1-trichloroethane vapor: relationship of expired air and blood concentrations to exposure and toxicity. Am. Indus. Hygiene Assoc. J. 22, 252-262.

Tay et al. (1995) Environmental and biological monitoring of occupational exposure to 1,1,1-trichloroethane. Occup. Med. 45, 147-150.

Tomicic et al. (2011) Sex differences in urinary levels of several biological indicators of exposure: a human volunteer study. Toxicol. Lett. 202(3), 218-25.

Wallace et al. (1989) The influence of personal activities on exposure to volatile organic compounds. Environ. Res. 50, 37-55.

RESPONSE: *Thank you for providing these excerpts. Pertinent information from these excerpts has been included in the profile. The following text has been included in the appropriate sections.*

In section 3.1.1 Absorption, following text was added-

- *"Human studies on 1,1,1-TCE use exhaled breath, blood, or urine as surrogates for estimating the exposure dose 1,1,1-trichlorethane. Droz et al. (1988) exposed volunteers to 1,1,1-TCE which was detected in breath for up to15 hours post exposure after inhalation of 200 ppm 1,1,1-TCE. Nagatoshi et al. (1994) concluded that worker exposure was extremely small in factories that exercised proper control over exposure to 1,1,1-TCE and other solvents. Nolan et al. (1984) used both blood and expired air concentrations of 1,1,1-TCE to validate absorption of the chemical via inhalation exposure after a 6 hour exposure. Correlations between absorption via inhalation exposure to 1,1,1 trichloroethane and blood concentrations have been observed in numerous studies (Tay et al. 1995; Gill et al. 1991; Hajimiragha et al. 1986;, and Monster & Houtkooper 1979)."*
- *"Studies involving dermal absorption showed rapid absorption related to the type or condition of skin exposed, duration of exposure, and exposure concentration (Stewart and Dodd 1964; Aitio et al. 1984; Poet et al. 2000). Other studies where exposure is via percutaneous absorption of solvent vapors have also been conducted and found similar rapid absorption occurring (Riihimäki & Pfäffli 1978; Wallace et al. 1989; Giardino et al. 1999)."*

In section 3.1.2 Distribution, following text was added-

- *"Additionally, most of absorbed 1,1,1-TCE in humans is rapidly excreted in exhaled air as the unmetabolized parent compounds (Gamberale & Hultengren, 1973; Caplan et al., 1976)."*
- *"Adipose tissue also exhibited delayed clearance compared with other tissues in the rat (Mortuza et al. 2018; Hajimiragha et al. 1986; Monster et al. 1979). Consistent with the conclusion that 1,1,1-TCE is stored and gradually released after repeated exposures in Seki et al. (1975).*

In section 3.1.3 Metabolism, following text was added-

- *"Of the 10% of 1,1,1-TCE that is absorbed, 2–5% is eliminated as trichloroethanol (half-life of 10–27 hours) and 1–2% as trichloroacetic acid (half-life of 70–85 hours) in urine, representing a minor elimination pathway (Humbert & Fernández, 1976; Monster, 1986; Imbriani et al., 1988). Human studies have demonstrated that trichloroethanol (TCOH) and trichloroacetic acid (TCA) are the primary metabolites, with TCOH being the more abundant one of the two (Nolan et al., 1984; Berode et al., 1990; Kawai et al., 1991; Pedrozo & Siqueira, 1996; Tomicic et al., 2011)."*
- *"Guengerich et al. (1991) concluded that metabolism of 1,1,1-TCE to TCOH occurs primarily by human cytochrome P450 2E1 (CYP2E1) which is supported by two additional studies (Berode et al., 1990; Johns et al., 2006) that provide indirect evidence for the function of various CYP enzymes in 1,1,1-TCE oxidation. These studies correlated metabolism of 1,1,1-TCE with that of*

other CYP2E1 substrates and showed that metabolism of 1,1,1-TCE is increased by ethanol consumption. 1,1,1-TCE is oxidized by one of several CYP enzymes to form TCOH, which subsequently undergoes either oxidation to TCA or glucuronidation to form the corresponding glucuronide conjugate TCOG. Both metabolites are recovered in urine, with the majority being TCOH. Most of the metabolic flux is to TCOH rather than TCA (Kawai et al., 1991). Other minor metabolites, including carbon dioxide and acetylene excreted in the exhaled air, have also been described (Tomicic et al., 2011)."

In section 3.1.4 Excretion following text was added-

- *"Stewart et al. (1961) performed controlled human exposures to 1,1,1-TCE vapor and identified an exponential decay curve for the concentration of 1,1,1-TCE in expired air. Additional studies demonstrate the predominance of exhalation of unmetabolized 1,1,1-TCE in the excretion of inhaled or absorbed 1,1,1-TCE (Seki et al. 1975; Abe & Wakui 1984; Nolan et al. 1984; Hajimiragha et al. 1986; Imbriani et al. 1988; Gill et al. 1991; Kawai et al. 1991; Laparé et al. 1995; Mizunuma et al. 1995; Tay et al. 1995; Tomicic et al. 2011). Measurement of 1,1,1-TCE concentration in expired air is the most reliable indicator of exposure (Nolan et al., 1984; Laparé et al., 1995)."*

Out of the 32 references suggested by the reviewer 21 references were already included in the text. The additional 11 references have also been included in the text in Chapter 3 and listed in Chapter 8.

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

COMMENT: The document presents a nice discussion of different PBPK models and how they are derived. However, there are a few minor points needing clarification.

RESPONSE: *The minor points have been incorporated into the Annotated Comments section. No revisions needed here.*

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: No, I do not believe this section is adequate. The primary reason is that it seems as if much of the database for human ADME has not been discussed at all (see response to Question 1 above). Inasmuch as the document notes an absence of studies in humans (which is incorrect), the presentation of the animal toxicokinetic information is done as the only available information. Thus, a direct discussion of comparisons between the animal and human data needs to be added.

RESPONSE: *Additional information from the suggested human toxicokinetic information as noted in our response to Question 1 has been added to the profile. See ATSDR response to Question 1.*

Children and Other Populations that are Unusually Susceptible:

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: No, there are no additional studies available relating to children and developmental effects that have not been presented and summarized.

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, the document appropriately discusses potential populations that are at higher risk of injury from exposure to 111-TCE. Due to the small number of relevant studies on this topic, much of the discussion here is inferences based on the limited data and some data for similar chemicals.

RESPONSE: *No revisions were suggested.*

Biomarkers of Exposure and Effect:

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

COMMENT: The biomarkers of exposure include blood, urinary, or expired air parent compound (111-TCE) and urinary trichloroethanol (TCOH) and trichloroacetate (TCE). As the document clearly explains, TCOH and TCA are also metabolites of other halogenated solvents (i.e., tri- and perchloroethylene). Hence, measurement of TCOH and TCA would not be specific to 111-TCE. Moreover, exposures to 111-TCE in both the environment and workplace often occur along with other solvents, especially trichloroethylene.

RESPONSE: *No revisions were suggested.*

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

COMMENT: As the document clearly explains, there are no biomarkers of effect that are specific for 111-TCE.

RESPONSE: *No revisions were suggested.*

Interactions with Other Chemicals:

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: The document provides a reasonably thorough discussion of potential interactions of 111-TCE with other chemicals, principally ethanol. There are few studies available that have directly investigated such interactions. Thus, the limited discussion is appropriate.

RESPONSE: *No revisions were suggested.*

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: Yes, there is brief discussion of the underlying mechanism by which ethanol and 111-TCE might interact. There is really few other mechanistic information available for chemical interactions, so any possible statements are supposition.

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: Chapter 4 is extremely brief and straightforward. All the key information about 111-TCE seems to be included.

RESPONSE: *No revisions were suggested.*

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

COMMENT: 111-TCE is a liquid that readily volatilizes. Hence, it is present in two forms, liquid and gas. Both are appropriately discussed.

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: Discussion of production, import/export, use, and disposal of 111-TCE is reasonably detailed and appropriate for the purposes of this document.

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, the text clearly discusses the production, uses, and fates of released 111-TCE. While this section is reasonably concise, all the essential information seems to be present.

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: Yes, the text concises but appropriately discusses key points related to the transport, partitioning, transformation, and degradation of 111-TCE.

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: Section 5.5 covers levels of 111-TCE in the environment. While this information is clearly provided, what seems to be missing is an integration of this information with the toxicology studies done in both humans and animals. As noted above, one of my major concerns with the document is that it does not seem to relate either the doses used in toxicology studies and determined NOAELs and LOAELs with environmental levels of 111-TCE. Clearer emphasis on these relationships is needed.

RESPONSE: *While animal studies in existing literature have been conducted at higher concentrations resulting in health effects, similar health effects have been observed in humans at lower doses. Neurological effects are observed in both humans and animals after inhalation exposure with dose ranges being 175-10,000 ppm and 100 – 22,250 ppm , respectively. Numerous inhalation studies in laboratory animals and a few human studies strongly support neurological effects following exposure to 1,1,1-trichloroethane. Observed health effects in controlled human exposure studies include impaired manual dexterity, eye-hand coordination, perceptual speed, and reaction time, as well as increased tiredness and disturbances of equilibrium and coordination (Gamberale and Hultengren 1973; Mackay et al. 1987; Savolainen et al. 1981; Muttray et al. 2000; Stewart et al. 1961; Torkelson et al. 1958). Dornette and Jones (1960) also found that administering 1,1,1-trichloroethane at high concentrations induced general anesthesia in hospital patients. The principal neurological effects observed in animals exposed to 1,1,1-trichloroethane are signs of central nervous system depression, such as impaired performance in behavioral tests, ataxia, and unconsciousness, and are similar to those seen in humans (Geller et al. 1982; Kjellstrand et al. 1985; Torkelson et al. 1958; Bowen and Balster 1996; Mullin and Krivanek 1982; Ohnishi et al. 2013; Bowen and Balster 1998; Hougaard et al. 1984; Balster et al. 1982). This suggests that even though the animals are exposed to higher levels of 111-TCE, similar effects are observed in humans at comparable doses. This is indicative of the fact that the underlying mechanism of toxicity could potentially be similar eliciting similar health effects in both animals and humans. Additionally, the potential for human exposures are discussed in detail in Chapter 5. The following text has been added to Chapter 5, Section 5.5 "While studies on levels monitored or estimated in the environment represent valid data, their relevance to potential human exposures needs to be further discussed and emphasized."*

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: Section 5.6 concisely presents information on how the general population is exposed to 111-TCE and also describes data from NHANES that was published in 2018. Section 5.7 provides a brief overview of populations that have potentially high exposures to 111-TCE. The presentation seems straightforward and is sufficient for the purposes of this document, especially in light of the limited information available.

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: Besides the human ADME studies described in response to Question 1 on Chapter 3, I do not know of other studies that would fill a data gap.

RESPONSE: *No revisions were suggested.*

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

COMMENT: Yes, the data needs are clearly explained and aligned with other, recent reviews of 111-TCE toxicology and risk assessments.

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, presentation of the data needs is done in a straightforward manner that indicates what types of conclusions would be sought from obtaining the additional experimental information. I do not detect any bias in this section.

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: No, I am not aware of any additional regulation s or guidelines for 111-TCE. Those listed in Table 7-1 seem to include all the major national and international organizations that are charged with regulating environmental or occupational chemicals.

RESPONSE: *No revisions were suggested.*

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

COMMENT: No, all the listed regulations and guidelines seem appropriate.

RESPONSE: *No revisions were suggested.*

Additional References from Reviewer*

**These are references cited within the reviewer's individual comments. Responses to the reviewer's comments specify the disposition of these references within the toxicological profile.*

11 additional references suggested by the reviewer were included in Chapter 3 and Chapter 8. This was addressed in detailed in earlier responses to Chapter 3 comments.

Appendices

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

COMMENT: There are 7 appendices. The most useful and substantive one is Appendix A, which presents MRL worksheets. This is a very useful and convenient presentation. My only comment is that besides giving composite uncertainty factors (UFs), the individual UF values that comprise these composite UFs should be given for all values. Only a couple of component UFs are given (e.g., page A-15). The other appendices are clear and provide important basic information on how to use the document and how it was written.

RESPONSE: *All uncertainty factors are justified in the worksheets, where the breakdown for uncertainty factors are listed with the values.*

Unpublished Studies (If Applicable to Review)

QUESTION: For each of the unpublished studies included with the profile, prepare a brief evaluation using the following questions as prompts:

- Did the study use an adequate number of animals and practice good animal care?
- Did the study account for competing causes of death?
- Did the study include a sufficient number of dose groups, and sufficient magnitude of dose levels?
- If you think the study was not adequately designed or reported, does that negate the utility of the study? Please explain.
- Do you agree with the conclusions of the author? If not, please explain.

COMMENT: The only "unpublished" study that was sent to me along with the profile document was a document contracted by the U.S. EPA IRIS program entitled: "Physiologically Based Pharmacokinetic Modeling of 1,1,1-Trichloroethane." The document was written in July 2006 by Dr. Raymond Yang of Colorado State University.

The document is divided into 6 main sections:

I. Purpose

II. Background information and scope of report

III. Reconstruction of PBPK models

IV. Evaluation of the reconstructed PBPK models

V. Calculation of internal doses based on PBPK modeling

VI. Overall conclusions

The document also contains 3 appendices that contain model code and data for reconstructed or original PBPK models (Appendix I), a summary table for human studies (Appendix II), and model code for the calculation of internal doses (Appendix III).

The report explains in clear detail how the models were chosen and evaluated. This is accomplished in Sections III and IV. In Section V, the application of the reconstructed model to calculate internal doses and compare internal doses to exposure concentrations is demonstrated.

The overall conclusions of the author, based on his reconstructed PBPK model were:

1) Of the 9 reconstructed PBPK models that were available, 2 were chosen based on clear criteria (e.g., quality of study, number of routes of exposure in model, extent and quality of experimental data, similarity with other available models);

2) Final evaluation was performed by comparison of simulation results with 11 data sets;

3) The Reitz et al. (1988) PBPK model was concluded to be the best model to support the human health risk assessment for 111-TCE; this was based on its versatility and accuracy for interspecies-, route-to-route, and inter-dose extrapolations;

4) The author concludes that use of PBPK modeling will allow regulators to move away from default extrapolation with uncertainty factors for better confidence in health assessments for 111-TCE.

Overall, I find the document easy to follow and systematic in its presentation of these rather complex models. The conclusions are reasonable and clearly supported by the data and analyses presented in the report.

RESPONSE: *This reference is already included in the profile in Chapter 3, Section 3.1.5 "Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models" and will be retained as a result of this reviewer's comments.*

Annotated Comments on the Profile

COMMENT: Figure 1-4, 1-5: Concludes that neurological and hepatic effects are most sensitive targets for oral exposure to 111-TCE for intermediate oral exposure. There are discrepancies between data for acute vs. intermediate and oral vs. inhalation exposure for sensitivity of liver as a target. This discrepancy needs some explanation. These figures are also unclear with respect to what values represent data from humans and what values represent data from experimental animals. In some cases, data are available from both humans and other animal species (e.g., rats and/or mice); this should be clearly illustrated in these summary figures.

RESPONSE*: This comment refers to Figure 1-4 (Summary of Sensitive Targets of 1,1,1-Trichloroethane-Inhalation) and Figure 1-5 (Summary of Sensitive Targets of 1,1,1-Trichloroethane-Oral). The description in the titles indicate that triangles represent the lowest LOAELS in humans and circles represent lowest LOAELs in animals. This figure represents the lowest doses observed/tested in human and animals from the existing literature.*

COMMENT: For example, page 94, line 4 mentions occupational dermal exposure but does not give the dose or exposure level. If this is not known, such a statement should be provided.

RESPONSE*: In Chapter 2 section 2.2, the first line is an introductory line that is discussed within the paragraph. The exposure concentrations for each of these studies are listed in the paragraph. The following is the text from the profile:*

"Lethal effects of inhalation of 1,1,1- trichloroethane were seen in case studies where individuals were exposed to 1,1,1-trichloroethane (Jones and Winter 1983; Northfield 1981; Silverstein 1983). Simulation of the circumstances of deaths of two people exposed while using 1,1,1-trichloroethane as a solvent showed that concentrations ≤6,400 ppm may have been generated in one case (Jones and Winter 1983), and concentrations ≤9,000 ppm may have been generated in the other (Silverstein 1983). Northfield (1981) reported a case in which a worker, whose death was attributed to respiratory failure, may have been exposed to 1,1,1-trichloroethane concentrations of 6,000 ppm or higher, depending on distance from the source."

COMMENT: Page 103, lines 6-7: Is it correct that you mean ≤ these two concentrations? It seems that ≥ would be more appropriate.

RESPONSE*: This comment refers to the following sentence in Section 2.7 (Hematological – Inhalation): "In Kramer et al.'s (1978) matched-pair analysis of textile workers, change in gamma-glutamyl transferase was positively associated with the current level of 1,1,1-trichloroethane exposure (at $p<0.025$), while change in alkaline phosphatase was positively associated with breath analysis and negatively associated with estimated dose on day of exam (both at $p<0.05$)." The change has been made and the less than sign (<) has been changed to a greater or equal to sign (≥).*

COMMENT: Page 110, line 21: Unclear what you mean by the correlation was unquantified. Maybe rewrite this for clarity.

RESPONSE*: This comment refers to the following sentence in Section 2.11 (Dermal – Inhalation): "In neither case control study could 1,1,1-trichloroethane exposure be quantified." This sentence has been edited for clarity "In both case- control studies 1,1,1-trichloroethane exposure could not be quantified".*

COMMENT: For example, Page 119, line 15: AST is a biomarker for liver function, not kidney function.

RESPONSE*: This comment refers to the following paragraph in Section 2.10 (Renal – Oral): "Urinalysis performed on male rats administered 165 mg/kg/day of 1,1,1-trichloroethane by gavage for*

21 days revealed significant increases in mean urinary protein and AST, but no histopathological evidence of renal damage (NTP 1996). The statistical significance of this finding is questionable since it was based on only 4 surviving rats. Male rats administered ≥10,000 ppm (600 mg/kg/day) of 1,1,1-trichloroethane in the diet for 13 weeks exhibited kidney lesions indicative of hyaline droplet nephropathy (NTP 2000); though this effect is specific to male rats and is not a human health concern. Chronic-duration oral exposure to 1,1,1-trichloroethane in rats and mice at doses of 1,500 mg/kg/day and 5,615 mg/kg/day, respectively, had no effect on the incidence of nonneoplastic lesions in the kidneys (NCI 1977)."

This has been edited and mention of AST in the renal section has been deleted and now included in the hepatic section.

2.9 Hepatic section reads "Urinalysis performed on male rats administered 165 mg/kg/day of 1,1,1-trichloroethane by gavage for 21 days revealed significant increases in AST but no histopathological evidence of renal damage were observed (NTP 1996)."

The mention of AST has been deleted from Renal and the Section 2.10 Renal reads "Urinalysis performed on male rats administered 165 mg/kg/day of 1,1,1-trichloroethane by gavage for 21 days revealed significant increases in mean urinary protein but no histopathological evidence of renal damage were observed (NTP 1996)".

COMMENT: Page 130, lines 24-27: Inappropriate to use the phrase "apparent decrease." If there was no statistical significance, then there was no difference or effect. There are a few other instances where statistical significance is not properly used in data evaluation. Examples include studies where effects are described as being "not statistically significant"; if there is no statistical significance, then no effect can be said to have occurred.

RESPONSE*: This comment refers to the following sentence in Section 2.16 (Reproductive – Inhalation): "An apparent decrease in fertility (as measured by number of menstrual cycles required for a woman to become pregnant) was noted in Finnish male workers with exposure to 1,1,1-trichloroethane, but the difference from controls was not statistically significant (Sallmen et al. 1998)."*

Edited the sentence to clarify the findings. It now reads "A Finnish study examined decreases in fertility (as measured by number of menstrual cycles required until pregnancy achieved) involving Finnish male workers with exposure to 1,1,1-trichloroethane. The women whose partners were exposed to 1,1,1-trichloroethane had increased numbers of menstrual cycles before becoming pregnant than those who were not exposed, but the difference from controls was not statistically significant (Sallmen et al. 1998)."

COMMENT: Page 135, lines 1-3: How can you say there was increased risk if no statistical significance?

RESPONSE*: This comment refers to the following sentence in Section 2.19 (Cancer – Inhalation): "Maternal exposure to 1,1,1-trichloroethane during pregnancy was associated with an increased risk of acute lymphoblastic leukemia in children (OR = 7.55, 95% CI: 0.92, 61.97), though the association failed to reach statistical significance (Infante-Rivard et al. 2005).*

Edited the sentence to clarify the findings. It now reads "A high odds ratio of 7.55 was observed in a study which examined acute lymphoblastic leukemia in children (95% CI: 0.92, 61.97) after maternal

exposure to 1,1,1-trichloroethane during pregnancy, though there was no statistical significance (Infante-Rivard et al. 2005)."

COMMENT: Page 135, lines 4-5: What does "non-significant elevations in risk" even mean?

***RESPONSE**: This comment refers to the following sentence in Section 2.19 (Cancer – Inhalation): "In a study of leukemia in Scandinavian adults, the most highly exposed participants showed non-significant elevations in risk (OR = 1.18, 95% CI: 0.95, 1.45) compared to unexposed participants (Talibov et al. 2017)."*

Edited the sentence to clarify the findings. It now reads "A Scandinavian study examined effects of occupational exposure in adults and leukemia. An OR of 1.18 (95% CI: 0.95, 1.45) was observed in the most highly exposed participants compared to unexposed participants (Talibov et al. 2017)."

COMMENT: Page 135, lines 7-9: What does the lack of dose response mean?

***RESPONSE**: This comment refers to the following sentences in Section 2.19 (Cancer – Inhalation): "No dose-response relationship was observed between 1,1,1-trichloroethane exposure and leukemia diagnosis. Gold et al. (2011) found that, compared to no exposure, ever exposure to 1,1,1-trichloroethane was associated with higher risk of multiple myeloma (OR = 1.8, 95% CI: 1.1, 2.9); however, no dose-response relationships were observed by level of exposure."*

This sentence was edited for clarity "Gold et al. (2011) found that, compared to no exposure, exposure to 1,1,1-trichloroethane at lower doses was associated with higher risk of multiple myeloma (OR = 1.8, 95% CI: 1.1, 2.9);the study authors hypothesize that the lack of effects at the highest dose indicated that carcinogenesis that is preceded by stimulated immunity might not be following a typical-exposure-response pattern".

COMMENT: Page 135, line 13: Inappropriate to conclude an increased risk if non-significant.

***RESPONSE**: This comment refers to the following sentences in Section 2.19 (Cancer – Inhalation): "A non-significant increased risk of mortality due to multiple myeloma was observed among all workers exposed to any chemical or solvent, while females exposed to 1,1,1-trichloroethane showed a significantly increased risk; however, only two cases were reported (Spirtas et al 1991). No cases were observed among male workers (Spirtas et al 1991). Male workers exposed to 1,1,1-trichloroethane showed a non-significant increased risk of mortality due to non-Hodgkin's lymphoma based on four cases, while no cases were observed among exposed females workers (Spirtas et al 1991)."*

This sentence was edited for clarity. Female workers exposed to 1,1,1-trichloroethane showed an increased risk of mortality (Spirtas et al 1991). No cases were observed among male workers (Spirtas et al 1991). Male workers exposed to 1,1,1-trichloroethane showed an increased risk of mortality due to non-Hodgkin's lymphoma based on four observed cases, while no cases were observed among exposed female workers due to non- Hodgkin's lymphoma (Spirtas et al 1991).

COMMENT: Page 135, line 26: Again, if non-significant, what risk can really be concluded?

***RESPONSE**: This comment refers to the following sentence in Section 2.19 (Cancer – Inhalation): "Neta et al. (2012) found that probable occupational exposure to 1,1,1-trichloroethane was associated with a non-significant elevated risk of glioma (OR = 4.1, 95% CI = 0.6, 28.6)."*

Rewritten to improve clarity of findings. "Neta et al. (2012) observed an odds ratio of 4.1 for risk of glioma (95% CI = 0.6, 28.6) after occupational exposure to 1,1,1-trichloroethane."

COMMENT: Regarding the overall organization of this section, the beginning portion of section 3.1 needs better set up. On page 142: Are these 4 ADME bullet points at the start of section 3.1 a sort of Executive Summary? If so, some sort of prefacing statement to that effect should be made.

***RESPONSE**: This comment refers to the bullets at the beginning of section 3.1. The sentence has been edited and now reads "Information on the toxicokinetics of 1,1,1-trichloroethane is available from a small number of human studies and several animal studies and a brief introduction is provided below."*

COMMENT: Page 155 (146), lines 29-31: What about metabolic parameters for humans and mice? I would think that with metabolic rates being son different across species, specific parameters would need to be used for each species.

***RESPONSE**: This comment refers to the following sentence in Section 3.1.5 (Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models): "Metabolic parameters for the rat (Vmax, Km) were derived from rat inhalation exposure data to 150 or 1,500 ppm for 6 hours in Schumann et al. (1982)." The metabolic parameters presented in the peer-reviewed study in Schumann et al. (1982) only presented information for rats.*

COMMENT: Table 3-1: Why are biochemical constants the same for all species?

***RESPONSE**: This comment refers to Table 3-1. These are listed as presented in the Reitz et al. (1988) study.*

COMMENT: Page 159, lines 9-10: Why would toxicokinetics be independent of exposure duration? What does this mean?

***RESPONSE**: This comment refers to the following sentence in Section 3.1.5 (Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models): "Modeling results suggested that toxicokinetics of 1,1,1-trichloroethane and its metabolites are independent of exposure duration."*

The sentence has been edited for clarity "Modeling results suggested that toxicokinetics of 1,1,1-trichloroethane and its metabolites increase proportionally with increases in exposure duration."

COMMENT: Page 160, lines 31-32: Earlier discussion of PK and toxicity for inhalation and oral exposures did not highlight major differences between routes of exposure. Thus, this conclusion seems confusing and not clearly in line with the data.

***RESPONSE**: This comment refers to the following sentence in Section 3.1.5 (Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models): "The study concluded that route-to-route extrapolation is not supported by the Reitz et al. (1988) PBPK model, due to the route-specific toxicity differences between inhalation and oral exposure." This sentence has been deleted.*

COMMENT: Page 163, line 22: Enzymes, not isozymes. Ethanol specifically induces CYP2E1.

RESPONSE*: This comment refers to the following sentence in Section 3.1.6 (Animal-to-Human Extrapolations): "Moderate to heavy alcohol drinkers may be more susceptible to the hepatotoxicity of some chlorinated alkanes, such as carbon tetrachloride, chloroform, and 1,1,2-trichloroethane, due to ethanol induction of hepatic cytochrome P-450 isozymes involved in the activation of these compounds to intermediate hepatotoxic metabolites." The sentence was revised by changing "isozymes" to "enzymes".*

COMMENT: Page 163, lines 28-29: Is this conclusion really validated? Is there enough data available to make this conclusion? There are some positive results with respect to alcohol and 111-TCE-induced hepatotoxicity.

RESPONSE*: This comment refers to the following sentence in Section 3.1.6 (Animal-to-Human Extrapolations): "Thus, alcohol ingestion is not likely to significantly potentiate the hepatotoxicity of 1,1,1-trichloroethane." This sentence was deleted as there is still some paucity of data.*