Disposition of Peer Review Comments for Toxicological Profile for 1,2-Dichloroethane

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

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Peer reviewers for the third pre-public draft of the Toxicological Profile for 1,2- Dichloroethane 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

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: The adverse health effects known to occur in humans are primarily associated with high intentional or accidental exposures. As human exposure levels, or doses are generally unknown or poorly documented, it is necessary to utilize results of experiments with laboratory animals to obtain dose-response data that can be used for MRL derivation.

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 majority of adverse effects seen in animals will probably occur in humans subjected to adequate doses. The relative sensitivity, or susceptibility of animals and humans will very likely differ and be dictated by species differences in toxicokinetics and/or toxicodynamics.

RESPONSE: *No revisions were suggested.*

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

COMMENT: The authors of this chapter have adequately described exposure conditions.

RESPONSE: *No revisions were suggested.*

Minimum Risk Levels (MRLs)

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

COMMENT: I agree that existing data do not support derivation of an acute or a chronic MRL for oral exposure. There have been a number of acute and short-term oral toxicity studies, but none provided clear dose-response data. Surprisingly, relatively modest adverse effects were manifest in target organs (e.g., liver and kidneys) frequently damaged by short-chain halocarbons. I was also surprised that the inhalation (Nagano et al., 2006) and oral (NTP, 1991) cancer bioassays revealed relatively few chronic non-carcinogenic effects in mice or rats.

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: I agree with the two proposed MRL values. I do not have a problem with their derivation.

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: No comment provided.

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: No comments are necessary.

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: The authors of this Tox Profile have done an excellent job in the composition of this chapter. It is very well written. It is very comprehensive, detailed, and accurately reflects the manuscripts which are cited.

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: There appear to be few, if any adequately designed human studies of 1,2-dichloroethane (DCE). Most published manuscripts were clinical case reports without reliable exposure/dose data. The studies' limitations were adequately described in the text.

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: There were a reasonable number of adequately designed animal studies that were well described in the text. Some of these had a sufficient number of animals per dose, a sufficient number of doses, and or sufficient range of doses. Studies with design or performance deficiencies were clearly noted in the text of this document (i.e., Tox Profile).

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: A range of species was utilized in investigations that were reviewed. Mice and rats were most commonly used, which is typically the case.

RESPONSE: *No revisions were suggested.*

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

COMMENT: There were no human data suitable for dose-response analysis. The study selected for acute MRL calculation had a wide range of doses, a NOAEL, LOAEL and clear dose-response. This allowed the authors to conduct BMD modeling.

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 was able to locate several additional manuscripts describing studies that may be useful in evaluating the toxicity of DCE. One (Li et al., 2015) addresses mechanisms of nephrotoxicity, one (Yaqin et al., 2018) addresses mechanisms of hepatotoxicity and apoptosis, one assesses the relative toxicity of DCE in 3 strains of rats, while still another (Morgan et al., 1990) contrasts the toxicity of DCE given as an oral bolus versus in drinking water. I obtained/have enclosed complete copies of several of these papers, as well as abstracts of the others. The citations of all of these are listed under the title of "Additional References" on separate pages.

RESPONSE: *Though the Li et al. (2015) and the Pang et al. (2018)[1] studies contain potentially relevant information, neither of these studies were added to the profile as neither study included information about how many animals were included in the studies and therefore do not meet the data quality requirements of inclusion in the profile. The Morgan et al. (1990) study uses the same underlying data as the NTP*

[1] Pang et al. (2018) is the study that was referred to as Yaqin et al. (2018) in the reviewer comment.

(1991) study, and as such, it was not included in and of itself in the profile. A note was added to the profile in the oral paragraphs for sections 2.2 (Death), 2.9 (Hepatic), and 2.10 (Renal) that reads: "Morgan et al. (1990) presents the same information, as it is a more specific publication of the larger results contained within NTP (1991)."

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: The investigation by Morgan et al. (1990) yielded data that could be considered for MRL derivation. Unfortunately, I could only obtain the Abstract. A wide range of concentrations of DCE were ingested in drinking water by rats. The range of doses given by gavage was not stated in the Abstract.

RESPONSE: *This Morgan et al. (1990) study uses the same underlying data as the NTP (1991) study, which was ultimately used for MRL derivation. A note was added to the oral paragraphs in the profile in sections 2.2 (Death), 2.9 (Hepatic), and 2.10 (Renal) that reads: "Morgan et al. (1990) presents the same information, as it is a more specific publication of the larger results contained within NTP (1991)." No further revisions have been made to the profile based on this comment."*

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: I did some spot-checking and did not find any incorrect NOAELs or LOAELs. The document's authors appear to have done a very careful job.

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: I agree with most of the categorizations of health effects. I do not think a 21% decrease in mouse body weight (Sherwood et al., 1987) constitutes a serious effect. Similarly, I do not believe that a 22% decrease in body weight gain in rats dosed with DCE for 90 days should be considered serious.

RESPONSE: *The first sentence of this comment refers to the Jin et al. 2018a entry in Table 2-1, figure key 20. The second sentence of this comment refers to the van Esch et al. 1977 entry in Table 2-2, figure key 19. ATSDR's "Guidance for the Preparation of Toxicological Profiles" defines weight loss or decrease in body weight gain of greater than or equal to 20%, assuming normal food consumption, as a serious effect. Thus, these effects were characterized as such to remain consistent with current Agency guidance on the topic.*

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: It is great to see more focus on mechanism of action (MOA) in this Tox Profile. MOAs should also be discussed in the Toxicokinetics chapter, with the role(s) of parent compound or specific metabolites linked to different target organs, where information is available.

Recent publications have provided information relevant to liver MOAs. Yaqin et al. (2018) reported apoptosis in HepG2 cells and in the liver of DCE-exposed rats. Apoptosis was attributed to inhibition of ERK1/2 pathways. Zeng et al. (2019) attributed hepatic apoptosis to down-regulation of an anti-apoptosis insulin growth factor *in vitro*. The researchers tentatively attributed this action to 2-chloroacetaldehyde (CA), an oxidative metabolite of DCE. CA is a very potent mutagen *in vitro* (McCann et al., 1975).

Several researchers have presented *in vitro* evidence that DCE is activated to a mutagen by glutathione (GSH) conjugation (Rannug et al., 1978; van Bladeren et al., 1979). Electrophilic episulfonium ions formed via the GSH pathway are believed to bind to DNA and cause genetic damage (Guengerich et al., 1987). Kramer et al. (1987) described the role GSH-generated episulfonium ions in DCE-induced nephrotoxicity in rats. Results of relatively recent research indicate that oxidative metabolites of DCE are also responsible for kidney injury. Li et al. (2015), however, attributed apoptosis in rat distal proximal tubules and human embryonic kidney cells to CYP2E1-generated reactive oxidants. This MOA information and additional references can be used to supplement the discussion on page 102 of the Tox Profile.

RESPONSE: *Based on this comment, we added language to section 3.1.3 (Metabolism) that says the following: "Zeng et al. (2019) attributed hepatic apoptosis to down-regulation of an anti-apoptosis insulin growth factor in vitro. The researchers hypothesized this was due to 2-chloroacetaldehyde (CA), an oxidative metabolite of DCE. CA is a very potent mutagen in vitro (McCann et al., 1975). Several researchers have also presented in vitro evidence that DCE is activated to a mutagen by glutathione (GSH) conjugation (Rannug et al. 1978; van Bladeren et al. 1979). Electrophilic episulfonium ions formed via the GSH pathway are believed to bind to DNA and cause genetic damage (Guengerich et al. 1987). Kramer et al. (1987) described the role GSH-generated episulfonium ions have in DCE-induced nephrotoxicity in rats. Results of relatively recent research indicate that oxidative metabolites of DCE are also responsible for kidney injury." Information from the Pang et al. (2018) and the Li et al (2015) studies were excluded as these two studies did not meet the minimum quality criteria for inclusion in the profile.*

QUESTION: Are the conclusions appropriate given the overall database? If not, please discuss your own conclusions based on the data provided and other data provided to you but not presented in the text.

COMMENT: The conclusions about health effects of DCE in humans and experimental animals are appropriate and adequately supported in Chapter 2.

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: The Toxicokinetics section does a good job describing published information on DCE absorption, distribution, metabolism and excretion for different routes of exposure.

RESPONSE: *No revisions were suggested.*

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

COMMENT: It would be worthwhile to contrast the efficacy of the updated Sweeny et al. (2016) model versus its predecessor (Sweeny et al., 2008).

RESPONSE: *This comment refers to the discussion of PBPK models in section 3.1.5 (Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models). Sweeny et al. (2016) was not an update of the Sweeny et al. (2008) model, but instead was a study that extrapolated the oral NOAEL and LOAEL of existing health effect studies in rats to the inhalation route using the Sweeny et al. (2008) model. Thus, there is no way to contrast the efficacy of the model in Sweeny et al. (2016) since it used the Sweeny et al. (2008) model. No changes were made to the profile based on this comment.*

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: It is clearly stated on page 123 that the lack of information on the metabolism and toxicokinetics of DCE precludes discussion of potential interspecies differences.

No discussion of species differences in the toxicokinetics of DCE is necessary, as human data are lacking.

RESPONSE: *This comment refers to the first paragraph in section 3.1.6 (Animal-to-Human Extrapolations), which states "The lack of this information precludes a non-speculative attempt to discuss potential interspecies differences or similarities in the toxicity of 1,2-dichloroethane, as well as a determination of which animal species is the most appropriate model for humans." No changes were made based on this comment, as the reviewer suggests that no discussion of the species differences in the toxicokinetics of 1,2-DCE is necessary.*

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 am not aware of the availability of any data on the potential susceptibility of children to DCE.

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: I do not know of any subpopulations at higher risk other than diabetics or those who frequently consume alcohol.

RESPONSE: *No revisions were suggested as diabetics and those who frequently consume alcohol are already discussed in the profile..*

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

COMMENT: Levels of the parent compound and certain metabolites are specific biomarkers, but are only present for a short time post exposure.

RESPONSE: *No revisions were suggested.*

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

COMMENT: Levels of the parent compound and certain metabolites are specific biomarkers, but are only present for a short time post exposure.

RESPONSE: *The rapid elimination of 1,2-dichloroethane from the body is already referenced in the profile with respect to biomarkers of exposure in Section 3.3.1. Thus, no revisions were needed.*

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: There is a good discussion of interactions of DCE with some MFO inducers and inhibitors. It might be added that ethanol and DCE are both CYP2E1 substrates, and thus are competitive metabolic inhibitors when administered together. There is a description of the results of an interaction study by Pott et al. (1998) of DCE and three other chemicals commonly found at hazardous waste sites.

RESPONSE: *This comment refers to section 3.4 (Interactions With Other Chemicals). Language was added in section 3.4 related to ethanol and 1,2-DCE being competitive metabolic inhibitors when they are jointly administered based on this comment. The added sentence is as follows: "Since ethanol and 1,2-dichloroethane are both cytochrome P-450 2E1 substrates, they act as competitive metabolic inhibitors when administered together."*

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: The text does an adequate job describing mechanisms of observed interactions when they are included in publications.

p. 128, lines 8 & 12-14: It is widely recognized that reduced glutathione (GSH) protects against oxidative hepatotoxic metabolites of many VOCs/halocarbons. GSH conjugation occurs in the liver, with subsequent metabolic modification and transport to the kidneys, followed by renal B-lyase-mediated formation of reactive, nephrotoxic metabolites.

128, lines 25-32: Fasting results in increased triglyceride utilization and increased circulating levels of ketone bodies. The ketones serve to stabilize/preserve existing CYP2E1, rather than inducing its synthesis. As noted in the text, fasting also substantially lowers hepatic GSH levels. Liver CYP2E1 and GSH thus exhibit pronounced diurnal rhythms dictated by food intake or its lack during fixed parts of each 24-hour period. Bruckner et al. (2002) found that rats were much more susceptible to liver injury by carbon tetrachloride (CCl4) during their initial waking hours when CYP2E1-mediated metabolic activation was highest and GSH levels were lowest.

p. 129: The antagonistic interactions of DCE with CCl4 (Aragno et al., 1992) and 3 other chemicals/2 VOCs (Pott et al., 1998) were very likely due to competitive metabolic inhibition, as DCE, CCl4, trichloroethylene and vinyl chloride are all CYP2E1 substrates.

RESPONSE: *The comments refer to Section 3.4 (Interactions With Other Chemicals). The first comment refers to the discussion in the sixth paragraph about the protective effect of glutathione. The text states "However, studies also show a protective effect of glutathione. The administration of glutathione, precursors of glutathione, or amino acids capable of donating a sulfhydryl group for the biosynthesis of glutathione all decrease the toxic effects and mortality in rats given 1,2-dichloroethane orally (Heppel et al. 1947)."*

The second comment refers to the sixth paragraph in section 3.4, which discusses nutritional status and the rate of metabolic formation of toxic intermediates. The paragraph reads:

> *"Nutritional status affects the rate of metabolic formation of toxic intermediates; liver from fasted animals showed an increased rate of 1,2-dichloroethane metabolism in vitro (Nakajima and Sato 1979) because fasting induces the formation of cytochrome P-450 2E1 (Johansson et al. 1988), the primary MFO enzyme involved in oxidation of 1,2-dichloroethane (Guengerich et al. 1991). Fasting also may lower hepatic levels of glutathione. According to the hypothesis that reactive intermediates formed by glutathione conjugation are responsible for 1,2-dichloroethane-induced toxicity, toxicity would be reduced under these conditions. However, the actual effect of fasting on 1,2-dichloroethane toxicity is unknown."*

The last comment refers to the last paragraph in section 3.4, which states:

> *"Oral administration of 1,2-dichloroethane in drinking water for 16 weeks together with 3 other chemical carcinogens commonly found at hazardous waste sites (arsenic, vinyl chloride, and trichloroethylene) resulted in inhibition of the promotion of preneoplastic hepatic lesions and pulmonary hyperplasia and adenomas (Pott et al. 1998). The four chemicals, including 1,2-dichloroethane, have been shown to be individually carcinogenic in laboratory animals, yet they interacted antagonistically to inhibit promotion of precancerous lesions. The study is limited, however, by a short exposure duration, small numbers of test animals, and the use of only male rats; the interactive effect of lifetime exposure to the four chemicals cannot be inferred with confidence from these results. The mechanism for this interactive effect has not been elucidated, but Pott et al. (1998) hypothesized that decreased cell proliferation, increased apoptosis, or enhanced remodeling of preneoplastic lesions may play a role."*

Added language to the last paragraph of Section 3.4 to suggest that a possible reason for the effect of the antagonistic interaction between DCE, trichloroethylene, and vinyl chloride was that they are all CYP2E1 substrates. The added sentence is as follows: "It is also possible that this effect could have been due to competitive metabolic inhibition, as vinyl chloride, trichloroethylene, and 1,2-dichloroethane are all CYP2E1 substrates (Pohl et al 2011)." No other changes were made based on this comment.

Chapter 4. Chemical and Physical Information

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

COMMENT: I am not knowledgeable about the physical and chemical properties of DCE.

RESPONSE: *No revisions were suggested.*

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

COMMENT: Pertinent information on DCE in its liquid and gaseous forms is provided.

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: Information on the production, import, use and disposal appears to be comprehensive and up-to-date.

p. 136, lines 12 & 13: Which trichloroethane is referred to in line 12?

RESPONSE: *This comment refers to the sentence in Section 5.2.3 (Use) that says "About 95% of produced 1,2-dichloroethane, is used as an intermediate in the production of vinyl chloride (OECD 2002), and less often in the production of chlorinated solvents, including 1,1,1-trichloroethane , trichloroethane and tetrachloroethane (De Wildeman et al. 2001; Dreher et al. 2014)". This reference to "trichloroethane and tetrachloroethane" comes from De Wildeman et al. (2001), and does not specify the particular trichloroethane. Since this is redundant to the mention of 1,1,1-trichloroethane in the same sentence, we deleted the mention of trichloroethane that does not further specify the chemical form.*

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: The environmental fate of DCE has been adequately described and referenced. DCE's occurrence at NPL site is illustrated in Figure 5-1. I am not aware of additional information on this topic.

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: Pertinent information is provided on the transport, partitioning, transformation, and degradation of DCE in environmental media. This is not an area of my expertise or research.

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: A considerable amount of information on DCE concentrations in air, water, soil and sediments was provided in Chapter 5. It would be helpful in Table 53 to present levels in the same units for given media. DCE, of course, is present/measured as a gas or liquid. I am not aware of any additional information.

RESPONSE: *This comment refers to Table 5-3 in section 5.5 (Levels in the Environment). We originally presented information in the units specified in the original source. We have added a consistent unit in parenthesis for ease of comparison based on this comment.*

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: The text describes sources and pathways of exposure of the general population and occupationally-exposed populations, as well as people with potentially high exposures. These selections are quite reasonable and complete.

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: The NOAEL (50 ppm) and LOAEL (100 ppm) of Hotchkiss et al. (2010) for nasal olfactory degeneration/necrosis are a suitable basis for derivation of the acute duration MRL. It might be noted that Yaqin et al. (2018) and Li et al. (2015) published dose-response data with NOAELs, which were considerably higher than those of Hotchkiss et al. (2010).

RESPONSE: *This comment refers to the Acute-Duration MRLs portion of Section 6.2 (Identification of Data Needs). As Pang et al. (2018) and Li et al. (2015) do not include information about the number of animals used in their studies, we cannot include them in the profile as they do not meet the minimum*

requirements for inclusion in the profile. Thus, no changes were made to the profile based on this comment.

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

COMMENT: I agree with the data needs identified in Chapter 6. The content of the text is well reasoned and scientifically supported.

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: Data needs are reasonable and are presented in a neutral, unbiased manner.

p. 165, lines 28-31: It is stated here and in a number of other places in the Tox Profile that gavage doses were more potent than comparable inhalation doses. It is also hypothesized that toxicity, DNA adducts, carcinogenicity, etc. are associated with saturation of MFO enzymes. Again I would point out that DCE is very rapidly and extensively absorbed from the GI tract, such that large, saturating quantities of the chemical arrive in and pass on through the liver and lungs into the systemic circulation. Substantially smaller amounts of DCE reach the liver over an extended period during inhalation or upon repetitive ingestion of the chemical in drinking water. The relatively high liver dose following gavage can exceed toxicity thresholds and the capacities of protection (e.g., GSH level) and repair (e.g., DNA base excision) processes. Sanzgiri et al. (1995) conducted an experiment designed to assess the influence of route of exposure on the kinetics and hepatotoxicity of carbon tetrachloride (CCl4). The total quantity of CCl4 systemically absorbed by rats inhaling the VOC for 2 hours was determined and administered over 2 hours to another group of rats by gastric infusion. The two groups exhibited comparable area under the blood concentration versus time curves and hepatotoxicity of comparable magnitude.

I would emphasize again the need for a better understanding of the roles of the oxidative and GSH conjugation metabolic pathways in DCE toxicity and mutagenicity/carcinogenicity. It is generally assumed that MFO-generated 2-chloroacetate is an important hepatotoxic metabolite, and that subsequent products of GSH conjugates (e.g., episulfonium ions) are active in DNA alkylation and tumor induction. The identities of key metabolites in other target organs (e.g., brain, nasal olfactory tissue, immune system) remain to be determined. There is little metabolic basis for addressing/predicting the relative susceptibilities of humans versus rodents, or of different human subpopulations.

RESPONSE: *This comment refers to statements made in the discussion of genotoxicity health effects in section 6.2 (Identification of Data Needs). The text in this section states "Inhalation exposure of rats to very high concentrations of 1,2-dichloroethane for short durations produced greater amounts of DNA binding in liver and lung than do longer-duration inhalation to low concentrations (Baertsch et al. 1991), and oral gavage doses were more potent in causing DNA damage in liver than were comparable inhalation doses in mice (Storer et al. 1984)." Added additional language suggesting a data need for more information about the roles of the oxidative and GSH conjugation metabolic pathways in 1,2-DCE toxicity. Added sentence to the profile in the Absorption, Distribution, Metabolism, and Excretion portion of Section 6.2 which reads: "Additional studies investigating the saturation of MFO metabolism by inhaled and ingested 1,2-dichloroethane, as well as the roles of the oxidative and GSH conjugation*

metabolic pathways in 1,2-dichloroethane toxicity and mutagenicity/carcinogenicity, would enable better understanding of the metabolism of this compound." No other changes were made to the profile based on this comment.

Chapter 7. Regulations and Guidelines

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

COMMENT: Does the American Conference of Government Industrial Hygienists (ACGIH) have a TLV for DCE? Has EPA published an Acute Exposure Guideline Level (AEGL) for the chemical?

RESPONSE: *This comment refers to Table 7-1 in Chapter 7 (Regulations and Guidelines). No, there is not a TLV or an AEGL for 1,2-dichloroethane.*

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

COMMENT: I do not know of any values that should be removed.

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.*

Allegaert, K., van den Anker, J. (2019). Ontogeny of phase I metabolism of drugs. Clin Pharmacol S9(S1), S33-S41.

Bruckner, J. V., Ramanathan, R., Lee, K. M., Muralidhara, S. (2002). Mechanisms of circadian rhythmicity of carbon tetrachloride hepatotoxicity. J Pharmacol Exp Therap 300, 273-281.

Bruckner, J. V., White, C. A., Muralidhara, S., Dallas, C. E. (2010). Effect of exposure route and dosage regimen on the toxicokinetics and target organ toxicity of 1, 1-dichloroethylene. J Pharmacol Exp Therap 333, 519-527.

Dang, J., Chen, J., Bi, F., Tian, F. (2019). The clinical and pathological features of toxic encephalopathy caused by occupational 1,2-dichloroethane exposure. Medicine 98(17).

Guengerich, F. P., Peterson, L. A., Cmarik, J. L., Koga, N., Inskeep, P. B. (1987). Activation of diholoalkanes by glutathione conjugation and formation of DNA adducts. Environ Health Perspect 76, 15-18.

Hines, R. N. (2008). The ontogeny of drug metabolism enzymes and implications for adverse drug events. Pharmacol Therap 118, 250-267.

Hines, R. N. (2009). Ontogeny of human hepatic cytochromes P450. J Biochem Mol Toxicol 21(4), 169-175.

Jin, X., Wang, T., Liao, Y., Guo, J., Wang, G., Zhao, F., Jin, Y. (2019). Neuroinflammatory reactions in the brain of 1,2-DCE-intoxicated mice during brain edema. Cells 8, 987.

Kim, H. J., Odend'hal, S., Bruckner, J. V. (1990a). Effect on oral dosing vehicles on acute hepatotoxicity of carbon tetrachloride in rats. Toxicol Appl Pharmacol 102, 34-49.

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Appendices

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

COMMENT:

RESPONSE: *No revisions were suggested.*

Unpublished Studies (If Applicable to Review)

COMMENT:

RESPONSE: *No revisions were suggested.*

Annotated Comments on the Profile

COMMENT: What is meant by the phrase "after an initial rapid release"? Highly lipophilic volatile organic chemicals (VOCs) are slowly/steadily released from fat. The rate of release is governed by their high fat:blood partition coefficient, as well as the slow rate of perfusion of adipose tissue.

RESPONSE*: This comment refers to the sentence in the second paragraph of section 3.1.1.1 (Inhalation Exposure) that says "An alternative explanation is that the 1,2-dichloroethane is, in part, slowly released from adipose tissue or other compartments after an initial rapid release (see Section 3.1.3)." The phrase "after an initial rapid release" in Section 3.1.1.1 was deleted after review. The sentence now reads: "An alternative explanation is that the 1,2-dichloroethane is, in part, slowly released from adipose tissue or other compartments (see Section 3.1.3)."*

COMMENT: Blood profiles of inhaled VOCs are asymptotic. Concentrations in blood don't really plateau, but attain near-steady state.

RESPONSE*: This comment refers to a sentence in the third paragraph of section 3.1.1.1 (Inhalation Exposure) that says "The plateau concentration in blood was approximately 8 µg/mL and was reached within 2 hours." The word "plateau" was changed to "near-steady state" within the following sentence found in Section 3.1.1.1: "The near-steady state concentration in blood was approximately 8 µg/mL and was reached within 2 hours."*

COMMENT: The paper by Spreafico et al. (1980) is not included in the References.

RESPONSE*: This comment refers to Chapter 8 (References). This study was added to the references section.*

COMMENT: Kim et al. (1990b) observed that corn oil similarly delayed and diminished the system absorption of carbon tetrachloride (CCl_4) when it was administered orally to rats. CCl_4 given in corn oil was less acutely hepatotoxic to the rats than when given in water or another aqueous vehicle (Kim et al., 1990a).

***RESPONSE**: This comment refers to the last paragraph in section 3.1.1.2 (Oral Exposure). This paper is related to another chemical – therefore the reference has not been added to the profile.*

COMMENT: It should be pointed out that the dermal exposure conditions employed by Morgan et al. (1991) were highly artificial. Shaving the animals' back abrades the stratum corneum, the barrier to percutaneous absorption. Keeping a concentrated VOC in direct contact with the skin's surface defats it and further compromises its integrity. The majority of DCE will normally evaporate, as noted above by Gajjar et al. (2014).

***RESPONSE**: This comment refers to section 3.1.1.3 (Dermal Exposure). A note was added to this Section 3.1.1.3 describing the uncertainty raised in the comment that is as follows: "It should be noted that some degree of uncertainty exists with results from Morgan et al. (1991), as the shaving of the animals' backs abrades the stratum corneum (Hamza et al. 2015), which in turn removes a main barrier to the percutaneous absorption of VOCs like 1,2-dichloroethane. Thus, this shaving could have affected the levels of dermal absorption of 1,2-dichloroethane in the study in a way that would not be applicable in a naturally occurring setting."*

COMMENT: Morgan et al. (1991) is not included in the References.

***RESPONSE**: This comment refers to Chapter 8 (References). This study was added to the references section.*

COMMENT: I am not sure that detection of DCE in the breath and milk after leaving the workplace reflects rapid systemic distribution. The employees likely worked with DCE some days before the day of testing, as well as a number of hours prior to testing.

***RESPONSE**: This comment refers to section 3.1.2.1 (Inhalation exposure) and the sentence that says "This observation suggests a rapid distribution of 1,2-dichloroethane in humans following inhalation exposure." The sentence in Section 3.1.2.1 was edited to say that detection of 1,2-DCE in breath and breast milk suggests a possible rapid distribution of 1,2-DCE following inhalation exposure. Additionally, language was added in Section 3.1.2.1 to suggest that this outcome could have been due to exposure to the chemical over a number of days prior to and up to the observation.*

COMMENT: It may be premature to conclude that the route of exposure does not significantly influence tissue/target organ deposition and toxicity. Bruckner et al. (2010) found that inhaled 1,1-dichloroethylene (1,1-DCE) was more nephrotoxic to rats than was the ingested chemical, while orally administered 1,1-DCE was more hepatotoxic. Route-dependent tissue deposition and ensuing toxicity is particularly important with low-level VOC exposure, in that first-pass hepatic uptake and metabolic activation of potential carcinogens can protect extrahepatic tissues, but place the liver at greater risk upon oral exposure. Liu et al. (2009) found that some 95% of very low oral doses of trichloroethylene in drinking water was subject to presystemic elimination in rats.

***RESPONSE**: This comment refers to Section 3.1.2.2 (Oral Exposure). We changed the phrase in Section 3.1.2.2 "Thus, there is little difference between oral and inhalation exposure with regard to tissue distribution in animals, and specific target organ toxicity cannot be explained by differential distribution of 1,2-dichloroethane." The sentence now reads: "Thus, there appears to be little difference between oral and inhalation exposure with regard to tissue distribution in animals, and specific target organ toxicity cannot be explained by differential distribution of 1,2-dichloroethane."*

COMMENT: Where in the GSH metabolic pathway (in Figure 3-1) is N-acetyltransferase (NAT) involved? NAT commonly serves to detoxify reactive cysteine conjugates of intermediates in GSH pathways of a number short-chain aliphatic halocarbons.

RESPONSE*: The comment refers to Figure 3-1 at the end of Section 3.1.3 (Metabolism). There are several steps in the oxidative metabolic pathway that also involve GSH, and subsequent to those GSH steps are steps involving NAT, as noted in the figure. No changes were made to the profile based on this comment.*

COMMENT: Omit the word "may" in favor of "does" in line 2. DCE and other VOCs are very quickly and extensively absorbed from the GI tract, such that bolus administration results in saturation of hepatic first-pass uptake and metabolism. Much of the absorbed VOC passes on through the liver and lungs into the arterial circulation. The higher the gavage dose, the greater the % that is not eliminated presystemically (Lee et al., 1996; Liu et al., 2009).

VOCs are much less toxic and carcinogenic when ingested by animals in their drinking water than when they are given in the same doses by gavage. Blood and target organ levels are much lower when the extensively metabolized chemicals are consumed in divided doses in water over an extended period.

RESPONSE*: This comment refers to the statement "Gavage administration may not represent typical oral exposure in humans" in section 3.1.3.2 (Oral Exposure). Suggested change to replace the word "may" with the word "does" was made, relating to how gavage administration does not represent typical oral exposure in humans.*

COMMENT: Did the authors of the Tox Profile find any information on the relative magnitude, or capacity of DCE's oxidative and GSH metabolic pathways? The major (quantitatively) pathway for most VOCs/halocarbons is oxidation catalyzed by P450s.

RESPONSE*: This comment refers to the discussion in Section 3.1.3.4 (Other Routes of Exposure). We did not find any information on the relative magnitude between the oxidative and GSH metabolic pathways.*

COMMENT: It would be worthwhile to briefly describe the ontogeny of the P450 oxidative and the GSH conjugation pathways in humans and to address potential implications of age-related increases or decrease in either. Reviews have been published by a number of authorities including Allegaert and van den Anker (2019) and Hines (2008, 2009).

RESPONSE: *This comment refers to section 3.2.1 (Children's Susceptibility). The following sentences were added to section 3.2.1 of the profile in response to this comment: "Additionally, CYP2E1 levels in human infants steadily increase from infancy to adulthood, where fetal samples were found to have undetectable levels of CYP2E1, infants 1 to 3 months of age exhibited mean levels of the enzyme of about 10% of adult values, infants 3 to 12 months of age exhibited mean values of about 30% of adult values, and children between 1 and 10 years of age exhibited mean values no different than adults, suggesting an age-dependent increase in CYP2E1 levels (Vieira, 1998; Hines, 2008). There is less of a consensus about the general ontogeny of GSH in humans (Hines, 2008)."*

COMMENT: Change the word "possible" to "likely". Change "metabolite" to "increased quantities of oxidative metabolites".

RESPONSE: *This comment refers to the sentence in section 3.2.2 (Other Populations that are Unusually Susceptible) that says "It is possible that the induction of this enzyme increases the amount of 1,2-*

dichloroethane that is metabolized via this pathway rather than by glutathione conjugation, allowing for binding of the metabolite to the target organ". The aforementioned edits were made, yielding the following sentence: "It is likely that the induction of this enzyme increases the amount of 1,2-dichloroethane that is metabolized via this pathway rather than by glutathione conjugation, allowing for binding of the increased quantities of oxidative metabolites to the target organ."

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.

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: This document section does a good job outlining human vs. animal model effects. Many of the observed effects in animal models are at high exposures that are not likely to occur in humans. For the most part, the document includes exposure context with observed effects.

RESPONSE: *No revisions were suggested.*

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

COMMENT: Figures 1-1 through 1-4 are extremely useful for adding exposure context to the observed effects. There are few spots where more specifics could be included (e.g. page 20, line 4). However, for the most part, yes, exposure conditions have been provided.

RESPONSE: *This comment refers to Figures 1-1 through 1-4 in Section 1.2 (Summary of Health Effects). Slight revisions were made based on these comments regarding specifics about exposure. These revisions resulted in the following sentences in Section 1.2 in the paragraphs discussing reproductive effects:*

"*In contrast to these findings, a well-designed study of reproductive toxicity found no adverse effects on the fertility, gestation, or survival of the pups of rats exposed by inhalation to 150 ppm of 1,2-dichloroethane for 60 days pre-mating, then throughout mating, gestation, and lactation in a one-generation reproduction study."*

"The overall indication of the data is that 1,2-dichloroethane appears to induce embryotoxic effects in rats and cause reproductive toxicity in male mice at doses as low as 25 ppm for 4 weeks, but it is unlikely to impair reproduction at doses that do not also cause other toxic manifestations in females."

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: I am not sure I understand ATSDR's process for assigning "serious" vs. "not serious" biological effects. What the philosophy behind not calculating MRLs for "serious" effects? If ATSDR

assessors use MRLs to screen hazardous waste sites, then I would assume that "serious effects" would provide a compelling basis for MRL calculations.

RESPONSE: *Less serious effects are generally reversible cellular alterations, moderate serum chemistry changes, and other effects that are not associated with a decrement in organ function. Serious effects are generally non-reversible, major changes in serum chemistry, and other clinical effects that result in significant organ impairment or dysfunction. It is ATSDR policy to not calculate MRLs based on serious effects, as this would raise concern that less serious effects that have yet to be identified may occur at lower levels than the MRL.*

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: ATSDR outlines the calculations and assumptions very clearly. Consistent with my previous comment, I question not including "serious" effect data for MRL calculations.

RESPONSE**:** *It is ATSDR policy to not calculate MRLs based on serious effects, as this would raise concern that less serious effects that have yet to be identified may occur at lower levels than the MRL.*

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: The uncertainly factors seem appropriate and consistent. Does a human physiologically based pharmacokinetic (PBPK) model exist for dichloroethane? I see published rodent models and was unable to locate additional human models. If human versions were available, ATSDR could consider using PBPK modeling to extrapolate toxicokinetic differences between animal models to humans in an effort to evaluate, reduce, or replace uncertainty factors. PBPK models could also be used to evaluate human variability and associated uncertainty factors. As an example, GST metabolism of dichloromethane, a similar compound, has been linked to cancer endpoints. David et al. (2006) used PBPK modeling to evaluate variability of GST in the human population. Similar approaches may be useful for evaluating assumed uncertainty factors here, if the tools exist.

David RM, Clewell HJ, Gentry PR, Covington TR, Morgott DA, Marino DJ. 2006. Revised assessment of cancer risk to dichloromethane II. Application of probabilistic methods to cancer risk determinations. Regul Toxicol Pharmacol 45:55–65.

If human models for 1,2-dichloroethan do not exist, rodent PBPK models do exist for dichloroethane (Sweeney et al. 2008 & 20016). Did ATSDR consider linking inhalation and oral exposure studies by an internal dose metric and using that dose metric for a point of departure for MRL calculations? This would allow inhalation and oral studies to be lumped together for consistency. MRLs for various exposure routes could be calculated for any route of interest, and MRLs for different exposures would be consistent with each other.

RESPONSE: *ATSDR has not located a published human PBPK model for 1,2-dichloroethane. ATSDR did not consider linking inhalation and oral exposure studies by an internal dose metric, and using that dose metric as a point of departure for MRL calculations. This sort of generalization between routes of exposure or durations of exposure runs counter to ATSDR guidelines for the development of MRLs. Thus, no changes have been made to the profile based on this comment.*

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

COMMENT: I have no other comments.

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: Conclusions in Chapter 2 are consistent with those published in the literature.

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: Yes. Human studies were adequately described including limitations.

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: Neither species-specific mechanisms of action nor differences in pharmacokinetics for dichloroethane are known. As such, all data should be considered as ATSDR has done. Use of species-specific PBPK models could help quantitatively identify and assess pharmacokinetic differences.

RESPONSE: *No revisions were suggested.*

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

COMMENT: ATDR presented excellent figures demonstrating NOEALS and LOEALs across various studies for numerous endpoints. These visual summaries are a strength of the report.

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: As far as I can tell, yes. Disclaimer: I did not review each individual reference.

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, these seem appropriate and consistent. I am not sure about the serious/less-serious designations used for MRL derivations. See previous comments.

RESPONSE: *Less serious effects are generally reversible cellular alterations, moderate serum chemistry changes, and other effects that are not associated with a decrement in organ function. Serious effects are generally non-reversible, major changes in serum chemistry, and other clinical effects that result in significant organ impairment or dysfunction. The ATSDR Guidance for the Preparation of Toxicological Profiles contains tables of specific effects for each type of health endpoint that are considered "less serious" and "serious", and oftentimes these designations are agreed upon at internal ATSDR health effect meetings. It is ATSDR policy to not calculate MRLs based on serious effects, as this would raise concern that less serious effects that have yet to be identified may occur at lower levels than the MRL.*

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: There are no well-known mechanisms of action for this compound. As such, there is nothing to discuss.

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: I believe so. The review identifies published effects at given doses in animal models and humans.

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, the ATDSR outlines known data for 1,2-dichloroethane data for each of these processes well.

RESPONSE*: No revisions were suggested.*

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

COMMENT: As far as I know, yes, all models have been presented.

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, not to my knowledge.

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. These populations make sense for being more susceptible to 1,2-dichloroethane exposures.

RESPONSE: *No revisions were suggested.*

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

COMMENT: Yes. Measuring 1,2-dichloroethane indicates recent exposure to 1,2-dichloroethane due to a short biological half-life. I am not aware of other chemicals could breakdown to form 1,2-dichloroethane in vivo, and ATSDR does not report any possible chemicals breaking down to form 1,2-dicholoethane. Regardless, the organism will still be exposed to the 1,2-dichloroethane if it were a metabolic breakdown product from another chemical exposure. NHANES uses 1,2-dichloroethane levels in blood as a biomarker for 1,2-dichloroethane exposures.

RESPONSE: *Given these biomarkers are summarized in Section 3.3.1 (Biomarkers of Exposure) in the profile, no revisions were needed in response to this comment.*

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

COMMENT: No. ATSDR correctly states that other chemicals can cause similar effects, and none of the observed biological effects are specific to 1,2-dichloroethane.

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, there is adequate discussion. I do not have additional references.

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: Induction of Cyp2E1 or depletion of GST are probably the two biggest interactions that could significantly alter the pharmacokinetics of 1,2-dichloroethane. ATSDR has correctly identified these factors and summarized supporting studies for evidence.

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: Consider using or double referencing consistent units here and throughout the document. For example, pressure units in the table are not consistent. This will allow the reader to make quick comparisons.

RESPONSE: *Consistent units were added to the vapor pressure in Table 4-2 to match what was reported as the critical pressure based on this comment. All other units in Table 4-2 were consistent.*

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

COMMENT: Yes, properties are given for both gas and liquid states.

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: As far as I can tell, yes, it looks complete.

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, ATSDR identified sources appropriately. I do not know of other relevant references.

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. Environmental fate seems well covered.

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. ATSDR reports near detection limit levels in air as background. Except for concentrations in air I suggest that ATSDR refrain from ratio (ppb/ppm/etc.) units and report in consistent mass per volume, mass per mass, or molar units. Ratio units are ambiguous and can lead to confusion.

RESPONSE: *This comment refers to Table 5-3 in Section 5.5 (Levels in the Environment). Mass per volume or mass per mass units were added to table 5-3 when ratio units were reported.*

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, I agree. Due to rapid volatilization, inhalation exposures appear most likely for the general population. I like Table 5-6 outlining sources of 1,2-dicholorethane in the air. These summaries are very useful for readers.
Occupational exposures and exposures to children are potentially sensitive populations due to high exposures and general susceptibility, respectively. ATSDR highlights potential exposures to these groups. I would agree that these populations are of concern

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: ATSDR calls for additional data to calculate an acute oral MRL (pg. 173 section 6.2). An alternate approach could extrapolate from internal dose metrics following inhalation exposures and calculate and equivalent oral dose. For example, the acute inhalation MRL is based on nasal regeneration, a portal of entry effect. However, if NOAELs for other systemic effects could be identified from available data, PBPK modeling could be used to calculate the internal dose metric associated with that exposure (e.g. concentration in blood or target tissue or AUC, etc.). Then the PBPK model could extrapolate an equivalent oral dose to achieve the same internal dose metric. This would allow consistent MRLs among routes of administration and not require additional toxicity studies. PBPK models exist for this approach. I am not sure if adequate systemic dose-response data is available.

Other route-specific MRLs could be extrapolated in this fashion as well.

As a potential data need, I would suggest new toxicity studies include doses relevant to human exposures.

A PBPK model for humans would be useful for future MRL refinement.

RESPONSE: *ATSDR did not consider linking inhalation and oral exposure studies by an internal dose metric, and using that dose metric as a point of departure for MRL calculations. This sort of generalization between routes of exposure or durations of exposure runs counter to ATSDR guidelines for the development of MRLs. Thus, no changes have been made to the profile based on this comment.*

A sentence was added to the Health Effects subsection of section 6.2 (Identification of Data Needs) in response to the suggestion of toxicity studies including doses relevant to human exposures as a data need. This sentence reads as follows: "Additionally, toxicity studies that include doses relevant to human exposures would be useful in providing information toward a further understanding of the potential health implications of current human exposure patterns."

Also, phrasing was added to the "comparative toxicokinetics" section, within the Absorption, Distribution, Metabolism, and Excretion subsection of section 6.2 (Identification of Data Needs) to suggest that more information on the toxicokinetics in other animal species, including humans, would be useful for more fully addressing interspecies differences and the implications for human exposure. The "comparative toxicokinetics" section now reads as follows: "Toxicity data in humans and animals suggest similar target organs in each. Toxicokinetic studies have not been performed in humans. The database with regard to comparative toxicokinetics consists primarily of studies in rodents (D'Souza et al. 1987, 1988; Morgan et al. 1991; Reitz et al. 1980, 1982; Spreafico et al. 1980; Sweeney et al. 2008). More information on the toxicokinetics of 1,2-dichloroethane in other animal species, including humans, would be useful for more fully assessing interspecies differences and the implications for human exposure."

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

COMMENT: Yes, language is neutral.

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: Probably not. Reported values could offer value to readers.

RESPONSE: *No revisions were suggested.*

Appendices

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

COMMENT: No comments provided.

RESPONSE: *No revisions were suggested.*

Unpublished Studies (If Applicable to Review)

COMMENT: There are no unpublished studies that need reviewed for 1,2-dichloroethane.

RESPONSE: *No revisions were suggested.*

Annotated Comments on the Profile

Summary comment:

NCEH/ATSDR Office of Science requested a review the draft Toxicological Profile for 1,2-dichloroethane for the purpose of pre-dissemination peer review. As such over the last four weeks, I reviewed the draft document, conducted brief literature searches, and reviewed selected references cited by the draft *Toxicological Profile for 1,2-Dichloroethane* in an effort to evaluate data presented, conclusions made by ATSDR, and questions posed for this process.

Within these timelines and context, I found the draft *Toxicological Profile for 1,2-Dichloroethane* provided a comprehensive review to my knowledge of toxicity, pharmacokinetics, environmental levels, and human exposures of 1,2-dichloroethane. I generally agreed with ATSDR's assessments and conclusions regarding 1,2-dicholorehtane. I did have some specific comments and suggestions for improvement, mostly regarding units used within the document and possible alternative approaches for MRL derivations using pharmacokinetic models. I notated specific comments and suggestions in a tracked-changes draft of the *Toxicological Profile for 1,2-Dichloroethane* and responses to specific charge questions below in blue. Please let me know if you have questions regarding these comments or suggestions.

General comments

COMMENT: Is the following sentence due to vapor pressures and Henry's Law Constant? "Volatilization is expected to be an important environmental fate process for 1,2-dichloroethane in soil and bodies of water."

RESPONSE*: The sentence quoted in the comment is in section 1.1 (Overview and U.S. Exposures). It is correct that the cited sentence is explained by vapor pressure and Henry's Law Constant. Language was added to the above sentence and it is now as follows: "Volatilization is expected to be an important environmental fate process for 1,2-dichloroethane in soil and bodies of water due to its Henry's law constant of 1.1x10^{-3} atm-m^3/mol at 20 °C."*

COMMENT: Broken reference/link

RESPONSE*: This comment refers to the sentence "The LC50 value and LOAEL values from each reliable study for death in each species and duration category are presented in Error! Reference source not found.,Error! Reference source not found., and plotted in Figure 2 2" in the inhalation subsection in Section 2.2 (Death). Links to Tables 2-1 and 2-1, as well as Figures 2-2 and 2-3, have been fixed.*

COMMENT: p. 66, lines 9-: Unnecessary space gap

RESPONSE*: This comment refers to the end of section 2.4 (Respiratory). Formatting issue resolved.*

COMMENT: I suggest desiminating this information in a table: "Based on this potency factor, oral doses of 1,2-dichloroethane associated with excess human lifetime cancer risks of 10^{-4}, 10^{-5}, 10^{-6}, and 10^{-7} are 1x10^{-3}, 1x10^{-4}, 1x10^{-5}, and 1x10^{-7} mg/kg/day, respectively. These risk levels correspond to one excess cancer death in 10,000, 100,000, 1 million, and 10 million persons, respectively, and are derived based on the assumption that individuals are exposed continuously for their entire lifetime (estimated as 70 years) to these oral doses of 1,2-dichloroethane.

RESPONSE*: This comment refers to the information in the oral subsection of Section 2.18 (Cancer) that says "Based on this potency factor, oral doses of 1,2-dichloroethane associated with excess human lifetime cancer risks of 10-4, 10-5, 10-6, and 10-7 are 1x10-3, 1x10-4, 1x10-5, and 1x10-7 mg/kg/day, respectively. These risk levels correspond to one excess cancer death in 10,000, 100,000, 1 million, and 10 million persons, respectively, and are derived based on the assumption that individuals are exposed continuously for their entire lifetime (estimated as 70 years) to these oral doses of 1,2-dichloroethane." These few sentences were reworded to increase clarity. These sentences now read as follows: "Based on this potency factor, oral doses of 1,2-dichloroethane associated with excess human lifetime cancer risks are: 1x10^{-3} mg/kg/day with a risk of 10^{-4}, 1x10^{-4} mg/kg/day with a risk of 10^{-5}, 1x10^{-5} mg/kg/day with a risk of 10^{-6}, and 1x10^{-7} mg/kg/day with a risk of 10^{-7}. A risk level of 10^{-4} corresponds to one excess cancer death in 10,000, a risk level of 10^{-5} corresponds to one excess cancer death in 100,000, a risk level of 10^{-6} corresponds to one excess cancer death in 1 million, and a risk level of 10^{-7} corresponds to one excess cancer death in 10 million persons. These affected population figures are derived based on the assumption that individuals are exposed continuously for their entire lifetime (estimated as 70 years) to these oral doses of 1,2-dichloroethane."*

COMMENT: What is the vapor pressure and serum/air partition coefficient of 1,2-dichlorethane?

RESPONSE*: This comment refers to the following sentence in Section 3.1.1.1 (Inhalation Exposure): "This is expected, based on 1,2-dichloroethane's high vapor pressure and high serum/air partition coefficient." Appropriate information has been added, as seen in this sentence: "This is expected, based on 1,2-dichloroethane's high vapor pressure of 78.9 mmHg at 20°C and high serum/air partition coefficient of 19.5 (Gargas et al. 1989)."*

COMMENT: What is the Kow of 1,2-dichlorethane?

RESPONSE*: This comment refers to the following sentence in Section 3.1.1.2 (Oral Exposure): "1,2-Dichloroethane is lipophilic and is expected, therefore, to be absorbed largely via passive diffusion across the mucosal membranes of the gastrointestinal tract." Appropriate information has been added, as seen in this sentence: "1,2-Dichloroethane is lipophilic, with a log K_{OW} of 1.48, and is expected to be absorbed largely via passive diffusion across the mucosal membranes of the gastrointestinal tract."*

COMMENT: What is the exposure level of referenced experiment?

RESPONSE*: This comment refers to the sentence in section 3.1.1.2 (Oral Exposure) that says "This implies that at least 90% of the inhaled or orally administered 1,2-dichloroethane was absorbed" that is concluded based on the experiment described by Reitz et al. 1980. Exposure levels are specified in the revised sentence: "This implies that at least 90% of the inhaled or orally administered 1,2-dichloroethane was absorbed at 150 ppm and 150 mg/kg, respectively."*

COMMENT: Figure appears a bit blurry. You may want to include a higher definition figure for the publication.

RESPONSE: *This comment refers to Figure 3-1 at the end of Section 3.1.3 (Metabolism). Figure 3-1 updated in response to this comment.*

COMMENT: This needs to be verified: "Payan et al. (1993) showed that total excreted urinary thioethers increased linearly with increasing oral dose (for doses between 0.25 and 4.04 mmol/kg [11.9 mg/kg/d and 400 mg/kg/d, respectively]) in male Sprague-Dawley rats during a 24-hour post-administration period, at a rate of 0.028 mmol thiol group eliminated per millimole of 1,2-dichloroethane administered."

RESPONSE: *The sentence cited above is found in Section 3.3.1 (Biomarkers of Exposure). Information cited from the study was verified. No changes were made based on this comment.*

COMMENT: In reference to Table 4-2, Consider using or double referencing consistent units here and throughout the document. For example, pressure units in the table are not consistent.

RESPONSE: *This sentence refers to Table 4-2. We have added a double reference for pressure units to make sure units are consistent. We have also added double references in other tables throughout the document where needed.*

COMMENT: In reference to Table 5.3 row "Air and Soil gas", why does this have no units? Also it's not in the references. Maybe delete? In reference to Table 5.3 row "Table ready foods", Except for concentrations in air I suggest that ATSDR refrain from ratio (ppb/ppm/etc.) units and report in consistent mass per volume or molar units. Ratio units are ambiguous and can lead to confusion.

RESPONSE: *This sentence refers to Table 5-3 in section 5.5 (Levels in the Environment). For the "Air and Soil gas" row, added units but could not locate PDF of reference. Row deleted. For the "Table ready foods" row, added mass per volume units to remove confusion.*

COMMENT: ATSDR should provide a reference to support these classifications and procedures. I am not sure I completely understand the "serious" "not serious" desginations and use thereof in MRL calculations.

RESPONSE: *This comment refers to the sentence in the Intermediate-Duration MRLs subsection of Section 6.2 (Identification of Data Needs) that says "Since effects on sperm are always considered serious effects, this precludes the derivation of an intermediate inhalation MRL." Added references of*

Pohl et al. (2005) and ATSDR (2018) to specify "serious" and "not serious" designations. Of note: ATSDR uses the designations "serious" and "less serious". The reviewer's comment specifically mentions the designation "not serious", which is assumed to refer to the "less serious" designation.

COMMENT: I suggest offering a translation of this value to ppm, other reported values to mg/m3, or at least some consistent units to allow readers to easily compare across various cited values.

RESPONSE: *This comment refers to the statement in Chapter 7 (Regulations and Guidelines) that says "The WHO continuous exposure air quality guideline of 0.7 mg/m^3 listed in Table 7-1 is a time-weighted average over a 24-hour day." PPM value added in the following sentence: "The WHO continuous exposure air quality guideline of 0.7 mg/m^3 (0.2 ppm) listed in Table 7-1 is a time-weighted average over a 24-hour day."*

COMMENT: Wouldn't the point of departure technically be 57 ppm (the BMDL)? Then the human equivalent concentration is translated from the BMDL/point of depature?

RESPONSE: *This comment refers to the MRL Worksheet for acute inhalation that references Hotchkiss 2010. The comment is specifically about the sentence in the Human Equivalent Concentration section that says "The BMCLHEC of 9.19 ppm was selected as the point of departure over the NOAEL of the study because it provides a better indicator of the dose-response relationship than the NOAEL, which is based on a single data point." Yes. We have updated this language. The finalized sentence incorporating Reviewer's remarks is: "Using the benchmark dose modeling results was selected over the NOAEL given it uses the full dose-response data as opposed to the NOAEL, which is based on a single data point."*

COMMENT: If ATSDR assessors use MRLs to screen hazardous waste sites, then why would you not want to use a "serious effect" as the basis for MRL calculations?

RESPONSE: *This comment refers to the sentence in the Rationale for Not Deriving an MRL section of the MRL Worksheet for intermediate inhalation that says "Since effects on sperm are always considered serious effects, this precludes the derivation of an intermediate inhalation MRL." It is ATSDR policy to not calculate MRLs based on serious effects, as this would raise concern that less serious effects that have yet to be identified may occur at lower levels than the MRL. Please see Pohl et al. (2005) and ATSDR (2018) for further information about sperm abnormalities being considered a serious effect. Citations to these two references have been added to this sentence.*

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: I agree.

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: It is possible that some effects so far only observed in animals may not have been examined in humans. In instances where the evidence suggests this (species difference), the data do not indicate that the effects noted are more sensitive than the effects used to derive the points of departure. If there are any such instances in this document, they are of no material consequence.

RESPONSE: *No revisions were suggested.*

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

COMMENT: Yes.

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: This is an area worthy of a little more attention. As we naturally assume that the threshold for adversity decreases with both exposure dose/concentration and exposure duration, it is natural to expect chronic MRL values to be lower than intermediate MRL values and intermediate MRL values to be lower than acute MRL values. This is complicated by the data available for 1,2-dichloroethane in that a different suite of toxicities have been evaluated with respect to duration. The olfactory epithelium was examined in an acute exposure scenario, but no other durations. It appears that OE degeneration is at least as sensivtive if not more sensitive than other effects, and it occurs in a portal of entry tissue (category 1 default) for which the DAF is approximately 0.25. Tissues examined for other durations (as well as for acute durations) mostly represent systemic tissues (category 3 default), for which EPA (2012) has interpreted blood gas partition coefficient data from Gargas et al. (1989) as supporting a DAF of approximately 1.6. SO, the human would be expected to be "more sensitive" than the animal for the

category 1 (OE) effects, but less sensitive than the animal for the category 3 (systemic, e.g., liver, kidney) effects. The liver and kidney effects noted from several exposures do not seem to this reviewer to be too severe to serve as the basis for MRL derivation; it does not seem that the data as presented for these effects is too limiting to serve as the basis for MRL derivation. For example, the 28-day LOAEL of 86 ppm for hepatic effects observed by Wang et al. (2017) equates to an HEC value of 86 x 1.6 = 137.6 ppm. Dividing 137.6 ppm by a CUF of 300 (10H, 3A, 10L) = 0.46 ppm, which is not that much higher than the MRL of 0.3 ppm derived for acute MRL on the basis of OE degeneration.

Gargas ML, Burgess RJ, Viosard DE, Cason GH, Andersen ME. Partition coefficients of low-molecular-weight volatile chemicals in various liquids and tissues. Tox Appl Pharm. 98:87-99.

US EPA, 2012. Advances In Inhalation Gas Dosimetry For Derivation of A Reference Concentration (RfC) and Use In Risk Assessment. At: https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=244650

RESPONSE: *An intermediate inhalation MRL was not derived because the most sensitive endpoint, a 570% increase in total sperm abnormalities at an adjusted daily concentration of 6.3 ppm, is considered a serious effect by ATSDR guidance. It is ATSDR policy not to derive MRLs based on a serious effect, and thus no MRL was derived. Since the Wang et al. (2017) study reports altered serum chemistry changes at an adjusted daily concentration of 21.5 ppm, which is a higher concentration than that of the Zhang et al. (2017) total sperm abnormalities endpoint, an MRL cannot be derived based on this endpoint.*

COMMENT: The draft TP text in some cases (e.g., inhalation intermediate MRL) indicates that the data are insufficient or represent too severe an effect to support MRL derivation, and this is a statement with which I cannot agree. I do agree that it does [not] make logical sense to develop an intermediate MRL at a value higher than the acute MRL, but this circumstance does not indicate that the data are inappropriate, insufficient or represent an effect too severe for MRL derivation. In some cases, as with EPA's Provisional Advisory Level values (PALs), EPA (2017) has advocated for this exact circumstance, that the more restrictive of the values be applied for the next-longer duration. However, this remedy may not be acceptable according to policies covering MRL derivation.

I was not aware that sperm effects were covered by ATSDR policy as being too severe to serve as the basis for MRL derivation. This point might be made a little more directly in the draft assessment.

US EPA. 2017. Provisional Advisory Levels (PALs) for Hazardous Agents. U.S. Environmental Protection Agency, Washington, DC, EPA/600/S-17/044, 2017. At:

https://cfpub.epa.gov/si/si_public_record_report.cfm?Lab=NHSRC&dirEntryId=336979

RESPONSE: *An intermediate inhalation MRL was not derived because the most sensitive endpoint was represented by what ATSDR considers a serious effect, since sperm abnormalities are always considered serious effects based on guidance outlined in ATSDR's "Guidance for the Preparation of Toxicological Profiles". More information about the classification of sperm abnormalities as a serious effect can also be found in Pohl et al. (2005). There was also extensive discussion of this sperm endpoint in the MRL workgroup, and it was concluded that it was too serious to be used as the basis for an MRL. It is ATSDR policy not to derive MRLs based on a serious effect, and thus no MRL was derived.*

COMMENT: Regarding the lack of derivation of an acute oral MRL value, two issues become apparent. GThis reviewer disagrees with the rationale given for failing to rely on the results from Munson's

immunological study (gavage dosing may not be appropriate). Instread, the study's reliability might be better centered on a lack of dose-response, potential diminished value of predictive nature of the effect observed, and failure to verify the findings in the results of other studies. This reviewer cautions against general or blanket verbiaging indicating that reliance on gavage studies may not be recommended; instead, less prescriptive advice should be used in all cases, leading the reader to understand that differences in TK between gavage and feed/water may exacerbate toxicity, leading to the conclusion that tox/risk values derived on the basis of dose response evaluation developed from gavage studies may over-estimate potency, resulting in an even more conservative estimate of risk.

RESPONSE: *Language in the MRL worksheet for the acute oral MRL was slightly altered to specify that the lack of a dose-response was the primary reason for not deriving an MRL, and this lack of dose response could have been due to administering the chemical by gavage as opposed to drinking water. The language now reads as follows: "However, administration of 1,2-dichloroethane in the drinking water at doses as high as 189 mg/kg/day for 90 days failed to induce immunosuppressive effects in mice in the Munson et al. (1982) study. Because of this lack of dose-response, it was determined that it may not be appropriate to base an MRL on an effect level from this gavage oil study due to toxicokinetic considerations of administration of the chemical by gavage as opposed to drinking water (e.g., possible bolus saturation of the detoxification/excretion mechanism can occur which may exacerbate toxicity at lower concentrations)."*

COMMENT: Further, it seems that the findings in Daniel et al. (1994) may not have received the attention warranted. Findings from the acute exposure duration phase of this study indicate a NOAEL value of 100 mg/kg/day and a LOAEL of 3000 mg/kg/day for multiple effects, as summarized in Table 2-2 (acute oral section). Serious consideration should be given to the oral dose of 100 mg/kg/day as a POD value for derivation of an acute oral MRL. If it is to be dismissed, then careful attention should be given to the basis for such a dismissal. True, we prefer oral drinking water or feed exposures over oral gavage exposures, but from the perspective of this reviewer, we should not discound oral gavage studies only on the basis that they were not conducted using feed or water as the delivery vehicle.

RESPONSE: *The acute oral portion of the Daniel et al. (1994) study uses a gavage oil vehicle for administration of 1,2-dichloroethane. The study finds a less serious LOAEL at 100 mg/kg/day of minimal inflammatory changes in the forestomach, and an associated NOAEL of 30 mg/kg/day. There are no other acute oral studies that focus on this endpoint to corroborate this evidence of inflammatory changes in the forestomach, which would be necessary in a situation where we may have a priori concerns about gavage oil potentially exacerbating toxicity. In this case, there is not enough certainty to derive an MRL based on this value, keeping in mind the uncertainties that arise around oral administration of 1,2-dichloroethane via gavage oil. Therefore, no edits were made to the profile based on this comment.*

COMMENT: Regarding potential POD values, for example, Section 2.5, Cardiovascular , page 69, lines 25-26 states, "Histological examinations showed no cardiovascular effects following gavage exposure in rats treated with <100 mg/kg/day for 10 days", implying that such effects were seen at higher doses (i.e., were not seen at 300 mg/kg/day for 10 days. Section 2.7, Hematological states on page 73, lines 2-3, "In rats, hematological parameters were unaffected by exposure to 100 mg/kg/day by gavage for 10 or 14 days". Table 2-2 entry for Daniel et al. (1994) acute oral findings indicates a hepatic NOAEL of 100 mg/kg/day, but the section on Hepatic injury (section 2.9) does not include a textual description of Daniel's acute findings, only findings from the 90-day exposure duration.

As shown in the study tabulation for Daniel et al. (1994) in Table 2-2. Daniel demonstrated NOAEL values of 100 mg/kg/day for multiple effects; appropriate reflections of these findings should be included in the respective endpoint-specific sections.

RESPONSE: *We added a mention of Daniel et al. (1994) acute gavage findings to the text of section 2.9 related to hepatic effects. This new text reads as follows: "Daniel et al. (1994) also found no significant hepatic effects in rats administered 100 mg/kg/day by gavage for 10 days." The remainder of the endpoint-specific sections included references to both the 10 day and the 90 day results.*

COMMENT: The limitations identified with the oral studies considered as the basis for a chronic oral MRL were also used as a justification by US EPA (2010) when they also decided not to derive a chronic oral PPRTV for 1,2-dichloroethane.

US EPA. 2010. Provisional peer reviewed toxicity values for 1,2-dichloroethane. US Environmental Protection Agency, Office of Research and Development, Cincinnati, OH. EPA/690/R-10/011F. Availble at: https://cfpub.epa.gov/ncea/pprtv/documents/Dichloroethane12.pdf

RESPONSE: *No additional changes were made based on this comment.*

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: I agree with the proposed MRL values.

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 with the values and rationales used to justify the values assigned for the various components of the uncertainty factor values employed.

RESPONSE: *No revisions were suggested.*

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

COMMENT: The information contained in this compendium of health effects, interpreted int eh context of MRL value determination seems sufficient.

Some research reports (e.g., NTP reports) are developed on the basis of preliminary or range finding studies involving different doses and shorter durations than those reported in the "primary" study (e.g., reports summarizing chronic findings). In some cases, reports aimed at communicating findings form chronic durations do include findings from intermediate sacrifice points, and these circumstances may indicate the presence of data applicable to shorter exposure durations. I encourage ATSDR to ensure that the results of range-finding or preliminary investigations, as well as comments made during periods of observation shoter than indicated durations be carefully examined. It is possible that such has been done already, and if so, a specific statement somewhere in the text would be appropriate.

Findings from NCI, 1978 and from Zeng et al. (2018) should appearin Table 2-1.

EDITORIAL, MRL APPENDIX. Some tabkles for inhalation MRL data (e.g., Table A-4, etc) contain column headings "NOAELADJ, LOAELADJ, etc. But, there is no evidence that the actual exposure concentrations used in the studies have been adjusted. Please fix or explain the "adjusted" notation.

RESPONSE: *With respect to the NTP (1991) study, interim results were presented related to death and mean body weight. However, the death endpoint did not occur at a frequency that could be reported as significant during the acute duration timeframe. Additionally, the body weight results were presented as growth curves, which cannot be used to determine statistically significant differences in body weight without the presence of error bars. In any case, the differences in the first two week of the study do not appear to be statistically significantly different from one another. Intermediate duration results from the NCI (1978) and the Alumot et al. (1976) chronic duration studies are reported in the profile, and thus, no change was needed based on this comment.*

Findings from NCI (1978) already appear in Table 2-2, as this table is the appropriate LSE table for oral route studies. Table 2-1 is the LSE table for inhalation studies, and the NCI (1978) study is an oral route study. Also, the findings from Zeng et al. (2018) are the same underlying findings from Wang et al. (2017), and as such we did not add these findings as they would have been duplicative. We did add sentences throughout the document when Wang et al. (2017) results were presented that states: "Zeng et al. (2018) presents the same [body weight/hepatic] results as Wang et al. (2017), as the two studies use the same underlying data." We also added an additional sentence explaining that $NOAEL_{ADJ}$ *and* $LOAEL_{ADJ}$ *represent values that have been duration adjusted to estimate continuous exposure when exposures were delivered intermittently in the Rational for Not Deriving an MRL section of the intermediate inhalation MRL Worksheet.*

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, no change required.

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: The available human studies were appropriately presented, discussed and categorized.

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: It seems that the most often encountered limitation with the aminal studies were the single-dose nature of some studies, and the higher range of doses employed compared to the POD identified for the most sensitive endpoint. The available animal studies seem to nhave been adequately evaluated, summarized and characterized.

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. No revisions necessary

RESPONSE: *No revisions were suggested.*

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

COMMENT: An explanation might be added to the text as to why BMD modeling was not applied to the dose response data for the critical effect (kidney weight) used to derive the Intermediate Oral MRL value. Likewise, findings other than OE degeneration demonstrate roughly similar potentiall POD values for the acute inhalation MRL. However, because of large difference in the DAF value for respiratory (category 1; here, DAF roughly 0.25) effects versus the DAF value for systemic (category 3; here roughly 1.6), identical POD values for respiratory versus systemic effects would yield HEC values approximately 6.4-fold lower for respiratory (category 1) effects. This point might be considered when explaining why BMD modeling was not attempted for other acute effects demonstrating roughly similar POD values.

RESPONSE: *As stated in the profile in the Selection of the Point of Departure for the MRL section of the Intermediate Oral MRL Worksheet, "[b]enchmark dose modeling was attempted using the F344/N female rat data for increased absolute and relative kidney weight, but no models adequately fit the data." Although findings from Sun et al. (2016) demonstrate roughly similar potential point of departure values, the large differences in the dose adjustment factor value for a category 1 respiratory endpoint like the one from Hotchkiss et al. (2010) versus the dose adjustment factor for a category 3 systemic endpoint like the one in Sun et al. (2016) would lead to an approximately 6.4-fold lower human equivalent concentration for the category 1 respiratory endpoint (EPA, 2012). Thus, no benchmark dose modeling was attempted using the Sun et al. (2016) study data."*

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 not aware of any such 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.

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: As noted elsewhere, findings from NCI, 1978 and Zeng et al., 2018 should be added to Table 2.1

RESPONSE: *Findings from NCI (1978) already appear in Table 2-2, as this table is the appropriate LSE table for oral route studies. Table 2-1 is the LSE table for inhalation studies, and the NCI (1978) study is an oral route study. Also, the findings from Zeng et al. (2018) are the same underlying findings from Wang et al. (2017), and as such we did not add these findings as they would have been duplicative. We did add sentences throughout the document when Wang et al. (2017) results were presented that states: "Zeng et al. (2018) presents the same [body weight/hepatic] results as Wang et al. (2017), as the two studies use the same underlying data."*

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: On the basis of information presented in this draft TP, I cannot agree. The issue is that the distinction between "less serious" and "serious" is not clearly enough presented, and is unaccompanied by reference to an ATSDR policy document or statement that guides the characterization of effects accordingly.

RESPONSE: *Less serious effects are generally reversible cellular alterations, moderate serum chemistry changes, and other effects that are not associated with a decrement in organ function. Serious effects are generally non-reversible, major changes in serum chemistry, and other clinical effects that result in significant organ impairment or dysfunction. The ATSDR Guidance for the Preparation of Toxicological Profiles contains tables of specific effects for each type of health endpoint that are considered "less serious" and "serious", and oftentimes these designations are agreed upon at internal ATSDR health effect meetings. Further information about the designation of effects specific to particular health endpoints as "less serious" or "serious" can be found in the ATSDR Guidance for the Preparation of Toxicological Profiles.*

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: No. As noted above, the exceptions are those relevant to the lack of derived MRL value and the justification for such a decision. While I might agree with the decisions made in the draft TP, they are not adequately supported. All other conclusions (e.g., human relevance, dose response, critical effect, point of departure, uncertainty factors) are appropriate.

RESPONSE: *Language in the MRL worksheet for the acute oral MRL was slightly altered to specify that the lack of a dose-response was the primary reason for not deriving an MRL, and this lack of dose response could have been due to administering the chemical by gavage as opposed to drinking water. The language now reads as follows: "However, administration of 1,2-dichloroethane in the drinking water at doses as high as 189 mg/kg/day for 90 days failed to induce immunosuppressive effects in mice in the Munson et al. (1982) study. Because of this lack of dose-response, it was determined that it may not be appropriate to base an MRL on an effect level from this gavage oil study due to toxicokinetic considerations of administration of the chemical by gavage as opposed to drinking water (e.g., possible bolus saturation of the detoxification/excretion mechanism can occur which may exacerbate toxicity at lower concentrations)."*

An intermediate inhalation MRL was not derived because the most sensitive endpoint was represented by what ATSDR considers a serious effect, since sperm abnormalities are always considered serious effects based on guidance outlined in ATSDR's "Guidance for the Preparation of Toxicological Profiles". There was also extensive discussion of this sperm endpoint in the MRL workgroup, and it was concluded that it was too serious to be used as the basis for an MRL. More information about the classification of sperm abnormalities as a serious effect can also be found in Pohl et al. (2005). It is ATSDR policy not to derive MRLs based on a serious effect, and thus no MRL was derived. Since the Wang et al. (2017) study reports altered serum chemistry changes at an adjusted daily concentration of 21.5 ppm, which is a higher concentration than that of the Zhang et al. (2017) total sperm abnormalities endpoint, an MRL cannot be derived based on this endpoint either.

As such, no changes to the profile were made based on this comment.

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

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

COMMENT: The breadth and level od detail of the ADME of 1,2-dichloroethane is sufficient for this draft TP.

RESPONSE: *No revisions were suggested.*

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

COMMENT: The original PBPK model by D'Souza and the revision as Sweeney are presented briefly, but there is no distinction between them relative to the reliability, validity or quantitative predictive abilities of them relative to informing the reader which model would be better and better for which purposes (dose extrapolation, route extrapolation, species extrapolation. The use of such models to extrapolate across various chasms is a function of the extent to which we know which entity (parent or metabolite; which metabolite) and which time-normalized measure of internal exposure (Cmax or AUC) is better associated with toxicity. Short of knowing these things, we cannot employ the model for extrapolation purposes. With that in mind, the reader may be expecting the use of this/these models for species extrapolation. Because of this lack of knowledge, we cannot employ the models in that manner. Some explanation of this issue should be included in the Section.

Gargas et al. (1989) measured and presented blood:air partition coefficients for chemicals, including 1,2-dichloroethane. These values are used to develop the DAF value for category 3 effects (e.g., liver, kidney), for which 1,2-dichloroethane produces at exposures relevant for consideration. EPA (2012) used these data to develop a DAF (value 1.6) for 1,2-dichloroethane. These data and this application should be presented and discussed in the section.

Gargas ML, Burgess RJ, Viosard DE, Cason GH, Andersen ME. 1989. Partition coefficients of low-molecular-weight volatile chemicals in various liquids and tissues. Tox Appl Pharm. 98:87-99.

US EPA, 2012. Advances In Inhalation Gas Dosimetry For Derivation of A Reference Concentration (RfC) and Use In Risk Assessment. At: https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=244650

RESPONSE: *Language was altered in section 3.1.5 (Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models) as a result of this comment. The new language reads as follows: "The Sweeney et al. (2008) model was used in Sweeney et al. (2016) to extrapolate the oral NOAEL and LOAEL of existing health effect studies in rats to the inhalation route. However, it is unclear how well the Sweeney et al. (2008) model would perform in extrapolating between species, such as between rats and humans."*

The following language was added to section 3.1.6 (Animal-to-Human Extrapolations) in response to this comment: "Gargas et al. (1989) measured and presented blood:air partition coefficients for chemicals, including 1,2-dichloroethane. Gargas et al. (1989) estimated a blood:air partition coefficient of 19.5 ± 0.7 for humans, and a blood:air partition coefficient of 30.4 ± 1.2 for F-344 rats. These values are used to develop the DAF value for category 3 effects (e.g., liver, kidney), for which 1,2-dichloroethane produces at exposures relevant for consideration. EPA (2012) used these data to develop a dose adjustment factor (value 1.6) for 1,2-dichloroethane."

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: These issues are sufficiently covered.

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: To my knowledge, there are not.

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: This issue is reasobably presented, though without knowledge of which metaboilic pathway leads to given toxicities, the age dependent increase in NAT enzymes cannot indicate whether such an age dependent shift in expression will or might have any impact on toxicity.

RESPONSE: *Given our lack of knowledge of which metabolic pathway leads to particular toxicities, we have made no changes based on this comment.*

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

COMMENT: As noted in the text, the only biomarker of exposure that is specific for 1,2-dichloroethane is the presence of 1,2-dichloroethane, itself, in body fluids.

RESPONSE: *No revisions were suggested.*

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

COMMENT: The lack of chemical specific biomarkers of effect is adequately and accurately treated.

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: Such discussion is incomplete, and perhaps a little biased. Most of the presentation relates to interactions with chemicals like disulfiram, which are specifically used to modify enzymatic activity for the express purpose of promoting an interaction. Typically, doses of the interacting-chemical have been selected specifically because they do produce such an impact, and the experiments are conducted to demonstrate that the enzyme known to be impacted is/is not active in the metabolism of a substrate. This should be made clear in the text. In addition, research using PBPK models and extrapolated metabolic rates allows for the interpretation of inhibition likelihood under the constraints of the intact system. Dennison et al (2004), US EPA (2006) and others have shown that given usual environmental exposures to halogenated compounds (gasoline components, drinking water disinfection byproducts) who are known/suspected to be metabolized by the same enzyme, that in vivo, there is no metabolic interaction –

their metabolism proceeds as it would under a single-chemical exposure. While the data sets may not contain 1,2-dichloroethane, the results pertinent to CYP2E1 are valid. Inclusion of findings like these will reduce the potential bias toward supposing that a multi-chemical exposure may lead to perturbations of 1,2-dichloroethane metabolism in vivo.

Dennison JE, Andersen ME, Dobrev ID, Mumtaz MM, Yang RSH. 2004. PBPK Modeling of Complex Hydrocarbon Mixtures: Gasoline. Environ Toxicol Pharmacol 16:107-119.

U.S. EPA. Exposures and Internal Doses of Trihalomethanes In Humans: Multi-Route Contributions From Drinking Water (Final). U.S. Environmental Protection Agency, Washington, DC, EPA/600/ R-06/087, 2006. At: https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=153303

RESPONSE: *Although the reviewer states that disulfiram has been chosen in these interaction experiments because it is a known modifier of enzymatic activity, and because of this believes that results showing an effect of concurrent administration of disulfiram and 1,2-dichloroethane are biased, we disagree that these results need to include a caveat related to that point. Whether the researchers knew or did not know that disulfiram would produce an interactive effect a priori is inconsequential to the presentation of the results of these studies, as this does not change the outcomes that suggest an interaction exists. As such, no changes were made to the profile based on this comment, though additional information on disulfiram was added for complete clarity. The following text was added after the first mention of disulfiram: "also known as tetraethylthiuram disulfide, Antabuse, and DSF; disulfiram is common in the rubber industry and as a treatment for alcohol use disorder".*

Because the Dennison et al. (2004) and the EPA (2006) data do not contain 1,2-dichloroethane, they cannot be included as evidence for these differences between in vitro and in vivo effects. Thus, these references have not been added to the profile. That said, we did add a sentence in section 3.4 (Interactions with Other Chemicals) that states the following: "Studies of in vitro interactions produced more positive results, though interactions observed in vitro do not always generalize to the intact system."

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: See comment immediately above. In addition….

The document should indicate that findings of interactions (e.g., metabolic inhibition) observed in vitro should not be generalized to the intact system (they should not automatically be expected to occur in vivo). In vitro, there are not the limitations of substrate concentration (or inhibitor concentration) that are produced in vivo. In vitro, the experimentalist can study concentrations of chemical not attainable in the liver, in vivo, due to limitations of e.g., blood solubility, liver blood flow, blood:liver partitioning, etc. This is what was shown by Dennison, EPA, etc, noted above.

RESPONSE: *Added a note in section 3.4 (Interactions with Other Chemicals) that interactions observed in vitro do not always generalize to the intact system.*

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: Not to my knowledge, it seems to be fine.

RESPONSE: *No revisions were suggested.*

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

COMMENT: No, there is only one form of the substance. No deficiencies

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 is complete.

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: The path from source to exposure is as completely filled in as possible. The conclusions regarding geospatial arrangements and inhalation exposure is clear.

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; I know of no data that are missing or should be added.

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: What is presented is appropriate. On page 151, sentence beginning, "1,2-Dichloroethane has been detected….", please convert the concentration of 33.83 ug/L to ppb and include in the text for ease of comparison.

RESPONSE: *The sentence quoted in the comment is found in section 5.5.1 (Air). The complete sentence says "1,2-Dichloroethane has been detected in samples of indoor air taken from newly renovated homes in Shanghai at a mean concentration of 33.83 µg/L, which is noticeably higher than concentrations reported in previous studies in Hong Kong, Japan, and Canada (Dai et al. 2017)." Change was made as requested and now reads: "1,2-Dichloroethane has been detected in samples of indoor air taken from newly renovated homes in Shanghai at a mean concentration of 33.83 µg/L (8,364 ppb), which is noticeably higher than concentrations reported in previous studies in Hong Kong, Japan, and Canada (Dai et al. 2017)."*

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: The treatment of this issue seems complete, no revisions are necessary.

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 know of no other studies that should be included, beyond those already identified in the preceding comments. There seem to be sufficient data from Daniel et al. (1994), as noted elsewhere in these comments, to derive an acute oral MRL.

As noted elsewhere, tehre seem to be sufficient data to derive an intermediate inhalation MRL. However, it is likely that the derived MRL value may be higher (not lower, as expected) than the appropriately-derived acute inhalation MRL. This is not a deficiency, per se, but a limitation of the data – concisely stated, the limitation fo the intermediate inhalation MRL may be that the most sensitive target tissue (nasal epithelium) has not yet been evaluated in studies of a duration appropriate for an intermediate MRL. This latter point might be identified in the Health Effects section.

RESPONSE: *The acute oral portion of the Daniel et al. (1994) study uses a gavage oil vehicle for administration of 1,2-dichloroethane. The study finds a less serious LOAEL at 100 mg/kg/day of minimal inflammatory changes in the forestomach, and an associated NOAEL of 30 mg/kg/day. There are no other acute oral studies that focus on this endpoint to corroborate this evidence of inflammatory changes in the forestomach, which would be necessary in a situation where we may have a priori concerns about gavage oil potentially exacerbating toxicity. In this case, there is not enough certainty to derive an MRL based on this value, keeping in mind the uncertainties that arise around oral administration of 1,2-dichloroethane via gavage oil. Therefore, no edits were made to the profile based on this comment.*

An intermediate inhalation MRL was not derived because the most sensitive endpoint was represented by what ATSDR considers a serious effect, since sperm abnormalities are always considered serious effects based on guidance outlined in ATSDR's "Guidance for the Preparation of Toxicological Profiles". There was also extensive discussion of this sperm endpoint in the MRL workgroup, and it was concluded that it was too serious to be used as the basis for an MRL. More information about the classification of sperm abnormalities as a serious effect can also be found in Pohl et al. (2005). It is ATSDR policy not to derive MRLs based on a serious effect, and thus no MRL was derived. Since the Wang et al. (2017) study reports altered serum chemistry changes at an adjusted daily concentration of 21.5 ppm, which is a higher concentration than that of the Zhang et al. (2017) total sperm abnormalities endpoint, an MRL cannot be derived based on this endpoint either.

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

COMMENT: The usefulness of parent chemical as a Biomarker of Exposure (page 173, lines 19-20) should be restated for complete accuracy. It isn't that the measurement of parent necessarily need to be made "soon" after exposure, but the measure of parent should be taken "at a known time since exposure". Admittedly, the level of quantitative certainty is increased when the duration between exposure and measurement is less.

RESPONSE: *This comment refers to the Genotoxicity discussion in the Health Effects subsection of Section 6.2 (Identification of Data Needs). The original sentence which reads, "However, use of the parent compound as a biomarker would only be possible soon after exposure, and the other proposed biomarkers are not specific for 1,2-dichloroethane." was changed to the following: "However, use of the parent compound as a biomarker would only be possible at a known time since exposure, and the other proposed biomarkers are not specific for 1,2-dichloroethane." A change was made as suggested. This change was also made in Section 3.3.1 when describing the usefulness of the parent chemical as a biomarker of exposure. As a result of this comment, the sentence that reads, "However, these measurements would have to be made soon after exposure, since 1,2-dichloroethane is rapidly eliminated from the body (see Section 3.1.4)." was changed to read as follows: "However, these measurements would have to be made at a known time since exposure, since 1,2-dichloroethane is rapidly eliminated from the body (see Section 3.1.4)." Also, a similar sentence in Section 3.3.1, "As discussed above for the parent compound, rapid excretion of 1,2-dichloroethane and metabolites (essentially complete after 48 hours in animal studies) means that measurements would have to be made soon after exposure to be of any value." was changed to read as follows: "As discussed above for the parent compound, rapid excretion of 1,2-dichloroethane and metabolites (essentially complete after 48 hours in animal studies) means that measurements would have to be made at a known time since exposure to be of any quantitative value."*

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

COMMENT: Yes, the data needs are appropriately presented.

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: Capitalize Permissible Exposure Level and Recommended Exposure Level. The value of the section would be increased if a short phrase describing the intent of the (e.g.) PEL and REL as well as the population to which they apply could be included.

EPA's Health Advisories: There is no longer-term HA value in EPA (2018). There is a 1-day and a 10-day HA value for children, based on a 10-kg child ingesting 1 L drinking water per day. The HA value of 0.7 mg/L is the same for both, and should be included in the draft TP, as should the reference:

US EPA, 2018. 2018 Edition of the Drinking Water Standards and Health Advisories Tables. EPA 822-F-18-001. US Environmental Protection Agency, Office of Water, Washington, DC. March, 2018. Available at: https://www.epa.gov/sites/production/files/2018-03/documents/dwtable2018.pdf

This section should indicate that there is no RfD and that there is no RfC derived by US EPA, and that the drinking water standard (the maximum contamination Level; MCL) is established at 0.005 mg/L on the basis of the derived oral cancer slope factor of 9.2 x 10-2 per mg/kg-day (US EPA, 1987 – the IRIS Assessment).

U.S. EPA. 1987 Integrated Risk Information System assessment for 1,2-dichloroethane. Available at: https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0149_summary.pdf.

The section on Water and Food on page 181 needs to be cleaned-up and references checked. For instance, the references cited for EPA are wrong, do not appear in the bibliography and are inconsistent.

RESPONSE: *The following language related to the intent of the PEL and REL was added to Chapter 7 of the profile:*

"The Permissible Exposure Limit (PEL) listed in Table 7-1, enforced by OSHA, is measured by a time-weighted average during an 8-hour work shift of a 40-hour workweek. PELs are intended to be enforceable limits on exposure to workers, however PELs are generally considered outdated due to the legislative time and other issues involved with the update process and therefore, potentially inadequate for ensuring protection of worker health…

…Alternatively, the NIOSH Recommended Exposure Limit (REL) listed in ***Error! Reference source not found.*** *is measured by a time-weighted average during a 10-hour work shift of a 40-hour workweek. RELs are developed to recommend standards to OSHA, and are considered to be the more current, evidenced based values than the OSHA PELs, though they are non-enforceable limits. The REL of 1,2-dichloroethane is 1 ppm. The NIOSH Short-Term Exposure Limit (STEL) is 2 ppm."*

The EPA Health Advisory changes mentioned were made to the profile, including adding the One-day and Ten-day values, and indicating that there was no longer-term health advisory value. EPA 2018 was appropriately cited. Language was also added to mention there is no final RfD and no final RfC derived by EPA, though provisional RfD and RfC values exist, and that there exist values for an MCL and an MCLG. The added language reads as follows: "EPA has a 1-day and 10-day health advisory value for 1,2 dichloroethane which are both 0.7 mg/L, based on a 10-kg child ingesting 1 liter of drinking water per day (EPA 2018). There is no longer-term health advisory value for 1,2-dichloroethane developed by EPA (EPA 2018). There are no derived final RfD or RfC values, though EPA established a subchronic provisional RfD (0.02 mg/kg-day) and both a chronic and subchronic provisional RfC (0.007 mg/m^3 and

0.07 mg/m^3, respectively) for 1,2-dichloroethane. There is an MCL at 0.005 mg/L that is based on the derived oral cancer slope factor of 9.2 x 10^{-2} per mg/kg-day (EPA 1987), as well as an MCLG at 0 mg/L (EPA 2018)."

In response to the comment about the section on Water and Food needing to be cleaned up, we performed a verification of all of the data and references in Table 7-1. The most notable change was to add the FDA 2019a reference to the references section in Chapter 8. We also updated the WHO drinking water quality guideline from 0.3 mg/L to 0.03 mg/L, as this was a typographical error. We also corrected the year of the IRIS assessment from 2001 to 1987, and updated the reference in Chapter 8 accordingly.

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

COMMENT: [above comment was used to address this question and the preceding question.]

RESPONSE: *No response needed*

Appendices

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

COMMENT: Where necessary, comments on information contained in the Appendices have been included in comments for sections 1 and 2.

RESPONSE: *No response needed.*

Unpublished Studies (If Applicable to Review)

COMMENT: *None received.*

RESPONSE: *No response necessary.*

Annotated Comments on the Profile

COMMENT: delete "therefore" because lipophilicity has no impact in predisposing a chemical to either active or passive transport

RESPONSE: *This comment refers to the sentence in Section 3.1.1.2 (Oral Exposure) that says, "1,2-Dichloroethane is lipophilic, and is expected, therefore, to be absorbed largely via passive diffusion across the mucosal membranes of the gastrointestinal tract." The word "therefore" was deleted.*

COMMENT: sentence beginning "The percentage of recovered…" does not make sense as written.

RESPONSE: *This comment refers to the sentence in section 3.1.1.2 (Oral Exposure) that says, "The percentage of recovered radioactivity found in the feces following inhalation or oral exposure to [14C]-1,2-dichloroethane was 1.7–2.1%; 7.0–7.7% of the recovered dose was found in the expired air following exposure by either route (Reitz et al. 1980)." This sentence was revised to read as follows: "The*

percentage of radioactivity recovered in the feces following inhalation or oral exposure to [14C]-1,2-dichloroethane was 1.7–2.1%; 7.0–7.7% of the administered dose was recovered in the expired air following exposure by either route (Reitz et al. 1980)."

COMMENT: "significantly" should be replaced with another word – this statement as written seems to contrast with the percentages shown in lines 25-26.

RESPONSE: *This comment refers to the sentence in section 3.1.1.3 (Dermal Exposure) that says, "The findings of Urusova (1953) indicate that percutaneous absorption via contact with contaminated water or the chemical itself may be a significant route of exposure to 1,2-dichloroethane in humans". The word "significant" was replaced with "potential."*

COMMENT: The validity of the findings is not in question, though their quantitative value is in question; replace "validity".

RESPONSE: *This comment refers to the sentence in section 3.1.1.3 (Dermal Exposure) that says, "However, no details of analytical methodology were reported, and the sample size was not provided, and thus, the validity of these results cannot be assessed." The suggested change was addressed in the profile and "validity" was replaced with "reliability".*

COMMENT: clarify the meaning of "sooner".

RESPONSE: *This comment refers to the sentence in section 3.1.3 (Metabolism) that says, "Metabolic saturation appears to occur sooner after oral (gavage) administration than after inhalation exposure." "Sooner" was replaced with "at lower concentrations."*

COMMENT: Remove "proposed" the model is not proposed, it is completed.

RESPONSE: *This comment refers to the sentence in section 3.1.3 (Metabolism) that says, "A proposed physiological pharmacokinetic model explains the route-of-exposure difference in quantifying the amount of 1,2-dichloroethane-glutathione conjugate produced in target organs after oral and inhalation exposures (D'Souza et al. 1987, 1988)." The word "proposed" was deleted.*

COMMENT: The clarity of Figure 3.1 is not acceptable. Figure 3-1 references "NTP 1991a, but there is only one NTP 1991 reference in the bibliography.

RESPONSE: *This comment refers to Figure 3-1 at the end of section 3.1.3 (Metabolism). The figure source was updated in the profile.*

COMMENT: Mass balance should be addressed to the extent possible in the opening paragraph.

RESPONSE: *This comment refers to the opening paragraph of Section 3.1.4.1. The study in question (Urusova 1953) is unclear with respect to the actual mass balance of 1,2-dichloroethane in expired air at different time points other than explicitly mentioning that the amount in expired air was greater immediately following exposure and decreased gradually with time, which is what is currently described in this section of the profile. Thus, no additional changes were made based on this comment.*

COMMENT: potential typo: "…half-time of .90 minutes"; and change to "half-life" if appropriate.

RESPONSE: *This comment refers to the sentence in section 3.1.4.2 (Oral Exposure) saying, "The initial elimination phase had a half-time of 90 minutes, but elimination became more rapid when blood levels fell to 5–10 µg/mL, characterized by a half-life of approximately 20–30 minutes." The word "half-time" was updated to "half-life".*

COMMENT: sentence beginning, "However, the data…", suggest removing identification of potential sources of exposure.\; this seems to be out of place and inconsistent with the general nature of the document.

RESPONSE: *This comment refers to the sentence in section 3.2.1 (Children's Susceptibility) that states, "However, the data do suggest that it would be prudent to prevent 1,2-dichloroethane inhalation exposures in children such as those that might occur during, and for several days after, using old wallpaper or carpet adhesives that contain 1,2-dichloroethane." The sentence was updated to say, "However, the data do suggest that it would be prudent to prevent 1,2-dichloroethane inhalation exposures in children."*

COMMENT: as phrase to clarify – "In addition, without additional data, it is not possible….." The point is that it IS possible, but doing so requires more data, like time since exposure, etc.

RESPONSE: *This comment refers to the sentence in section 3.3.1 (Biomarkers of Exposure) that says, "In addition it is not possible to establish from such measurements the precise environmental levels of 1,2-dichloroethane to which these individuals were exposed." The words "without additional data" were added to this sentence to clarify.*

COMMENT: "…1,2-dichloroethane in air and water…" please include relevant concentrations.

RESPONSE: *This comment refers to the sentence in section 3.3.1 (Biomarkers of Exposure) that says, "In general, small amounts of 1,2-dichloroethane detected in the breath and urine were associated with exposure to 1,2-dichloroethane in air and water (trace-100 ng/m3 and 50 mg/L, respectively) (Barkley et al. 1980; Conkle et al. 1975)." The concentrations for each media were clarified in the sentence..*

COMMENT: "insufficient to characterize the…"; need to reword. The relationship is indeed established, but it is not quantified, "Characterized" is a too vague a term that may mislead some readers.

RESPONSE: *This comment refers to the sentence in section 3.3.1 (Biomarkers of Exposure) that says, "These data are insufficient to characterize the relationship between environmental exposure to 1,2-dichloroethane and resultant tissue and fluid levels." The word "characterize" was changed to the word "quantify".*

COMMENT: "… is another potentially useful biomarker…"; remove "potentially useful. It is a biomarker, but it is not chemical-specific.

RESPONSE: *This comment refers to the sentence in section 3.3.1 (Biomarkers of Exposure) that says, "Urinary excretion of thioethers is another potentially useful biomarker of exposure to 1,2-dichloroethane." The words "potentially useful" were deleted from the sentence.*

COMMENT: "…thioethers increased linearly with…"; please verify "linearly" because this is the range of concentrations previously used to demonstrate the range of metabolic saturation.

RESPONSE: *This comment refers to the sentence, "Payan et al. (1993) showed that total excreted urinary thioethers increased linearly with increasing oral dose (for doses between 0.25 and 4.04 mmol/kg [11.9 mg/kg/d and 400 mg/kg/d, respectively]) in male Sprague-Dawley rats during a 24-hour post-administration period, at a rate of 0.028 mmol thiol group eliminated per millimole of 1,2-dichloroethane administered" in section 3.3.1 (Metabolism). The claim was verified.*

COMMENT: "… to be of any value."; please revise to indicate that the "quantitative" value of such data is limited. Such a finding would certainly be of some value, even if the relationship to time of exposure is uncertain.

RESPONSE: *This comment refers to the sentence, "As discussed above for the parent compound, rapid excretion of 1,2-dichloroethane and metabolites (essentially complete after 48 hours in animal studies) means that measurements would have to be made soon after exposure of any value" in section 3.3.1 (Metabolism). This sentence was updated to read as the following: "As discussed above for the parent compound, rapid excretion of 1,2-dichloroethane and metabolites (essentially complete after 48 hours in animal studies) means that measurements would have to be made at a known time since exposure to be of any quantitative value."*

COMMENT: should include a summary statement of the NHANES data set – what do the data show, in general – no specifics needed.

RESPONSE: *This comment refers to the end of section 3.3.1 (Metabolism). A summary of the NHANES data has been added to the end of section 3.3.1; the updated section ends with the following paragraph: "The National Health and Nutrition Examination Survey (NHANES) also measures levels of 1,2-dichloroethane in the blood and has done so since the 2003-2004 data collection cycle of the survey to the 2015-2016 cycle. The NHANES used an analytical method that quantifies trace levels of 1,2-dichloroethane in the blood using solid-phase microextraction, capillary gas chromatography, and quadrupole mass spectrometry together (Blount et al. 2006). Blood levels of 1,2-dichloroethane from recent NHANES data are presented in* ***Error! Reference source not found.*** *and show that most of the values collected are below the limit of detection".*