DISPOSITION OF PEER REVIEW COMMENTS FOR TOXICOLOGICAL PROFILE FOR 1,2-DICHLOROETHENE

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 comment draft of the Toxicological Profile for 1,2-Dichloroethene were:

Mary Beth Genter, Ph.D.
Professor
Department of Environmental Health
University of Cincinnati
Cincinnati, Ohio

Matt Simcik, Ph.D.
Professor
Division of Environmental Health Sciences
School of Public Health
University of Minnesota
Minneapolis, Minnesota

G.A. Shakeel Ansari, Ph.D.
Professor
Department of Pathology
University of Texas Medical Branch
Galveston, Texas

Comments provided by Peer Reviewer #1

ATSDR Charge Questions and Responses and Reviewer Comments

Chapter 1

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 1: Yes. Pertinent details are added. No change is suggested.

RESPONSE: *No response needed.*

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 2: Yes. Especially significant are those where routes relevant to human exposure are used at reasonable doses.

RESPONSE: *No response needed.*

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

COMMENT 3: Agree. As they have been adequately described.

RESPONSE: *No response needed.*

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

COMMENT 4: Agree.

RESPONSE: *No response needed.*

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 5: N/A.

RESPONSE: *No response needed.*

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 6: Agree.

RESPONSE: *No response needed.*

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

COMMENT 7: Typos:
Appendix A
Page A-3, line 24: Colon from Hurtt et al. should be change to period.
Page A-5, line 48: Bracket probably needs a reference or a value.

RESPONSE: *The typos in Appendix A have been corrected:*

Few animal studies have investigated effects of acute-duration inhalation exposure to trans-1,2-dichloroethene (Freundt et al. 1977; Gradiski et al. 1978; Hurtt et al. 1993).

In accordance with these selection criteria, the Log-Logistic model, a frequentist, unrestricted model, provided the best fit, with a $BMCL_{10}$ of 256.47 ppm (Table A-3).

Chapter 2

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 8: Agree. No changes are needed.

RESPONSE: *No response needed.*

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 9: No suggestion.

RESPONSE: *No response needed.*

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 10: Yes.

RESPONSE: *No response needed.*

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 11: Yes.

RESPONSE: *No response needed.*

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

COMMENT 12: Yes. Appropriately discussed.

RESPONSE: *No response needed.*

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 13: No.

RESPONSE: *No response needed.*

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 14: None.

RESPONSE: *No response needed.*

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 15: Properly included.

RESPONSE: *No response needed.*

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 16: Yes.

RESPONSE: *No response needed.*

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 17: Yes.

RESPONSE: *No response needed.*

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 18: Yes.

Typos:
Page 8, line 20: Comma is missing. 'trans-12-dichloroethene' should be 'trans-1,2-dichloroethene'.
Page 48, line 12: Barnes et al. year is missing which should be 1985.
Page 68, Table 2-7. Period after Kirsch -Volders.1996 (second line)

RESPONSE: *The typos in Chapter 2 have been corrected:*

Figures 2-1, 2-2, and 2-3 provide an overview of the database of studies in humans or experimental animals for trans-1,2-dichloroethene, cis-1,2-dichloroethene, and mixtures of cis- and trans-1,2-dichloroethene.

Inhalation and oral exposures to trans-1,2-dichloroethene did not result in any adverse respiratory effects at the highest exposure concentrations tested: 90-day inhalation exposure of rats at concentrations up to 4,000 ppm, purity 99.86% (DuPont 1998); 14-day gavage exposure of rats to 210 mg/kg/day, purity 98% (Barnes et al. 1985).

Tafazoli and Kirsch-Volders 1996

Chapter 3

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

COMMENT 19: Yes. No suggestion.

RESPONSE: *No response needed.*

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

COMMENT 20: Yes.

RESPONSE: *No response needed.*

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 21: Yes.

RESPONSE: *No response needed.*

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 22: No.

RESPONSE: *No response needed.*

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 23: No.

RESPONSE: *No response needed.*

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

COMMENT 24: Yes.

RESPONSE: *No response needed.*

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

COMMENT 25: May not be specific.

RESPONSE: *No response 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 26: Not generally applicable but the metabolites may be reactive with other substances.

RESPONSE: *No response needed.*

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 27: I am not aware of such finding.

Typos:

Page 71, line 5. Period is missing

Page 73. Figure 3-1. The figure needs to be modified. The diol intermediate in bracket does not add to the mechanism and therefore should be deleted. Suggested changes are included in figure 3-1.

RESPONSE: *The suggested revision on page 71 (Section 3.1) was made:*

Studies conducted in rats indicate relatively rapid absorption of inhaled 1,2-dichloroethene with air:blood equilibrium occurring within 1–2 hours following initiation of a constant exposure.

Figure 3-1 was not revised since the diol is an intermediate.

Chapter 4

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 28: No.

RESPONSE: *No response needed.*

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

COMMENT 29: Not applicable.

RESPONSE: *No response needed.*

Chapter 5

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

COMMENT 30: No suggestion.

RESPONSE: *No response needed.*

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 31: None.

RESPONSE: *No response needed.*

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 32: No suggestion.

RESPONSE: *No response needed.*

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 33: No suggestion.

RESPONSE: *No response needed.*

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 34: Agree.
Typos:
Page 90, line 25: Correct is 'reductive' not 'deductive' as stated.
Page 90, line 32: I&I need to be explained.
Page 93, line 34: 'OH' should be replaced by 'hydroxyl'.
Page 119, line19: 'studies' should be changed to 'study'.
Line31: Needs clarification.

RESPONSE: *The suggested revisions were made in Chapters 5 and 6:*
Section 5.3.2

1,2-Dichloroethene is a reductive dehalogenation degradation product of TCE and PCE (cis-1,2-dichloroethene is most commonly the main degradation product) and, as a consequence, can be released to water or soil where there is contamination with these solvents (U.S. Army 2018).

Section 5.3.2

Such phenomena have been documented in Europe (Milde et al. 1988) and similar infiltration and inflow problems are common in most older U.S. cities.

Section 5.4.2

Tuazon et al. (1988) and Jeffers et al. (1989) provide other convenient summaries of the reaction chemistry of chloroethenes and hydroxyl radicals.

Section 6.2

Only one study evaluating developmental effects of trans-1,2-dichhloroethene was identified, and no studies evaluating developmental effects of cis-1,2-dichloroethene were located.

Section 6.2

Additional studies could provide supportive data on the immunotoxicity of trans-1,2-dichloroethene and determine if cis-1,2-dichloroethene also affects immune system function.

Chapter 6

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

COMMENT 35: No.

RESPONSE: *No response needed.*

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

COMMENT 36: Yes.

RESPONSE: *No response needed.*

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

COMMENT 37: Yes. Unbiased writeup.
Suggested typographical corrections:
Page 119: Line 19:'studies should be corrected as 'study'

RESPONSE: *As noted in the Response to Comment 34, the text has been revised:*

> Only one study evaluating developmental effects of trans-1,2-dichhloroethene was identified, and no studies evaluating developmental effects of cis-1,2-dichloroethene were located.

Chapter 7

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

COMMENT 38: No.

RESPONSE: *No response needed.*

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

COMMENT 39: No.

RESPONSE: *No response needed.*

Review of Unpublished Studies

ATSDR thanks the Reviewer for the comments on the unpublished studies.

E.I. DuPont De Nemours & Co. (1988). Eye irritation test in rabbits of trans-1,2-dichloroethylene with cover letter dated 05/10/94 (sanitized), Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. (cited in the toxicological profile as DuPont 1988c)

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

COMMENT 40: Yes.

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

COMMENT 41: Not applicable.

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

COMMENT 42: Single dose. Multiple time points.

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

COMMENT 43: Not applicable.

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

COMMENT 44: Yes.

DuPont (1998). trans-1,2-Dichloroethylene: 90-day inhalation toxicity study in rats, E.I. du Pont de Nemours and Company, 110-467.

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

COMMENT 45: Yes.

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

COMMENT 46: Not applicable.

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

COMMENT 47: Yes

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

COMMENT 48: No. Rather this is a very well-designed study using both male and female mice.

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

COMMENT 49: Yes.

Dow Chemical Company (1960). Results of range finding toxicological tests on 1,2-dichloroethylene, mixed isomers, with cover letter dated 05/10/94 (sanitized), Dow Chemical Company. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D.

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

COMMENT 50: Yes.

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

COMMENT 51: Not applicable.

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

COMMENT 52: Yes

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

COMMENT 53: Not Applicable

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

COMMENT 54: Yes.

Comments provided by Peer Reviewer #2

ATSDR Charge Questions and Responses and Reviewer Comments

Chapter 1

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 1: I know of no other human effects to include.

RESPONSE: *No response needed.*

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 2: I believe that the eye irritation effects observed in animals (Hurtt study) could occur in humans at high airborne concentrations. MLE proposed should be protective.

RESPONSE: *No response needed.*

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

COMMENT 3: Even if it's repetitive, I'd like to see the route of exposure mentioned for each study. It can be inferred where not indicated by the units (ppm vs. mg/kg/d), but it would be more clear to spell this out. I added this information (or what I believe to be correct) in several places in the annotated Profile document (included as an attachment).

RESPONSE: *ATSDR has reviewed the text in Chapter 1 and added route of exposure information.*

For example:

> Maternal body weight gain was reduced in pregnant rats exposed via inhalation to 12,000 ppm trans-1,2-dichloroethene during gestation (Hurtt et al. 1993).
>
> Other studies found no effects of oral acute-duration exposures to trans-1,2-dichloroethene in rats or mice at maximum oral doses tested of 210–220 mg/kg/day (Barnes et al. 1985; Munson et al. 1982) or 387–8,065 mg/kg/day (Barnes et al. 1985; Hayes et al. 1987; NTP 2002), respectively.
>
> In addition, no hematological effects were observed in rats exposed to 4,000 ppm for 90 days by inhalation (DuPont 1998).

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

COMMENT 4: Agree, lack of data should preclude derivation of MLE in the instances specified.

RESPONSE: *No response needed.*

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 5: Agree with calculations as presented.

RESPONSE: *No response needed.*

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 6: No comment

RESPONSE: *No response needed.*

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

COMMENT 7: No comment

RESPONSE: *No response needed.*

Chapter 2

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 8: To my knowledge, yes.

RESPONSE: *No response needed.*

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 9: There were really no good human studies identified, and I found none when doing a Pubmed search myself. The lack of such studies was clearly stated in the document.

RESPONSE: *No response needed.*

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 10: Animal studies were presented and most, except for the Dupont eye irritation study (very low numbers, no concurrent controls, as mentioned in the risk of bias section), were probably of acceptable design at the time that they were conducted. The 3R's would preclude some of the unpublished Dupont studies from being performed today.

RESPONSE: *ATSDR notes that although a concurrent control group was not used in the DuPont (1988c) study, the left eye of each rabbit was used as a control.*

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 11: If dermal studies were performed today, pigs or mini-pigs would probably have been used. However, this was not the case when those studies were performed.

RESPONSE: *No response needed.*

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

COMMENT 12: I do not understand how the 0.01 ml of trans-1,2-dichloroethene mentioned in the Dupont eye irritation potential study was converted to 3.3 mg/kg in the Profile (e.g. page 4). I believe that dose reponse information was accurately documented, where available.

RESPONSE: *The text was revised, and 0.01 mL was listed as the administered amount; note that the citation was changed from Brock (1990) to DuPont (1988c).*

Section 1.2

Instillation of 0.01 trans-1,2-dichloroethene to the eyes of rabbits for 20 seconds resulted in transient severe corneal opacity, moderate iritis, and conjunctivitis (DuPont 1988c).

Section 2.12

Instillation of 0.01 mL trans-1,2-dichloroethene to the eyes of rabbits for 20 seconds resulted in transient severe corneal opacity, moderate iritis, and conjunctivitis (DuPont 1988c).

Appendix A

In laboratory animals, instillation of 0.01 mL trans-1,2-dichloroethene to the eyes of rabbits for 20 seconds resulted in ocular irritation, transient severe corneal opacity, moderate iritis, and conjunctivitis (DuPont 1988c).

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 13: No comment.

RESPONSE: *No response needed.*

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 14: No

.

RESPONSE: *No response needed.*

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 15: No changes to suggest.

RESPONSE: *No response needed.*

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 16: Agree. No changes to suggest.

RESPONSE: *No response needed.*

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 17: I find nothing to add to what has been included.

RESPONSE: *No response needed.*

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 18: No changes to suggest.

> Additional comments on Chapter 2: I find that the figures such as Figure 2-4 take up a tremendous amount of space and impart very little useful information. I also did not find the figure on page D-6 to be useful.

RESPONSE: *ATSDR thanks the Reviewer for the comments and will take them into consideration when the Agency updates the Guidance for the Preparation of Toxicological Profiles.*

Chapter 3

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

COMMENT 19: No changes to suggest.

RESPONSE: *No response needed.*

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

COMMENT 20: I found no other information to include.

RESPONSE: *No response needed.*

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 21: There were insufficient data identified to make these assessments.

RESPONSE: *No response needed.*

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 22: I found no other information to include.

RESPONSE: *No response needed.*

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 23: There is only mention that children might be a susceptible population. I found no data to identify populations at higher risk of susceptibility.

RESPONSE: *No response needed.*

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

COMMENT 24: Profile states that there are none. However, my search of the literature found this reference which may identify a biomarker of exposure; I was unable to obtain the full-text article, so I do not know what they measured: Pleil JD, Lindstrom AB. Exhaled human breath measurement method for assessing exposure to halogenated volatile organic compounds. Clin Chem. 1997 May;43(5):723-30. PMID: 9166222.

RESPONSE: *The text in Section 3.3.1 was revised to incorporate the results of the Pleil and Lindstrom (1997) study:*

> cis-1,2-Dichloroethene can be measured in expired air; however, its usefulness as a biomarker may be limited since a half-life of <30 minutes was estimated in a study of two volunteers (Pleil and Lindstrom 1997).

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

COMMENT 25: None of which I am aware, which is consistent with information stated in the Profile.

RESPONSE: *No response 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 26: I found no other information to include

RESPONSE: *No response needed.*

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 27: I found no other information to include.

RESPONSE: *No response needed.*

Chapter 4

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 28: I found no other information to include.

RESPONSE: *No response needed.*

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

COMMENT 29: Yes, data are provided for cis-, trans-, and mixtures of 1,2-dichloroethene.

RESPONSE: *No response needed.*

Chapter 5

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

COMMENT 30: To my knowledge, yes.

RESPONSE: *No response needed.*

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 31: I found no other information to include.

RESPONSE: *No response needed.*

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 32: I found no other information to include.

RESPONSE: *No response needed.*

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 33: I found no other information to include.

RESPONSE: *No response needed.*

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 34: The following reference, also mentioned above, mentions showering in contaminated water as a possible source of exposure: Pleil JD, Lindstrom AB. Exhaled human breath measurement method for assessing exposure to halogenated volatile organic compounds. Clin Chem. 1997 May;43(5):723-30. PMID: 9166222.

RESPONSE: *Exposure to 1,2-dichloroethene from showering with contaminated water is listed as a potential source of exposure in Section 5.6. The Pleil and Lindstrom (1997) study was added to Section 3.3.1 (See the Response to Comment 24).*

Chapter 6

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

COMMENT 35: ***N/a.***

RESPONSE: *No response needed.*

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

COMMENT 36: Not really—this does not seem to be a sufficiently high-volume chemical (TRI data in Table 5.2) that spending the money and using the animals to perform all of the identified "nice-to-have" information would be justified. I acknowledge the caveats associated with using TRI data.

RESPONSE: *The intent of the data needs discussion is to identify gaps in the literature. The profile does not prioritize these data needs in accordance with ATSDR's Guidance for the Preparation of Toxicological Profiles.*

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

COMMENT 37: No objection to how these are presented; however the word "contention" is a very unscientific and confrontational word, and as indicated in the mark-up of the Profile, "hypothesis" would be preferred.

RESPONSE: *The suggested revision was made in Section 6.2 Bioavailability from Environmental Media:*

> The few available toxicity studies of animals exposed to 1,2-dichloroethene support this hypothesis (Filser and Bolt 1979; Gargas et al. 1988, 1989).

Chapter 7

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

COMMENT 38: No.

RESPONSE: *No response needed.*

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

COMMENT 39: No.

RESPONSE: *No response needed.*

Comments on Unpublished Studies

DuPont (1998). trans-1,2-Dichloroethylene: 90-day inhalation toxicity study in rats, E.I. du Pont de Nemours and Company, 110-467.

COMMENT 40: Why was cell proliferation analysis performed in livers? Were there some preliminary data from another study that suggested that liver was a target tissue?

RESPONSE: *The investigators did not provide a rationale for why cell proliferation analysis was performed in the liver.*

E.I. DuPont De Nemours & Co. (1988). Eye irritation test in rabbits of trans-1,2-dichloroethylene with cover letter dated 05/10/94 (sanitized), Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. (cited in the toxicological profile as DuPont 1988c)

COMMENT 41: I do not understand how the 0.01 ml of trans-1,2-dichloroethene mentioned in this study was converted to 3.3 mg/kg in the Profile (e.g. page 4 of Profile).

RESPONSE: *As noted in the Response to Comment 12, the text in the profile was revised and the administered dose of 0.01 mL was used rather than an estimated mg/kg dose.*

Dow Chemical Company (1960). Results of range finding toxicological tests on 1,2-dichloroethylene, mixed isomers, with cover letter dated 05/10/94 (sanitized), Dow Chemical Company. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D.

COMMENT 42: Results on the page labeled Page 3 indicate that they were looking for percutaneous absorption, but the methods do not suggest that that was actually the goal of the study (skin lesions were reported but no method to measure material in blood or tissues). Acute oral toxicity study performed in only two animals. Animal #s not mentioned in report for "Eye contact" study. Inhalation studies were performed at unethically high exposure concentrations, with death as the main endpoint.

RESPONSE: *ATSDR thanks the Reviewer for the comments.*

Dow Chemical Company (1994). The toxicity of 1,2-dichloroethylene as determined by repeated exposures on laboratory animals, with cover letter dated 05/10/94 (sanitized), Dow Chemical Company. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D.

COMMENT 43: Practically illegible due to poor quality of the reproduction of the document. Also, there are a lot of handwritten notations that are very difficult to read. There is mention of increased liver and kidney weight and that histopathology would be performed, but I did not find the results of histopathological evaluation.

RESPONSE: *ATSDR notes that this is the best available copy of the study. ATSDR agrees with the reviewers that the Dow Chemical Company (1960) study has several limitations.*

Annotated Comments on the Toxicological Profile

COMMENT 44: Regarding the following statement in Section 1.1-- Most studies indicate that both isomers of 1,2-dichloroethene are highly resistant to biodegradation in an aerobic environment, but may biodegrade under anaerobic conditions—the Reviewer commented: Please confirm that this is correct. It is counterintuitive to me…….

RESPONSE: *The statement referenced by the Reviewer is correct as written in the profile. As discussed in Section 5.4.2, 1,2-dichloroethene and other chlorinated ethenes generally resist biodegradation under aerobic conditions when released to surface waters (Fogel et al. 1986; Mudder 1981; Mudder and Musterman 1982) and undergo slow reductive dechlorination under anaerobic conditions (Barrio-Lage et al. 1986; Fogel et al. 1986).*

COMMENT 45: The Reviewer made the following (indicated in red) revision to the text in Section 1.1: Occurrences of 1,2-dichloroethene in air can be attributed to releases from factories that manufacture or use 1,2-dichloroethene, and/or evaporation from some landfills, solvents, and refrigerants.

RESPONSE: *The suggested revision was made in Section 1.1:*

Occurrences of 1,2-dichloroethene in air can be attributed to releases from factories that manufacture or use 1,2-dichloroethene and/or evaporation from some landfills, solvents, and refrigerants.

COMMENT 46: Regarding the following statement in Section 1.2**--** In female rats, erythrocyte counts in the 1,580 and 3,245 mg/kg/day exposure groups—the Reviewer commented: Incomplete sentence

RESPONSE: *The referenced sentence in Section 1.2 was revised:*

In female rats, erythrocyte counts were decreased in the 1,580 and 3,245 mg/kg/day exposure groups.

COMMENT 47: Regarding the following statement in Section 1.2-- However, other oral exposure studies did not observe adverse hematological effects following acute-duration exposure of rats and mice to maximum doses of 210–8,065 mg/kg/day (Barnes et al. 1985; Hayes et al. 1987; NTP 2002)—the Reviewer commented: route of exposure?

RESPONSE: *ATSDR notes that the beginning of the referenced statement indicates that these are oral exposure studies.*

COMMENT 48: The Reviewer suggested the following revision (marked in red) in Section 1.2: In addition, no hematological effects were observed in rats exposed to 4,000 ppm for 90 days by inhalation (DuPont 1998).

RESPONSE: *The suggested revision was made in Section 1.2:*

In addition, no hematological effects were observed in rats exposed to 4,000 ppm for 90 days by inhalation (DuPont 1998).

COMMENT 49: Regarding the following statement in Section 1.2-- In single-dose lethality studies in rats, clinical signs of neurotoxicity (central nervous system depression, decreased activity, ataxia, loss of righting reflex, and depressed respiration) have been observed (Barnes et al. 1985; Hayes et al. 1987)—the Reviewer commented: Route?

RESPONSE: *The referenced statement in Section 1.2 was revised:*

In single-dose oral lethality studies in rats, clinical signs of neurotoxicity (central nervous system depression, decreased activity, ataxia, loss of righting reflex, and depressed respiration) have been observed (Barnes et al. 1985; Hayes et al. 1987).

COMMENT 50: The Reviewer indicated typos in the title for Tables 1-1 and 1-2.

RESPONSE: *The titles for Tables 1-1 and 1-2 were corrected:*

Table 1-1. Provisional Minimal Risk Levels (MRLs) for trans-1,2-Dichloroethene

Table 1-2. Provisional Minimal Risk Levels (MRLs) for cis-1,2-Dichloroethene

COMMENT 51: In Section 1.3, the Reviewer made the following comment on the provisional intermediate oral MRL for trans-1,2-dichloroethene: mg/kg/d, I assume?

RESPONSE: *ATSDR notes that the exposure units (mg/kg/day) are reported in the table in the oral exposure header row.*

COMMENT 52: The Reviewer made the following suggested revision (indicated in red) in Section 2.1: Dose-related lacrimation (indicating ocular irritation) was observed in an acute-duration, whole-body exposure study in pregnant rats~~,~~.

RESPONSE: *The suggested revision was made:*

Dose-related lacrimation (indicating ocular irritation) was observed in an acute-duration, whole-body exposure study in pregnant rats.

COMMENT 53: Regarding the header row of Table 2-1, the Reviewer commented: If these are ppm in air, then technically they are not doses; they are exposure concentrations.

RESPONSE: *While ATSDR agrees with the Reviewer that technically these are concentrations, it notes that the term "doses" is standard boilerplate language for the LSE table. This toxicological profile has been developed in accordance with ATSDR's Guidance for the Preparation of Toxicological Profiles.*

COMMENT 54: Regarding the entry for the Hurtt et al. (1993) study in Table 2-1, the Reviewer commented: Correct as written, of is a space needed between CD and BR?

RESPONSE: *In Table 2-1, the strain used in the Hurtt et al. (1993) study was revised:*

(CD BR)

COMMENT 55: Regarding the entry for the Gradiski et al. (1978) study in Table 2-1, the Reviewer commented: Same comment as above.

RESPONSE: *In Table 2-1, the strain used in the Gradiski et al. (1978) study was revised: (OF1 SPF)*

COMMENT 56: In the title for Table 2-5, the Reviewer commented: I'm not aware of a way to express inhalation exposures in units of mg/kg/d

RESPONSE: *The typo in the title for Table 2-5 has been corrected:*
Table 2-1. Levels of Significant Exposure to Mixtures of cis- and trans-1,2-Dichloroethene – Inhalation (ppm)

COMMENT 57: Regarding the "Dose" column in Table 2-5, the Reviewer commented: Doses, or exposure concentrations? Units of ppm?

RESPONSE: *As noted in the Response to Comment 53, this is standard boilerplate language for the LSE table. This toxicological profile has been developed in accordance with ATSDR's Guidance for the Preparation of Toxicological Profiles.*

COMMENT 58: The Reviewer suggested the following revision (marked in red) to Section 2.7: Dow Chemical Company (1994) did not observe effects on hematocrit or hemoglobin in rats and rabbits to a mixture of 1,2-dichloroethene isomers (42% trans and 58% cis) following inhalation exposure to 1,000 ppm for 2 weeks or 6 months. No information on erythrocyte count was reported.

RESPONSE: *The suggested revision was made to Section 2.7:*
Dow Chemical Company (1994) did not observe effects on hematocrit or hemoglobin in rats and rabbits to a mixture of 1,2-dichloroethene isomers (42% trans and 58% cis) following inhalation exposure to 1,000 ppm for 2 weeks or 6 months. No information on erythrocyte count was reported.

COMMENT 59: In reference to the following statement in Section 2.9—In a case-control study of the general population (e.g., non-occupational), the risk of gallstone disease was positively associated with trans-1,2-dichloroethene levels in adipose tissue (Ji et al. 2016)—the Reviewer commented: Does 'gallstone disease" really belong in the hepatic section?

RESPONSE: *ATSDR discusses gallbladder effects in the Hepatic section of Chapter 2 (Section 2.9). This toxicological profile has been developed in accordance with ATSDR's Guidance for the Preparation of Toxicological Profiles.*

COMMENT 60: The Reviewer suggested the following revision (marked in red) to Section 2.11: In rabbits exposed for 24 hours to 170 mg/kg trans-1,2-dichloroethene ~~for 24 hours~~, mild-to-moderate erythema was observed; severe dermal irritation was observed at 5,000 mg/kg (Brock 1990).

RESPONSE: *The suggested revision was made in Section 2.11:*

In rabbits exposed for 24 hours to 170 mg/kg trans-1,2-dichloroethene, mild-to-moderate erythema was observed; severe dermal irritation was observed at 5,000 mg/kg (Brock 1990).

COMMENT 61: Regarding the reference to AFCs in Section 2.14, the Reviewer commented: I realize that the abbreviations in this paragraph were defined in the summary, but would it be appropriate to define them in this paragraph, too?

RESPONSE: *The following revision was made to Section 2.14:*

In these studies, humoral immunity was assessed by measurement of the number of spleen IgM antibody forming cells (AFCs) directed against sRBCs, serum antibody titers to sRBC, and spleen cell response to the B cell mitogen lipopolysaccharide.

COMMENT 62: The Reviewer suggested the following revision (marked in red) in Section 2.14: In the same study, a slight increase in female relative thymus weight (11%) at 90 days in the highest dose group ~~were~~ was not considered adverse given the lack of histological changes (McCauley et al. 1990, 1995).

RESPONSE: *The suggested revision was made in Section 2.14:*

In the same study, a slight increase in female relative thymus weight (11%) at 90 days in the highest dose group was not considered adverse given the lack of histological changes (McCauley et al. 1990, 1995).

COMMENT 63: Regarding the statement in Section 2.15—The reported changes consisted of a dose-related decrease in the duration of immobility in the "behavioral despair" swimming test—the Reviewer commented: If I understand this test correctly, and I believe that I do, this would not be an adverse effect; correct?

RESPONSE: *While one interpretation of a dose-related decrease in the duration of immobility of the "behavioral despair" swimming test is that 1,2-dichloroethene exhibits anti-depressive (thus non-adverse) effects, decreased time spent immobile could also be indicative of hyperactivity. Since this study did not evaluate baseline motor activity, one cannot distinguish between the two potential interpretations. Therefore, the toxicological significance of changes in the duration of swimming immobility is not known.*

COMMENT 64: Regarding the statement in Section 2.15**--**Frantik et al. (1994) studied effects of inhalation exposure to 1,2-dichloroethene on the propagation and maintenance of the electrically evoked seizure discharge in rats and mice. The isomeric composition of 1,2-dichloroethene was not reported. The concentration of 1,2-dichloroethene evoking a 30% depression in the duration of hindlimb tonic extension in rats was 1,810 ppm and in mice was 3,400 ppm—the Reviewer commented: I'm not sure that seizure discharge and hind limb tonic extension are measuring the same thing.

RESPONSE: *Duration of tonic extension and velocity of tonic extension were considered the most sensitive and reproducible responses in rats and mice, respectively. The text in Section 2.15 was revised to correct the effect measured in mice.*

The isomeric composition of 1,2-dichloroethene was not reported. The concentration of 1,2-dichloroethene evoking a 30% depression in the duration of hindlimb tonic extension in rats was 1,810 ppm and velocity of tonic extension in mice was 3,400 ppm.

COMMENT 65: The Reviewer suggested the following revision (marked in red) in Section 2.16: In addition, no histopathological changes were observed in male and female reproductive tissues.

RESPONSE: *The suggested revision was made in Section 2.16:*

In addition, no histopathological changes were observed in male and female reproductive tissues.

COMMENT 66: The Reviewer made the following comment on the Cerna and Kypenova (1977) study in Table 2-6: I am not familiar with a mouse host-mediated assay in S typhimurium; I suspect that others reading this document will similarly not understand what this assay is.

RESPONSE: *It is beyond the scope of the profile to provide an explanation of the genotoxicity tests. This toxicological profile has been developed in accordance with ATSDR's Guidance for the Preparation of Toxicological Profiles.*

COMMENT 67: The Reviewer made the following comment on Table 2-7: Strain(s) should be included for S typhimurium in in vitro genotoxicity assays.

RESPONSE: *The Salmonella strains were added to Table 2-7.*

COMMENT 68: Regarding the discussion of the Cerna and Kypenova (1977) chromosomal aberration study in Section 2.20, the Reviewer commented: How does 1/6LD50 compare to 2,000 mg/kg?

RESPONSE: *The investigator did not provide any additional information that could be used to estimate the administered dose.*

COMMENT 69: The Reviewer made the following suggested revision (marked in red) in Section 3.3: The preferred biomarkers of exposure are generally the substance itself, or substance-specific metabolites in readily obtainable body fluid(s) or excreta.

RESPONSE: *The sentence was revised as shown below.*

The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s), or excreta.

COMMENT 70: The Reviewer made the following comment in the footnote section of Table 4-1: Why no superscript b?

RESPONSE: *Table 4-1 was corrected to change* [c]Bennett 1981 to [b]Bennett 1981.

COMMENT 71: The Reviewer made the following comment on footnote a in Table 5-1: US Postal Service.

RESPONSE: *The suggested revision was made to Table 5-1:*

[a]U.S. Postal Service state abbreviations used.

COMMENT 72: The Reviewer suggested the following revision (marked in red) to the statement in Section 5.2.3—In many applications where 1,2-dichloroethene was previously used as an extraction solvent, methylene chloride is used instead, due to its higher ability to dissolve organics and its availability (Dreher et al. 2012).

RESPONSE: *The suggested revision was made in Section 5.2.3:*

In many applications where 1,2-dichloroethene was previously used as an extraction solvent, methylene chloride is used instead, due to its higher ability to dissolve organics and its availability (Dreher et al. 2012).

COMMENT 73: Regarding the text in Section 5.3, the Reviewer commented: This is a VERY long and complicated sentence; almost impossible to interpret.

RESPONSE: *This is standard text in all toxicological profiles. ATSDR will consider editing the text when it updates ATSDR's Guidance for the Preparation of Toxicological Profiles.*

COMMENT 74: The Reviewer suggested the following revision (marked in red) to Section 5.3.1: Estimated releases of 36,533 pounds (~16.6 metric tons) of 1,2-dichloroethene to the atmosphere from 19 domestic manufacturing and processing facilities in 2020~~,~~ accounted for about 96% of the estimated total environmental releases from facilities required to report to the TRI (TRI20 2021).

RESPONSE: *The TRI data were updated, and the suggested revision was made in Section 5.3.1:*

Estimated releases of 42,308 pounds (~19.2 metric tons) of 1,2-dichloroethene to the atmosphere from 20 domestic manufacturing and processing facilities in 2021 accounted for about 83% of the estimated total environmental releases from facilities required to report to the TRI (TRI21 2023).

COMMENT 75: The Reviewer made the following comment on footnote c in Table 5-2: US Postal Service.

RESPONSE: *The suggested revision was made in Table 5-2:*

[c]U.S. Postal Service state abbreviations are used.

COMMENT 76: The Reviewer made the following comment on the statement—Generally in the sub-ppb in 1 L air samples using the GC/MS operated in the full SCAN mode—in Table 5-3: Perhaps this unit is correct, as I see it used again below, but I'm not familiar with it. I suggest defining. Parts per billion by volume?

RESPONSE: *ATSDR notes that ppb is a standard unit. The term is defined in Appendix G of the profile.*

COMMENT 77: The Reviewer suggested the following revision (adding a space between al. and (1994)) to Section 5.6: Ashley et al. (1994) determined the internal dose of 32 VOCs in 600 or more people in the United States who participated in the Third National Health and Nutrition Examination Survey (NHANES III).

RESPONSE: *The suggested revision was made in Section 5.6:*

Ashley et al. (1994) determined the internal dose of 32 VOCs in 600 or more people in the United States who participated in the Third National Health and Nutrition Examination Survey (NHANES III).

COMMENT 78: The Reviewer suggested the following revision (marked in red) to Section 6.2 Bioavailability from Environmental Media: The few available toxicity studies of animals exposed to 1,2-dichloroethene support this ~~contention~~ hypothesis (Filser and Bolt 1979; Gargas et al. 1988, 1989).

RESPONSE: *The suggested revision was made in Section 6.2:*

The few available toxicity studies of animals exposed to 1,2-dichloroethene support this hypothesis (Filser and Bolt 1979; Gargas et al. 1988, 1989).

COMMENT 79: The Reviewer made the following comment in Chapter 8: Bolt reference, cited many times, is missing.

RESPONSE: *The only Bolt study cited in the profile is Filsner and Bolt (1979); a reference for this citation is included in Chapter 8.*

COMMENT 80: The Reviewer suggested the following revision (marked in red) in Appendix F: **Carcinogen—**A chemical or agent capable of inducing cancer.

RESPONSE: *The suggested revision was made in Appendix F:*

Carcinogen—A chemical or agent capable of inducing cancer.

COMMENT 81: The Reviewer suggested the following revision (marked in red) in Appendix F: Metabolism—Process in which chemical substances are biotransformed in the body that could result in less toxic and/or readily excreted compounds, or produce a biologically active intermediate.

RESPONSE: *The text in the profile is grammatically correct and no change was made to the profile to the following text in Appendix F.*

Metabolism—Process in which chemical substances are biotransformed in the body that could result in less toxic and/or readily excreted compounds or produce a biologically active intermediate.

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Comments Provided by Peer Reviewer #3

ATSDR Charge Questions and Responses and Reviewer Comments

Chapter 1

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 1: My major concern with the health effects portion of the draft is that it ignores the conclusions of the epidemiology studies performed at Camp LeJeune (Ruckart et al 2013, Bove et al 2014 and Ruckart et al 2015). In particular their were higher hazard ratios for several cancers and early onset of male breast cancer concluded from these studies. While there are other contaminants present, and the confidence intervals are wide, one cannot use these studies to conclude that there are no effects of 1,2 dichloroethene. Another major concern is the lack of using any QSAR information to determine toxic effects. Due to the lack of human and animal studies, our next best tool is quantitative structure activity relationships (QSAR). The Danish QSAR database (According to the European Chemicals Agency, ECHA) has determined that 1,2-dichloroethene is acutely toxid via the oral route. (https://qsardb.food.dtu.dk/db/index.html)

RESPONSE: *ATSDR disagrees with the Reviewer that the results of the Camp LeJeune studies were ignored. The studies reported odds ratios (ORs) greater than 1; however, the confidence intervals (CIs) included unity. Although ATSDR did not consider this to be indicative of an association, the ORs and CIs are presented in the profile to allow users to draw their own conclusions.*

ATSDR does not typically use QSAR to determine toxic effects in the toxicological profile. The scope of the profile is limited to discussions of chemical of concern. This toxicological profile has been developed in accordance with ATSDR's Guidance for the Preparation of Toxicological Profiles. Although the 1,2-dichloroethene toxicity database is somewhat small, the data were sufficient to identify critical targets and derive provisional acute-duration inhalation and intermediate-duration oral MRLs for trans-1,2-dichloroethene.

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 2: Given that we have so little information on effects in humans, I feel that the effects observed in animals are absolutely relevant.

RESPONSE: *No response needed.*

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

COMMENT 3: I only have minor concerns about some of the exposure condition statements. In particular, the statement that 1,2 dichloroethene "will rapidly be transferred in the atmosphere" is a bit misleading. First, this is not a quantitative statement. Second, calculations performed using EpiSuite (EPA's fate and transport modeling software) shows an atmospheric half-life of 98 hours. This isn't what I would consider a short-lived atmospheric contaminant.

RESPONSE: *The statement in question is regarding the ability of 1,2-dichloroethene to volatilize from water to the air compartment and is not referring to the atmospheric half-life. ATSDR changed the sentence in Section 5.4.2:*

> Since 1,2-dichloroethene is appreciably volatile, the usual assumption is that 1,2-dichloroethene introduced into surface waters will volatilize to the atmosphere.

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

The Reviewer did not provide a comment for this charge question.

QUESTION: If MRLs have been derived, do you agree with the proposed MRL values.

COMMENT 4: I agree with the lacrimation and humoral immunity MRL. The uncertainty factors of 10 for species and 10 for variability are appropriate.

RESPONSE: *No response needed.*

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

COMMENT 5: I am concerned that the report does not consider increased liver weight to be an adverse endpoint. Given this as an endpoint an MRL could be determined. Especially since there is a clear dose-dependent increase in relative liver weight.

RESPONSE: *The increase in liver weight was not considered an adverse effect because it was not associated with histopathological alterations in the liver or increases in serum liver enzymes.*

Chapter 2

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 6: I am concerned that the chapter relies too heavily on the high NOAEL's and LOAEL's for rats and ignores the much lower values in mice.

RESPONSE: *The rat and mouse data were given equal weight; ATSDR notes that the oral MRL for trans-1,2-dichloroethene was based on a mouse study.*

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 7: There is a paucity of human studies, so there isn't much the report can do.

RESPONSE: *No response needed.*

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 8: Yes, animal studies were identified.

RESPONSE: *No response needed.*

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 9: The report is limited to what is available, but as mentioned above, the mouse model seems more sensitive than the rat. Therefore, I would suggest using those data for human health implications.

RESPONSE: *The available data are inadequate to evaluate whether mice are more sensitive than rats or which species is a better model for humans. ATSDR notes that the oral MRL for trans-1,2-dichloroethene was based on a mouse study.*

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

COMMENT 10: Again, only what is available in the literature can be used.

RESPONSE: *No response needed.*

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 11: I am not aware of any other studies. This does not mean they don't exist, only my ignorance of any.

RESPONSE: *No response needed.*

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 12: I am not aware of any other studies. This does not mean they don't exist, only my ignorance of any.

RESPONSE: *No response needed.*

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 13: See comment above about mouse models.

RESPONSE: *See the Responses to Comments 6 and 9.*

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 14: I do not like the categorization. An “adverse” effect is adverse to health. While there may be some that are more serious, I’m afraid that it can cause underappreciation for an effect that does not present an obvious outcome of morbidity and mortality.

RESPONSE: *ATSDR thanks the Reviewer for the comment. This toxicological profile has been developed in accordance with ATSDR’s 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 15: It appears so.

RESPONSE: *No response needed.*

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 16: See comments about mouse model.

RESPONSE: *See the Responses to Comments 6 and 9.*

Chapter 3

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

COMMENT 17: This appears adequate.

RESPONSE: *No response needed.*

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

COMMENT 18: To the best of my knowledge they have.

RESPONSE: *No response needed.*

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 19: To the best of my knowledge there is.

RESPONSE: *No response needed.*

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 20: Not to my knowledge.

RESPONSE: *No response needed.*

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 21: The populations at higher risk of susceptibility identified in the text include children and those with diabetes. The only population that I would add would be immunocompromised given the humoral immunity effects observed.

RESPONSE: *The text in Section 3.2 was revised to include immunocompromised individuals as a potentially susceptible population:*

> Additionally, immunocompromised individuals may have increased susceptibility to 1,2-dichloroethene based on the findings of impaired immune response in mice exposed to trans-1,2-dichloroethene.

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

COMMENT 22: There are no biomarkers of Exposure identified in the text. This is puzzling given the ability to measure 1,2-dichloroethene and many of the intermediates and end products of metabolism shown in Figure 3-1.

RESPONSE: *The text in Section 3.3.1 was revised to include information on biomarkers of exposure:*

> 1,2-Dichloroethene can be measured in blood and expired air. Blood 1,2-dichloroethene levels have been used to quantify exposure in the U.S. general population (Ashley et al. 1994; CDC 2021). cis-1,2-Dichloroethene can be measured in expired air; however, its usefulness as a biomarker may be limited since a half-life of <30 minutes was estimated in a study of two volunteers (Pleil and Lindstrom 1997).

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

COMMENT 23: No biomarkers of effect have been identified.

RESPONSE: *No response 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 24: I would argue that the studies of Camp LeJeune are health effects studies that include associated contaminants.

RESPONSE: *The statement in Section 3.4 was revised to indicate that there are a lack of studies examining possible interactions between 1,2-dichloroethene and other chemicals:*

> No studies were located regarding possible interactions between 1,2-dichloroethene and other chemicals that are likely to be found with 1,2-dichloroethene in the environment, workplace, or at hazardous waste sites.

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 25: While there are studies involving mixtures as mentioned above, the exact interaction of those chemicals may not be known.

RESPONSE: *See the Response to Comment 24.*

Chapter 4

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 26: The only comment I have is regarding the melting point. The several values given are confusing. The Chemical Abstract Services gives the melting points of cis and trans 1,2-dichloroethene as -80 and -49.8° C. respectively.

RESPONSE: *Different sources report different melting points. To avoid confusion, the table was revised to only report one value for each compound.*

Melting point	-80.0°C	-49.8°C	NLM 2022a, 2022b

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

COMMENT 27: It can be inferred from the text that it is present as a liquid and a gas at room temperature given its very high vapor pressure, but the only form stated in the table is liquid.

RESPONSE: *1,2-Dichloroethene is considered a liquid at room temperature.*

Chapter 5

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

COMMENT 28: This chapter appears quite complete.

RESPONSE: *No response needed.*

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 29: Yes, it has.

RESPONSE: *No response needed.*

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 30: Yes, it does.

RESPONSE: *No response needed.*

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 31: I am satisfied with the information provided. It follows conventional units and media examined.

RESPONSE: *No response needed.*

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 32: Yes, in particular the shower modeling is quite extensive.

RESPONSE: *No response needed.*

Chapter 6

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

COMMENT 33: I am not aware of any other studies that haven't been included.

RESPONSE: *No response needed.*

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

COMMENT 34: I do agree with the identified needs.

RESPONSE: *No response needed.*

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

COMMENT 35: I felt that this chapter had much less judgement than other chapters. I was satisfied with a lack of bias.

RESPONSE: *No response needed.*

Chapter 7

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

COMMENT 36: While I couldn't find the exact regulation, REACH severely limits its use. Addditionally REACH has identified it as a known carcinogen.

RESPONSE: *With few exceptions (International Agency for Research on Cancer [IARC] cancer classification and World Health Organization [WHO] air and water quality guidelines), Table 7-1 is limited to U.S. regulations and guidelines. This toxicological profile has been developed in accordance with ATSDR's Guidance for the Preparation of Toxicological Profiles.*

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

COMMENT 37: Not that I am aware of.

RESPONSE: *No response needed.*

Review of Unpublished Studies

ATSDR thanks the Reviewer for the comments on the unpublished studies.

E.I. DuPont De Nemours & Co. (1988). Eye irritation test in rabbits of trans-1,2-dichloroethylene with cover letter dated 05/10/94 (sanitized), Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. (cited in the toxicological profile as DuPont 1988c)

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

COMMENT 38: I'm not sure what the animal use protocols were in 1988, nor today for ocular exposure, but two rabbits does not seem like a large number. Especially given that the washed eye showed corneal damage, but the unwashed eye did not. One would expect greater damage to an eye that wasn't washed (flushed with water). More rabbits could have determined if the washing was a significant contributing factor.

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

COMMENT 39: Death was not an endpoint.

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

COMMENT 40: There was only one dose group. Given the solubility of 1,2-dichloroethene different doses could have been used by diluting the amount administered.

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

COMMENT 41: Given the adverse outcome, I don't think design negates the utility.

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

COMMENT 42: I would agree that getting 1,2-dichloroethene in ones eye would be a severe eye irritant.

DuPont (1998). trans-1,2-Dichloroethylene: 90-day inhalation toxicity study in rats, E.I. du Pont de Nemours and Company, 110-467.

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

COMMENT 43: The study used OECD protocols, so I assume that includes good animal care. It appears that an adequate number of animals was used to given sufficient power to the study.

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

COMMENT 44: Death was not an endpoint.

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

COMMENT 45: Four levels of exposure were used. Given that some historical air concentrations were around two orders of magnitude lower, and the lack of any adverse outcome, I would have like to see higher exposure doses.

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

COMMENT 46: I think giving the highest exposure level the NOAEL is sufficient to be protective when considering a safety factor of 100 used by ATSDR.

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

COMMENT 47: I disagree that the decreased mean WBC and lymphocytes was not toxicologically important. The argument is that "causal relationship between treatment and leukocytic alteration is equivocal". How can this statement be made from a study showing causal association between treatment and effect? I also have an issue with the conclusion that decreases in liver enzymes are not indicitave of liver disfunction. Why couldn't a lower enzyme count in the liver indicate the inactivation of this mechanism of detoxification? There seem to be a lot of effects that the authors try and explain away as not toxicologically relevant by just saying that they are not relevant.

RESPONSE: *ATSDR notes that it considered the investigators comments on the relevance of observed effects. In agreement with study authors, ATSDR considers the toxicological significance of changes in white blood cells and lymphocytes to be uncertain due to the small magnitude of change. In addition, ATSDR does not consider a decrease in liver enzymes to be adverse. This toxicological profile has been developed in accordance with ATSDR's Guidance for the Preparation of Toxicological Profiles.*

Dow Chemical Company (1994). The toxicity of 1,2-dichloroethylene as determined by repeated exposures on laboratory animals, with cover letter dated 05/10/94 (sanitized), Dow Chemical Company. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D.

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

COMMENT 48: The study states that statistics were not performed because of the small number of animals. While, I may disagree that statistics could be performed, it would indicate that a larger number of animals may be warranted.

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

COMMENT 49: Death was not an endpoint.

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

COMMENT 50: Only two exposure levels were used. No dose-response curve is possible with only two doses.

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

COMMENT 51: I don't think it completely negates the utility of the study.

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

COMMENT 52: I agree that increased kidney and liver weights are negative outcomes of this study. The other non-effects are also significant.

Dow Chemical Company (1960). Results of range finding toxicological tests on 1,2-dichloroethylene, mixed isomers, with cover letter dated 05/10/94 (sanitized), Dow Chemical Company. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D.

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

COMMENT 53: It's not clear how many rabbits were exposed, and only 2 rats being treated orally is not sufficient, but 9 rats per treatment group is adequate.

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

COMMENT 54: It does not, but given the
ATSDR notes that the Reviewer did not complete the sentence.

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

COMMENT 55: Only the inhalation study appeared to have adequate number of dose groups.

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

COMMENT 56: This study appears to contradict the DuPont study that observed acute eye irritation. It's not clear how the study determined eye pain by the rabbits.

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

COMMENT 57: It's not clear on what the study concludes that no toxic amount of 1,2-dichloroethene is absorbed through the skin. I'm not sure how the study could conclude that there is no inhalation risk when they observed such acute effects in rats. It's also not clear that kidney injury being observed in the two rats exposed was used to conclude that there is "low acute oral toxicity and should present no problem from ingestion."

Annotated Comments on the Toxicological Profile

COMMENT 58: Regarding the following statement in Section 1.1-- When 1,2-dichloroethane is released to the environment, most will quickly end up as a gas in the atmosphere--the Reviewer commented: dichloroethane.

RESPONSE: *The typo in Section 1.1 was corrected:*

When 1,2-dichloroethene is released to the environment, most will quickly end up as a gas in the atmosphere.

COMMENT 59: Regarding the following statement in Section 1.1-- Once in the atmosphere, it will break down rapidly by reactions with substances in the air—the Reviewer commented: EPI Suite shows a half life of 98 hours.

RESPONSE: *ATSDR has removed rapidly from this statement in Section 1.1:*

Once in the atmosphere, it will break down by reactions with substances in the air.

COMMENT 60: Regarding the following statement in Section 1.1-- When released to moist soil surfaces or to lakes, rivers, and other bodies of water, most of it evaporates into the air, with small amounts entering groundwater—the Reviewer commented: EPI Suite calculations show less than half ending up in air. Most stays in soil.

RESPONSE: *If advection is turned off as is common for global modeling the level III model indicates over 80% partitions to the air compartment. In default mode only about 30% remains in the air compartment because advection is the primary removal process for this chemical in this model environment. ATSDR has reworded these sentences in Section 1.1:*

When released to lakes, rivers, and other bodies of water, most of it evaporates into the air. When released to soil, it also volatilizes to air but its high leachability indicates that it may migrate to groundwater.

COMMENT 61: Regarding the following statement in Section 1.1-- Based on the high measured vapor pressure and low estimated Henry's law constant, volatilization of 1,2-dichloroethene from water is expected to be an important fate process. —the Reviewer commented: low Henry's Law constant would indicate less volatilization

RESPONSE: *This is a typographical error; the Henry's law constant is large for 1,2-dichloroethene. The text in Section 1.1 was revised:*

Based on the high measured vapor pressure and large estimated Henry's law constant, volatilization of 1,2-dichloroethene from water is expected to be an important fate process.

COMMENT 62: Regarding the following statement in Section 1.1**--** Since 1,2-dichloroethane is a volatile liquid at room temperature, the most likely route of exposure would be from breathing air containing 1,2-dichloroethene—the Reviewer commented: dichloroethene

RESPONSE: *The typo in the referenced statement in Section 1.1 was corrected:*

Since 1,2-dichloroethene is a volatile liquid at room temperature, the most likely route of exposure would be from breathing air containing 1,2-dichloroethene.

COMMENT 63: Regarding the following statement in Section 1.2**--** Other effects observed in laboratory animals exposed to trans-1,2-dichloroethene are summarized below, although these effects to not appear to be sensitive targets—the Reviewer commented: do

RESPONSE: *The referenced sentence in Section 1.2 was corrected.*

Other effects observed in laboratory animals exposed to trans-1,2-dichloroethene are summarized below, although these effects do not appear to be sensitive targets.

COMMENT 64: Regarding the following statement in Section 1.2**--**Conflicting results have been observed regarding decreased body weight and body weight gain. Maternal body weight gain was reduced in pregnant rats exposed 12,000 ppm trans-1,2-dichloroethene during gestation (Hurtt et al. 1993), although body weight was similar to controls at the end of pregnancy—the Reviewer commented: exposed to 12,000

RESPONSE: *The referenced sentence in Section 1.2 was revised:*

Maternal body weight gain was reduced in pregnant rats exposed via inhalation to 12,000 ppm trans-1,2-dichloroethene during gestation (Hurtt et al. 1993), although body weight was similar to controls at the end of pregnancy.

COMMENT 65: Regarding the first several paragraphs in Section 2.1, the Reviewer commented: is there a reason these paragraphs are bolded?

RESPONSE: *These paragraphs are bolded in the draft toxicological profiles to indicate that they are boilerplate text. The bolding will be removed in the final profile. This toxicological profile has been developed in accordance with ATSDR's Guidance for the Preparation of Toxicological Profiles.*

COMMENT 66: Regarding the following statement in Section 2.1-- These data are discussed in terms of route of exposure (inhalation, oral, and dermal) and three exposure periods: acute (≤14 days), intermediate (15–364 days), and chronic (≥365 days)—the Reviewer commented: why not eye irritation from vapor? since lacrimation is a major endpoint for animal studies.

RESPONSE: *Ocular irritation due to direct contact with 1,2-dichloroethene vapor is discussed under dermal exposure.*

COMMENT 67: Regarding the following statement in Section 2.1-- Studies on the toxicity of cis-1,2-dichloroethene are limited two studies in rats: one study evaluating acute-duration lethality following a single dose inhalation exposure; and an oral exposure study evaluating comprehensive toxicological

endpoints in animals exposed for acute- and intermediate-durations—the Reviewer commented: limited to two

RESPONSE: *The suggested revision was made in Section 2.1:*

Studies on the toxicity of cis-1,2-dichloroethene are limited to two studies in rats: one study evaluating acute-duration lethality following a single dose inhalation exposure; and an oral exposure study evaluating comprehensive toxicological endpoints in animals exposed for acute- and intermediate-durations.

COMMENT 68: Regarding the following statement in Section 2.2-- For oral exposure, an of LD_{50} values of 9.932 mg/kg was determined in rats (Hayes et al. 1987)—the Reviewer commented: edit

RESPONSE: *The referenced statement was revised:*

For oral exposure, an of LD_{50} value of 9.932 mg/kg was determined in rats (Hayes et al. 1987).

COMMENT 69: Regarding the following statement in Section 2.2--An acute lethality study in male and female rats reported an LC_{50} value of 13,700 ppm for cis-1,2-dichloroethene (DuPont 1999)— the Reviewer commented: what mode of exposure?

RESPONSE*: The referenced statement in Section 2.2 was deleted from the profile.*

COMMENT 70: Regarding the following statement in Section 2.2--Information on lethality of mixed cis- and trans-1,2-dichloroethane in laboratory animals is available for acute- and intermediate-duration inhalation exposures and acute-duration oral exposure.— the Reviewer commented: dichloroethene

RESPONSE: *The typo in Section 2.2 was corrected:*

Information on lethality of mixed cis- and trans-1,2-dichloroethene in laboratory animals is available for acute- and intermediate-duration inhalation exposures and acute-duration oral exposure.

COMMENT 71: Regarding the following statement in Section 2.3-- The decrease in body weight gain at 12,000 ppm was accompanied by 16% decrease food intake during the exposure period, which was most likely secondary to 1,2-dichloroethene-induced narcosis— the Reviewer commented: decreased

RESPONSE: *The referenced sentence in Section 2.3 was corrected:*

The decrease in body weight gain at 12,000 ppm was accompanied by 16% decreased food intake during the exposure period, which was most likely secondary to 1,2-dichloroethene-induced narcosis.

COMMENT 72: Regarding the following statement in Section 2.3—Body weight loss was observed following a single 24-hour dermal exposure of rabbits to 5,000 mg/kg trans-1,2-dichloroethane (Brock 1990)— the Reviewer commented: dichloroethene

RESPONSE: *The typo in Section 2.3 was corrected:*

Body weight loss was observed following a single 24-hour dermal exposure of rabbits to 5,000 mg/kg trans-1,2-dichloroethene (Brock 1990).

COMMENT 73: Regarding the following statement in Section 2.4—The Freundt et al. (1977) study had several weaknesses: pulmonary capillary hyperemia and alveolar septal distention was observed in some control rats—the Reviewer commented: be quantitative

RESPONSE: *The referenced statement in Section 2.4 was revised:*

The Freundt et al. (1977) study had several weaknesses: pulmonary capillary hyperemia and alveolar septal distention was observed in some control rats (0, 17, or 33% in the different control groups)…

COMMENT 74: Regarding the following statement in Section 2.6—No gastrointestinal effects were noted in rats exposed by gavage to 1,900 mg/kg/day cis-1,2-dichloroethene for 14 days or 870 mg/kg/day cis-1,2-dichloroethene for 90 days based on histopathology (McCauley et al. 1990, 1995)—the Reviewer commented: were they looked for?

RESPONSE: *The study included histopathological examination of the stomach, small intestines, and large intestines.*

COMMENT 75: Regarding the following statement in Section 2.7—The toxicological significance of this finding is uncertain due to the small magnitude of change—the Reviewer commented: what reference is used to determine that this is a "small" magnitude of change?

RESPONSE: *ATSDR used scientific judgement in evaluating the adversity of the 26% change in lymphocyte levels. This toxicological profile has been developed in accordance with ATSDR's Guidance for the Preparation of Toxicological Profiles.*

COMMENT 76: Regarding the following statement in Section 2.9—The increases did not exhibit dose-dependences and no changes were observed for other serum liver enzymes (lactate dehydrogenase, ALT, and AST)—the Reviewer commented: what does this mean? Was it that there were only changes at one dose, or was the dose response relationship not able to put to a trend line?

RESPONSE: *As noted in the sentence prior to the referenced statement, the increased alkaline phosphatase (AP) level was higher at 175 mg/kg/day as compared to the level in the 387 mg/kg/day group.*

COMMENT 77: Regarding the following statement in Section 2.9—Therefore, the small increases in serum AP activity are not considered toxicologically significant—the Reviewer commented: those don't seem like small increases to me.

RESPONSE: *The referenced statement in Section 2.9 was revised:*

Therefore, the increases in serum AP activity are not considered toxicologically significant.

COMMENT 78: Regarding the following statement in Section 2.9—The toxicological significance of this transient effect is not established—the Reviewer commented: why is liver weight not considered toxicologically significant?

RESPONSE: *The referenced statement is not referring to the increased liver weight; rather, it is referring to the increased blood cholesterol level. As noted earlier in this paragraph, the increased liver*

weight was considered uncertain because histological alterations in the liver and/or alterations in serum enzymes were not observed.

COMMENT 79: Regarding the following statement in Section 2.15—However, an analysis conducted by ATSDR for this document shows that the incidence in treatment groups is not statistically compared to controls—the Reviewer commented: statistically significant?

RESPONSE: *There referenced statement in Section 2.14 was revised:*

> However, an analysis conducted by ATSDR for this document shows that the incidence in treatment groups is not statistically significant compared to controls.

COMMENT 80: Regarding the following statement in Section 2.14—Suppression in humoral immunity in male mice, as measured by reductions in spleen AFCs directed against sRBCs, was observed at all doses tested; decreases were 26, 26, and 36% at doses of 17, 175, and 387 mg/kg/day, respectively—the Reviewer commented: why is this not used for NOAEL or LOAEL then?

RESPONSE: *When the humoral response to sheep red blood cells (sRBC) was measured as AFCs/spleen, the decreased response was statistically significant at 17, 175, and 387 mg/kg/day; when expressed as AFCs/10^6 spleen cells, the difference was statistically significant at 175 and 387 mg/kg/day. Because the spleen weights were variable across groups, ATSDR favored expressing the response in AFCs/10^6 spleen cells units. The text in Section 2.14 was revised:*

> Suppression in humoral immunity in male mice, as measured by reductions in spleen AFCs directed against sRBCs, was observed at 175 and 387 mg/kg/day when expressed as AFC/10^6 spleen cells; the magnitude of the decrease was 26% in both groups.

COMMENT 81: Regarding the following statement in Section 2.15—however, due to the lack of incidence data, reliable NOAEL and LOAEL values could not be identified. Hayes et al. (1987) observed clinical signs of neurotoxicity, including central nervous system depression, ataxia, and depressed respiration, at all doses (not reported), with dose-dependent severity. Barnes et al. (1985) observed decreased activity, ataxia, and suppressed or total lack of righting reflex in rats following at doses of 1,600–3500 mg/kg—the Reviewer commented: The statement in the first sentence seems to be contradicted by the next two sentences, no?

RESPONSE: *Barnes et al. (1985) and Hayes et al. (1987) reported clinical signs of neurotoxicity in acute lethality studies; these effects are listed in the last two sentences of the referenced text. However, NOAEL and LOAEL values cannot be identified from these studies because incidence data were not reported.*

COMMENT 82: Regarding the following statement in Section 2.15— However, incidence data were not reported; therefore, NOAEL and LOAEL values could not be identified. —the Reviewer commented: then it seems to me the study data needs to be obtained from DuPont since they must have recorded the incidence.

RESPONSE: *The referenced statement is referring to the McCauley et al. (1990) study, not the DuPont (1999) study. ATSDR attempted to contact the investigators to request incidence data for the neurological signs. No contact information was provided in the unpublished paper (McCauley et al. 1990) or in the published version of the study (McCauley et al. 1995). ATSDR was able to locate an EPA*

email address for F.B. Daniel, the corresponding author. A message sent to this email address was returned undeliverable. Thus, ATSDR is unable to attain the incidence data for this study.

COMMENT 83: Regarding the following statement in Section 2.15— The concentration of 1,2-dichloroethene evoking a 30% depression in the duration of hindlimb tonic extension in rats was 1,810 ppm and in mice was 3,400 ppm—the Reviewer commented: why is this not reflected in Figure 1-1?

RESPONSE: *Figure 1-1 presents the health effects resulting from inhalation exposure to trans-1,2-dichloroethene. The results of the Frantik et al. (1994) were not included in that figure because the investigators did not provide information on the isomeric composition of the test substance.*

COMMENT 84: : Regarding the following statement in Section 2.19— A case-control study evaluating of children born to mothers exposed during pregnancy to trans-1,2-dichloroethene in drinking water at Marine Corps Base Camp Lejeune in North Carolina did not associations between exposure and childhood cancer (Ruckart et al. 2013).—the Reviewer commented: edit

RESPONSE: *The referenced text was revised:*

> A case-control study evaluating of children born to mothers exposed during pregnancy to trans-1,2-dichloroethene in drinking water at Marine Corps Base Camp Lejeune in North Carolina did not find associations between exposure and childhood cancer (Ruckart et al. 2013).

COMMENT 85: Regarding the following statement in Section 2.19— The study population consisted of 444 males, with 71 cases of breast cancer—the Reviewer commented: in fact, the Ruckart et al paper suggests that there are possible associations between exposures and male breast cancer.

RESPONSE: *Although the adjusted ORs were >1 for breast cancer in the high monthly 1,2-dichloroethene exposure and high cumulative 1,2-dichloroethene exposure groups, the 95% CIs included unity and were therefore not considered a significant finding.*

COMMENT 86: Regarding the following statement in Section 2.20— Reports on the genotoxic effects of cis-1,2-dichlorethene have been inconsistent. Repeated i.p. injections of cis-1,2-dichloroethene (1/6 LD_{50}) produced chromosomal aberrations in mouse bone marrow cells (Cerna and Kypenova 1977), whereas a single i.p. injection up to 2,000 mg/kg did not result in an increase in chromosomal aberrations or sister chromatid exchanges in mouse bone marrow (NTP 2002)—the Reviewer commented: use the same units to compare. It seems that 1/6 of the LD50 is pretty low and for a chronic exposure this would be significant.

RESPONSE: *ATSDR was unable to report the dose for the Cerna and Kypenova (1977) study because the investigators did not report the actual administered dose or the LD_{50} value used.*

COMMENT 87: Regarding the following statement in Section 2.20— However, in Chinese ovary cells, an increase in sister chromatid exchanges was observed following exposure to a mixture of cis- and trans-1,2-dichloroethene, although chromosomal aberrations were not increased (NTP 2002)—the Reviewer commented: Chinese hamster?

RESPONSE: *The suggested revision was made:*

However, in Chinese hamster ovary cells, an increase in sister chromatid exchanges was observed following exposure to a mixture of cis- and trans-1,2-dichloroethene, although chromosomal aberrations were not increased (NTP 2002).

COMMENT 88: Regarding the following statement in Section 3.1.1— The rate for the lower phase is dose-dependent consistent with saturable metabolism and inhibition of metabolism (Clewell and Andersen 1994; Lilly et al. 1998)—the Reviewer commented: slower?

RESPONSE: *The suggested revision was made:*

The rate for the slower phase is dose-dependent, consistent with saturable metabolism and inhibition of metabolism (Clewell and Andersen 1994; Lilly et al. 1998).

COMMENT 89: Regarding the following statement in Section 3.1.3— Dichlorination of dichloroacetate is catalyzed by glutathione S-transferase (Costa and Ivanetich 1982)—the Reviewer commented: dechlorination?

RESPONSE: *The suggested revision was made:*

Dechlorination of dichloroacetate is catalyzed by glutathione S-transferase (Costa and Ivanetich 1982).

COMMENT 90: Regarding the following statement in Section 3.1.3—The rate of the elimination phase is dose-dependent; first-order at low exposure concentrations and zero-order and higher "saturating" concentrations (e.g., 1,000 pp) (Filser and Bolt 1979)—the Reviewer commented: at?

RESPONSE: *The suggested revision was made:*

The rate of the elimination phase is dose-dependent; first-order at low exposure concentrations and zero-order and higher at "saturating" concentrations (e.g., 1,000 pp) (Filser and Bolt 1979).

COMMENT 91: The Reviewer questioned why the introductory text in Section 3.1.5 was bolded.

RESPONSE: *The text is bolded in the draft toxicological profile to indicate that it is boilerplate text. The bolding will be removed in the final version of the profile. This toxicological profile has been developed in accordance with ATSDR's Guidance for the Preparation of Toxicological Profiles.*

COMMENT 92: Regarding the following statement in Section 3.1.5—At steady state, the multi-compartment model reduced to parameters representing alveolar ventilation, cardiac output, liver blood flow, blood:air partition coefficient, liver:blood partition coefficient, and first order metabolism clearance coefficients (V_{max}/K_M)—the Reviewer commented: was reduced to?

RESPONSE: *The suggested revision was made:*

At steady state, the multi-compartment model was reduced to parameters representing alveolar ventilation, cardiac output, liver blood flow, blood:air partition coefficient, liver:blood partition coefficient, and first order metabolism clearance coefficients (V_{max}/K_M).

COMMENT 93: The Reviewer questioned why the introductory text in Section 3.2 was bolded.

RESPONSE: *The text is bolded in the draft toxicological profile to indicate that it is boilerplate text. The bolding will be removed in the final version of the profile. This toxicological profile has been developed in accordance with ATSDR's Guidance for the Preparation of Toxicological Profiles.*

COMMENT 94: Regarding the following statement in Section 3.2— No increase in the risk of birth defects (neural tube defect or oral cleft defects) or childhood hematopoietic cancers were observed in an epidemiological study in children born to women exposed to 1,2-dichlorethane in their drinking water during pregnancy (Ruckart et al. 2013) —the Reviewer commented: This reference does suggest an association between exposure and neural tube defect.

RESPONSE: *The Ruckart et al. (2013) study did not find an association for neural tube defects; the OR was 1.1 (95% CIs of 0.4, 3.1; p=0.85).*

COMMENT 95: The Reviewer questioned why the introductory text in Section 3.3 was bolded.

RESPONSE: *The text is bolded in the draft toxicological profile to indicate that it is boilerplate text. The bolding will be removed in the final version of the profile. This toxicological profile has been developed in accordance with ATSDR's Guidance for the Preparation of Toxicological Profiles.*

COMMENT 96: Regarding the following statement in Section 3.4—No studies were located regarding the health effects in humans or animals exposed to 1,2-dichloroethene in combination with other chemicals that are likely to be found with 1,2-dichloroethene in the environment, workplace, or at hazardous waste sites—the Reviewer commented: I would argue that the various studies of Camp LeJeune are health effects studies of exposure to 1,2-dichloroethene and other related chemicals.

RESPONSE: *This is statement in Section 3.4 was revised to indicate the lack of studies examining possible interactions between 1,2-dichloroethene and other chemicals:*

> No studies were located regarding possible interactions between 1,2-dichloroethene and other chemicals that are likely to be found with 1,2-dichloroethene in the environment, workplace, or at hazardous waste sites.

COMMENT 97: Regarding the following statement in Section 3.4— In an *in vitro* study, rat pancreatic tumor cells exposed to trans-1,2-dichloroethane alone or in combination with ethanol did not affect cell proliferation, viability, or fatty acid ethyl ester production of the cells (Bhopale et al. 2014)—the Reviewer commented: dichloroethene

RESPONSE: *The typo in Section 3.4 was revised:*

> In an *in vitro* study, rat pancreatic tumor cells exposed to trans-1,2-dichloroethene alone or in combination with ethanol did not affect cell proliferation, viability, or fatty acid ethyl ester production of the cells (Bhopale et al. 2014).

COMMENT 98: The Reviewer made the following comment on the melting point row in Table 4-2: melting points of organic molecules are quite specific. Why are there two values? Chemical Abstract Services give the cis and trans melting points as -80 and -49.8, respectively.

RESPONSE: *Different sources report different melting points. To avoid confusion, the table was revised to only report one value for each compound.*

Melting point	-80.0°C	-49.8°C	NLM 2022a, 2022b

COMMENT 99: The Reviewer questioned why the introductory text in Section 5.1 was bolded.

RESPONSE: *The text is bolded in the draft toxicological profile to indicate that it is boilerplate text. The bolding will be removed in the final version of the profile. This toxicological profile has been developed in accordance with ATSDR's Guidance for the Preparation of Toxicological Profiles.*

COMMENT 100: Regarding the following statement in Section 5.2.4— Improved waste water treatment methods at publicly owned treatment works (POTWs) use air stripping processes to remove most 1,2-dichloroethene and other VOCs from final effluents and deposit them in sludges or release them in air emissions (Bennett 1989)—the Reviewer commented: many POTWs do NOT use air strippers and doubtful you'd have them in sludge. Byrns 2001 shows model output predicting 0.02% in sludge. 95% dissolved and 4.5% volatilizing.

RESPONSE: *The Byrns (2001) reference discusses a conceptual model that is based upon a twin reactor system with the primary stage comprised of gravity separation and a secondary stage that contains air-stripping. In the primary stage, the model predicts 0.02% in sludge, 95% dissolved, and 4.5% volatilizing; however, the model predicts over 91% volatilization from the secondary stage containing air stripping processes. ATSDR has revised the statement in Section 5.2.4:*

> Improved wastewater treatment methods at publicly owned treatment works (POTWs) that employ air stripping processes will remove most 1,2-dichloroethene and other VOCs from final effluents and release them in air emissions (Bennett 1989).

COMMENT 101: The Reviewer questioned why the introductory text in Sections 5.3, 5.3.1, and 5.3.2 was bolded.

RESPONSE: *The text is bolded in the draft toxicological profile to indicate that it is boilerplate text. The bolding will be removed in the final version of the profile. This toxicological profile has been developed in accordance with ATSDR's Guidance for the Preparation of Toxicological Profiles.*

COMMENT 102: Regarding the following statement in Section 5.3.2— 1,2-Dichloroethene is a deductive dehalogenation degradation product of TCE and PCE (cis-1,2-dichloroethene is most commonly the main degradation product)—the Reviewer commented: reductive?

RESPONSE: *The suggested revision was made to Section 5.3.2:*

> 1,2-Dichloroethene is a reductive dehalogenation degradation product of TCE and PCE (cis-1,2-dichloroethene is most commonly the main degradation product) and, as a consequence, can be released to water or soil where there is contamination with these solvents (U.S. Army 2018).

COMMENT 103: The Reviewer questioned why the introductory text in Section 5.3.3 was bolded.

RESPONSE: *The text is bolded in the draft toxicological profile to indicate that it is boilerplate text. The bolding will be removed in the final version of the profile. This toxicological profile has been developed in accordance with ATSDR's Guidance for the Preparation of Toxicological Profiles.*

COMMENT 104: Regarding the following statement in Section 5.4.1— Experiments have shown that the degradation of t trans-1,2-dichloroethene is relatively slow due to ultraviolet irradiation, unless lamps of approximately 15–20 watts are used (Gürtler et al. 1994)—the Reviewer commented: delete "t"

RESPONSE: *The suggested revision was made in Section 5.4.1:*

Experiments have shown that the degradation of trans-1,2-dichloroethene is relatively slow due to ultraviolet irradiation, unless lamps of approximately 15–20 watts are used (Gürtler et al. 1994).

COMMENT 105: Regarding the following statement in Section 5.4.1—After a period of restrained degradation, sudden decomposition is observed, probably resulting from the start of a chain mechanism—the Reviewer commented: what is meant by "restrained" degradation?

RESPONSE: *ATSDR has removed this paragraph from Section 5.4.1. The study was conducted using irradiation energies below the environmental ultraviolet (UV) spectrum and thus it is not highly relevant to the fate of 1,2-dichloroethene under environmental conditions.*

COMMENT 106: The Reviewer questioned why the introductory text in Section 5.5 was bolded.

RESPONSE: *The text is bolded in the draft toxicological profile to indicate that it is boilerplate text. The bolding will be removed in the final version of the profile. This toxicological profile has been developed in accordance with ATSDR's Guidance for the Preparation of Toxicological Profiles.*

COMMENT 107: Regarding the following statement in Section 5.5.1— 1,2-Dichloroethane is a pollutant monitored for in the national Air Quality System (AQS) database which contains ambient air pollution data collected by EPA, state, local, and tribal air pollution control agencies from thousands of monitoring stations throughout the country—the Reviewer commented: dichloroethene

RESPONSE: *The typo in Section 5.5.1 was corrected:*

1,2-Dichloroethene is a pollutant monitored for in the national Air Quality System (AQS) database which contains ambient air pollution data collected by EPA, state, local, and tribal air pollution control agencies from thousands of monitoring stations throughout the country.

COMMENT 108: Regarding the following statement in Section 5.6— Ashley et al.(1994) determined the internal dose of 32 VOCs in 600 or more people in the United States who participated in the Third National Health and Nutrition Examination Survey (NHANES III). Detectable concentrations of cis- and trans-1,2-dichloroethene were found in <10% of the samples examined. —the Reviewer commented: since NHANES also does food, it might be appropriate to be specific and call these blood samples

RESPONSE: *The suggested revision was made in Section 5.6:*

Ashley et al. (1994) determined the internal dose of 32 VOCs in 600 or more people in the United States who participated in the Third National Health and Nutrition Examination Survey (NHANES

III). Detectable concentrations of cis- and trans-1,2-dichloroethene were found in <10% of the blood samples examined.

COMMENT 109: The Reviewer questioned why the introductory text in the introduction to Chapter 6 and Sections 6.1, and 6.2 were bolded.

RESPONSE: *The text is bolded in the draft toxicological profile to indicate that it is boilerplate text. The bolding will be removed in the final version of the profile. This toxicological profile has been developed in accordance with ATSDR's Guidance for the Preparation of Toxicological Profiles.*

COMMENT 110: Regarding the following statement in Section 6.2— Few studies have evaluated potential health effects intermediate-duration inhalation exposure, and the only reliable study did not identify adverse effects at the highest exposure concentration tested (4,000 ppm). —the Reviewer commented: effects of intermediate

RESPONSE: *The suggested revision was made in Section 6.2:*

Few studies have evaluated potential health effects of intermediate-duration inhalation exposure, and the only reliable study did not identify adverse effects at the highest exposure concentration tested (4,000 ppm).

COMMENT 111: Regarding the following statement in Section 6.2— Only one studies evaluating developmental effects of trans-1,2-dichhloroethene was identified, and no studies evaluating developmental effects of cis-1,2-dichloroethene were located—the Reviewer commented: study

RESPONSE: *The suggested revision was made in Section 6.2:*

Only one study evaluating developmental effects of trans-1,2-dichhloroethene was identified, and no studies evaluating developmental effects of cis-1,2-dichloroethene were located.

COMMENT 112: Regarding the reference for the Sanhueza et al. 1975b study in Chapter 8, the Reviewer commented: dichloroethene

RESPONSE: *The reference was corrected:*

Sanhueza E, Heicklen J. 1975b. Oxidation of cis- and trans-CHClCHCl. Int J Chem Kinet 7:589-604.

COMMENT 113: The Reviewer questioned why the introductory text in the introduction to Appendix A was bolded.

RESPONSE: *The text is bolded in the draft toxicological profile to indicate that it is boilerplate text. The bolding will be removed in the final version of the profile. This toxicological profile has been developed in accordance with ATSDR's Guidance for the Preparation of Toxicological Profiles.*