DISPOSITION OF PEER REVIEW COMMENTS FOR TOXICOLOGICAL PROFILE FOR CHLOROETHANE

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

December 2023

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

David Williams, Ph.D.
University Distinguished Professor
Department of Environmental and Molecular Toxicology
Oregon State University
Corvallis, Oregon

Robert Herrick, Sc.D.
Harvard School of Public Health
Department of Environmental Health
Boston, Massachusetts

Edward Levin, Ph.D.
Professor
Duke University
Durham, North Carolina

Comments provided by Reviewer #1

ATSDR Charge Questions and Responses and Reviewer Comments

GENERAL COMMENTS

COMMENT 1: Overall this is a well written and edited document.

RESPONSE: *ATSDR appreciates the comment from the Reviewer.*

Chapter 1. Relevance to Public Health

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

COMMENT 2: Yes. Adequate details are provided.

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 3: Yes. Particularly those which are relevant routes for human exposure

RESPONSE: *No response needed.*

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

COMMENT 4: Yes. Agree.

RESPONSE: *No response needed.*

Minimal Risk Levels (MRLs)

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

COMMENT 5: Yes.

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 6: Agree.

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 7: Agree.

RESPONSE: *No response needed.*

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

COMMENT 8: No comments.

RESPONSE: *No response needed.*

Chapter 2. Health Effects

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

COMMENT 9: 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 10: No changes are suggested.

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 11: Yes, looks adequate.

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 12: Yes.

RESPONSE: *No response needed.*

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

COMMENT 13: Yes.

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 14: 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 15: 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 16: No changes are suggested.

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 17: 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 18: 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 19: Yes.

RESPONSE: *No response needed.*

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

Toxicokinetics

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

COMMENT 20: Yes.

RESPONSE: *No response needed.*

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

COMMENT 21: 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 22: Yes.

RESPONSE: *No response needed.*

Children and Other Populations that are Unusually Susceptible

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

COMMENT 23: 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 24: Yes, No additional reference suggested.

RESPONSE: *No response needed.*

Biomarkers of Exposure and Effect

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

COMMENT 25: Yes, GSH conjugates and its derivatives.

RESPONSE: *No response needed.*

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

COMMENT 26: Symptoms and limitations are already explained.

RESPONSE: *No response needed.*

Interactions with Other Chemicals

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

COMMENT 27: As stated on page 75, line 22. No such studies are available.

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 28: No such studies are described in the literature.

RESPONSE: *No response needed.*

Chapter 4. Chemical and Physical Information

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

COMMENT 29: No.

RESPONSE: *No response needed.*

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

COMMENT 30: Not applicable.

RESPONSE: *No response needed.*

Chapter 5. Potential for Human Exposure

QUESTION: Is the information on production, import/export, use, and disposal of the substance complete?

COMMENT 31: 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 32: Relevant information is presented.

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 33: Yes. No additional information is added.

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?

COMMENT 34: Yes.

RESPONSE: *No response needed.*

QUESTION: Do you know of other relevant information?

COMMENT 35: No.

RESPONSE: *No response needed.*

QUESTION: Please provide references for added information.

COMMENT 36: Not applicable.

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?

COMMENT 37: Yes.

RESPONSE: *No response needed.*

QUESTION: Do you agree with the selection of these populations?

COMMENT 38: Yes.

RESPONSE: *No response needed.*

QUESTION: If not, why?

COMMENT 39: Not applicable.

RESPONSE: *No response needed.*

QUESTION: Which additional populations should be included in this section?

COMMENT 40: Not applicable.

RESPONSE: *No response needed.*

Chapter 6. Adequacy of the Database

QUESTION: Do you know of other studies that may fill a data gap?

COMMENT 41: No.

RESPONSE: *No response needed.*

QUESTION: Please provide any relevant references.

COMMENT 42: Not applicable.

RESPONSE: *No response needed.*

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

COMMENT 43: Not applicable.

RESPONSE: *No response needed.*

QUESTION: Are the data needs presented in a neutral, non-judgmental fashion?

COMMENT 44: Yes.

RESPONSE: *No response needed.*

QUESTION: Please note any bias in the text.

COMMENT 45: No bias is noted.

RESPONSE: *No response needed.*

Chapter 7. Regulations and Guidelines

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

COMMENT 46: No.

RESPONSE: *No response needed.*

QUESTION: Please provide citations.

COMMENT 47: Not applicable.

RESPONSE: *No response needed.*

QUESTION: Are there any that should be removed?

COMMENT 48: No.

RESPONSE: *No response needed.*

QUESTION: Please explain.

COMMENT 49: Not applicable.

RESPONSE: *No response needed.*

Appendices

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

Unpublished Studies

Breslin et al 1988.pdf

COMMENT 50: Ethyl chloride effects on estrous cycle is studied in B6C3F1 mice using good laboratory practices. Adult virgin female mice exposed to ethyl chloride 15,000 ppm for 6 hr. a day for a minimum of 14 consecutive days and submitted to genital track for microscopic examination daily for clinical observation and weekly body weight.

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

COMMENT 51: Yes

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

COMMENT 52: Not applicable

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

COMMENT 53: Not applicable

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

COMMENT 54: Not applicable

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

COMMENT 55: Yes

Dow 1941.pdf

COMMENT 56: This document was produced dated 08.04.1941 by Dow Chemical consist of two parts. Part, one deals with Toxicity of ethyl chloride in (both male and female rats) and rabbits given via inhalation. Rabbits were also treated orally with ethyl chloride. Additionally, a single monkey was exposed to ethyl chloride vapors for eight hours. Pertinent experimental details are provided. Part two of this document provide literature survey of chloroethanes including ethyl chloride.

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

COMMENT 57: Yes

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

COMMENT 58: Not Applicable

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

COMMENT 59: Not applicable

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

COMMENT 60: Not applicable

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

COMMENT 61: Yes

Dow 1985.pdf

COMMENT 62: This document was produced on 10.17.85. with letter sanitized on 10.25.91 by Dow Chemical Co dealing with Inhalation Teratology. CF-1 female mice were exposed via inhalation at various doses for six hours a day from six to fifteen days of gestation. Exposed animal group exhibited increased level of activity with highly repetitive patterns during exposures. A dose response study was conducted based upon earlier study at 5000 ppm which was slightly toxic in pregnant mice.

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

COMMENT 63: Yes

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

COMMENT 64: Not applicable

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

COMMENT 65: Yes

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

COMMENT 66: Not applicable

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

COMMENT 67: Yes

Dow 1992.pdf

COMMENT 68: This toxicokinetics study was conducted in female rat and mice following inhalation exposure.

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

COMMENT 69: Yes

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

COMMENT 70: Not applicable

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

COMMENT 71: Not applicable

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

COMMENT 72: Not applicable

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

COMMENT 73: Yes

Dow 1995.pdf

COMMENT 74: This study was conducted for palatability and 14-day drinking water toxicity in both male and female Fischer 344 rats. No-observed effect level (NOEL) 297 and 361 mg. is estimated for male and female rats.

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

COMMENT 75: Yes

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

COMMENT 76: Not applicable

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

COMMENT 77: A single dose is used.

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

COMMENT 78: Not applicable

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

COMMENT 79: Yes

Williams 1983.pdf

COMMENT 80: This study conducted for DNA repair test on eleven chlorinated hydrocarbons including ethyl chloride in rats. The ethyl chloride was not genotoxic at highest nontoxic concentration of 5%.

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

COMMENT 81: Yes

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

COMMENT 82: Not applicable

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

COMMENT 83: Not applicable

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

COMMENT 84: Not applicable

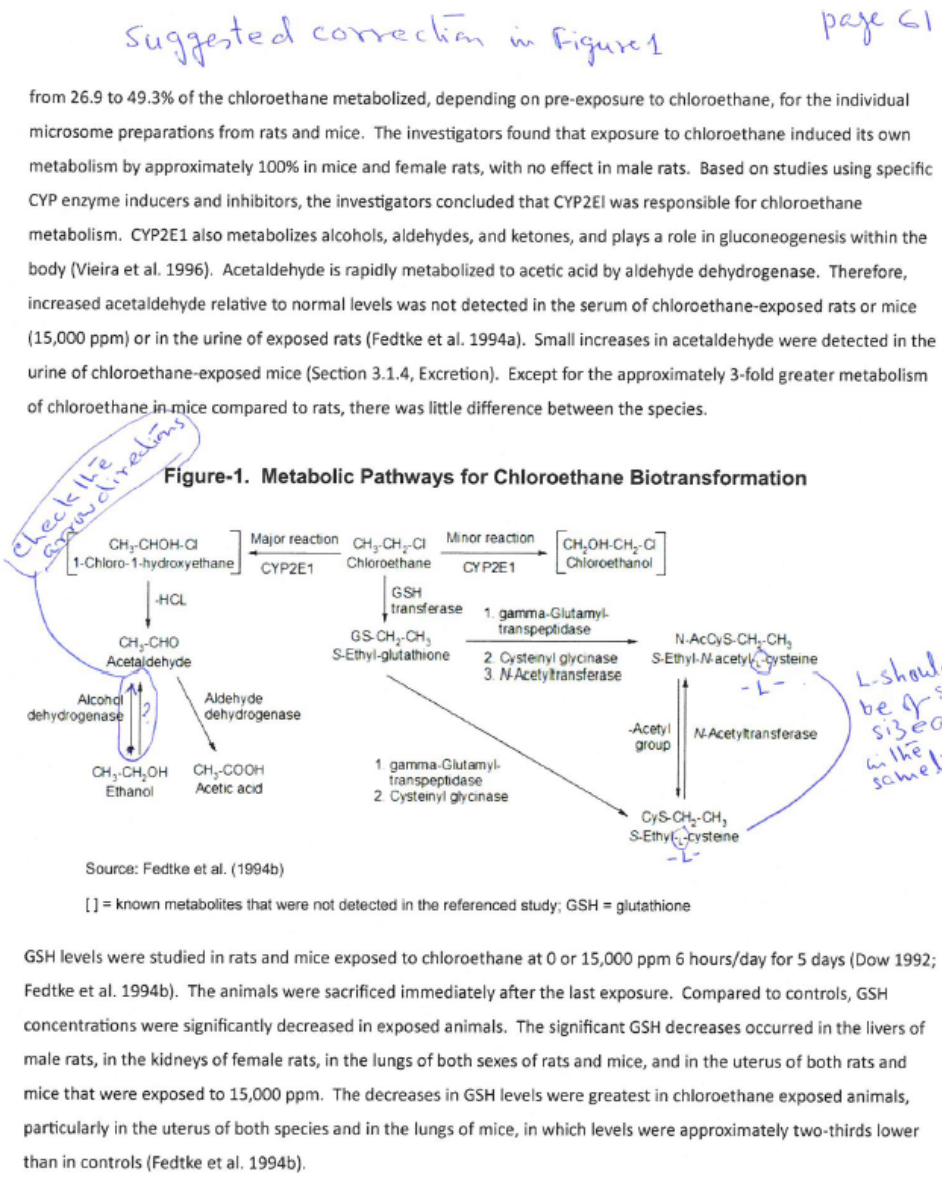
QUESTION: Do you agree with the conclusions of the author? If not, please explain.

COMMENT 85: Yes.

Annotated Comments

The Reviewer provided annotated comments on the toxicological profile. Many of these comments are identical or nearly identical to specific comments above. This section focuses on comments not previously addressed.

COMMENT 86: (Section 3.1.3, page 61, line 14) Suggested corrections on page 61, Figure 3-1. L should be at the same level as other words as shown on page 61 of the attached copy. Also, the direction of the arrows be corrected as shown in the attached copy of page 61.



RESPONSE: *The "L" in S-Ethyl-N-acetyl-L-cysteine and S-Ethyl-L-cysteine have been changed to be the same size font and on the same line as the rest of the chemical as suggested by the Reviewer.*

The Reviewer requested that the arrow direction in Figure 3-1, which indicates acetaldehyde (AC), can be converted back to ethanol (ECL) through alcohol dehydrogenase be checked. Fedtke et al. (1994b)

does report this in Figure 5. The reduction of acetaldehyde back to ethanol is a minor pathway in comparison to acetaldehyde being oxidized to acetic acid (Fedtke et al. 1994a). The following statement was made in the Discussion of Fedtke et al (1994a): "The analyses of urine for the presence of non-bound AC showed minor increases in the AC concentration from ECL exposed animals compared to air exposed animals. AC was not detected in blood samples. These results indicated rapid metabolism of AC formed from ECL in vivo and are consistent with observations made with regard to the metabolism of ethanol and the subsequent rapid conversion of the formed AC. A minor pathway is the reduction by alcohol dehydrogenases to ethanol. The major part is oxidized to acetic acid by several enzyme reactions with oxidation via the mitochondrial NAD+-dependent aldehyde dehydrogenase being the main pathway (Lundquist et al. 1962; Lieber et al. 1975)." The following statement was added to Section 3.1.3 Metabolism to clarify Figure 3-1.

Most acetaldehyde is rapidly metabolized to acetic acid by aldehyde dehydrogenase; a small portion may be reduced by alcohol dehydrogenase to ethanol.

Comments provided by Reviewer #2

ATSDR Charge Questions and Responses and Reviewer Comments

Chapter 1. Relevance to Public Health

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

COMMENT 1: I agree with the human health effects reported in the profile.

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 agree that the available inhalation data for chloroethane has identified that renal, neurological, reproductive, and developmental effects are the most sensitive targets of toxicity. Neurological effects have been observed in exposed humans. Renal, reproductive, and developmental toxicities can occur in humans, therefore, these toxicities may also be of concern for humans.

RESPONSE: *No response needed.*

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

COMMENT 3: The exposure conditions for animal studies were adequately described in this section.

RESPONSE: *No response needed.*

Minimal Risk Levels (MRLs)

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

COMMENT 4: I agree that the oral database for chloroethane is inadequate for the derivation of acute-, intermediate-, and chronic-duration MRLs, and also is inadequate for the derivation of a chronic inhalation MRL.

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: Using the Scortichini et al. 1986 study to derive an acute inhalation MRL has limitations. The study authors concluded that critical effect selected (Increased incidence of foramina in skulls of fetuses) was statistically significant, however, ATSDR's analysis of the data determined that there was a significant trend (p=0.0488) of the fetal data, but no significance in a pairwise comparison to the control group. Incidence data for number of litters affected were also not significantly different from control, or trend test. However, if this study remains selected, I agree with the MRL calcultions and derived values.

Similarly, using the Bucher et al., 1995 to derive an intermediate inhalation MRL has limitations. The Bucher 1995 study noted an increase in length of the estrous cycle 7% from 5.15 to 5.52 days in mice exposed to 15,000 ppm for 21 days. The limitations of this study and endpoint include that only one concentration was tested in this study, and the finding was not statistically significant. While the document states that the Bucher study may not have had the statistical power to detect the small increase, the Breslin et al., 1988 did observe a significant increase using the same dose for a shorter duration (14 days) with a smaller group size (10 v 30/group). Given that these are provisional MRLs, and two studies identified the same target and relative magnitude (although one is an acute exposure), if this study remains selected, I agree with the MRL calcultions and derived values.

RESPONSE: *ATSDR agrees with the Reviewer's assessment regarding the limitations of the Scortichini et al. (1986) study used to derive an acute-duration inhalation MRL. These concerns were acknowledged in the MRL worksheet in Appendix A of the profile. Although incidence of delayed fetal foramina closure (DFFC) in skulls of fetuses was not statistical significantly different in pairwise comparison, there was a statistically significant increase in trend when fetal data were analyzed. These developmental changes in the skull are biologically relevant for risk evaluation; therefore, this study was chosen as the principal study.*

ATSDR agrees with the Reviewer that testing only one concentration of chloroethane is a limitation of the Bucher et al. (1995) study. This prevented a dose-response assessment and the determination of a NOAEL for reproductive effects. However, this study is valid to use as a principal study for an intermediate-duration MRL derivation. Bucher et al. (1995) was the only intermediate-duration study that reported a toxicologically relevant adverse effect.

The Reviewer's concern regarding the lack statistical significance of estrous cycle length in the Bucher et al. (1995) study is due to a misunderstanding. The average duration of the estrous cycle was significantly increased in this study by 7% from 5.15±0.15 days prior to exposure to 5.52±0.19 days during exposure in mice exposed to 15,000 ppm (n=30). It was the acute-duration study conducted by Breslin et al. (1988) in which there was a lack of statistical significance in the length of the estrous cycle (5.0±0.7 days pre-exposure versus 5.6±0.8 days during exposure) in mice (n=10) exposed for 14 days to 15,000 ppm of chloroethane.

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: For the acute inhalation MRL, a composite uncertainty factor of 30 was applied, 3 for extrapolation from animals to humans (after dosimetric adjustment); and 10 for human variability. These UF's are appropriate.

For the intermediate inhalation MRL, a composite uncertainty factor of 300 was applied, 10 for use of a LOAEL, 3 for extrapolation from animals to humans (after dosimetric adjustment), and 10 for human variability. These UFs are appropriate.

RESPONSE: *No response needed.*

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

COMMENT 7: Consideration should be given to using the Breslin et al., 1988 study for the derivation of an acute inhalation MRL. Similarly, whether another study would be more suitable for the derivation of an intermediate inhalation MRL, or whether an intermediate MRL should not be derived should be considered.

RESPONSE: *As suggested by the Reviewer, consideration was given to using Breslin et al. (1998) for derivation of an acute-duration inhalation MRL. Breslin et al. (1988) studied the length of the estrous cycle in mice after 14 days of exposure to 14,955 ppm for 6 hours/day (n=10). No significant increase in the estrous cycle length was seen during exposure compared to pre-exposure (5.0±0.7 days pre-exposure versus 5.6±0.8 days during exposure). No histological changes in the ovaries, oviduct, uterus, cervix, or vagina were observed after exposure. Based on these finding, a NOAEL of 14,955 ppm for the reproductive endpoint was determined. The study did include a control group of mice (n=10) that were exposed to air. The mean cycle length in this control group did not change over the course of the study (4.5±0.8 days pre-exposure versus 4.5±0.7 days during exposure). The estrous cycle length during chloroethane exposure was not compared to the control group given the difference in cycle length between the two groups prior to exposure. A more appropriate comparison was cycle length pre-exposure and during exposure in the same animals. This comparison was not significantly different; therefore, this study was not considered for derivation of an acute-duration inhalation MRL.*

An intermediate-duration inhalation MRL was derived based on increased estrous cycle length in mice exposed to 15,000 ppm chloroethane (only concentration tested) for 21 days (Bucher et al. 1995). The average duration of the estrous cycle increased significantly by 7% from 5.15±0.15 prior to exposure to 5.52±0.19 days during exposure in mice exposed to 15,000 ppm. In the control group, mean estrous cycle length was not affected by the sham-exposure (5.02±0.2 versus 5.0± 0.2, pre-exposure and during exposure, respectively). ATSDR acknowledges the limitation of the Bucher et al. (1995) study for the derivation of an intermediate-duration inhalation MRL. This study only tested one concentration of chloroethane, and an increase in estrous cycle was not seen in an acute-duration study at a similar concentration level (Breslin et al. 1988). Bucher et al. (1995) was the only intermediate-duration inhalation study that reported a toxicologically relevant adverse effect. ATSDR agrees that the lack of dose-response data is a limitation of the study. The discrepancy between the two studies regarding increased estrous cycle length may be due to duration of exposure (14 versus 21 days) or number of animals studied. Bucher et al. (1995) studied 30 females/group, whereas Breslin et al. (1988) studied 10 females/group. The larger sample size would lend itself to greater statistical power to distinguish differences. ATSDR believes that this study is appropriate for derivation of an intermediate-duration inhalation MRL despite its limitations.

Chapter 2. Health Effects

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

COMMENT 8: I agree that the conclusion made concerning the health effects of chloroethane adequately reflect the published literature. A few suggestions are offered below.

P53 lines 1- 9 – "Mechanisms of liver toxicity". It seems that no studies demonstrated clear evidence of liver toxicity (and the document concluded that this endpoint was not considered for derivation of MRLs). However, the studies described in this paragraph describe that chloroethane exposure elicited acute depletion of ATP and glutathione, but since these effects were not associated with histopathological changes, the relevance of this section and its inclusion in Table 2-1 is questioned.

Page 56 – paragraph ending on line 17 – since the exposure cannot be quantified, should a qualifying statement be added stating that the studies are not included in the summary tables and figures.

Page 63, lines 9-11. Concerning this sentence "At 22.7 ppm, the effect subsided after the exposure period ended, but at 216 ppm, no recovery occurred during the month after exposure." It is unclear what effect and what study this sentence is referring to.

Most often, the document clearly indicated reasons why studies were not included in Table 2 1 or plotted in Figure 2 2 (for example, studies in which control groups were not included).

RESPONSE: *The Reviewer questioned the relevance of the "Mechanism of liver toxicity" paragraph in Section 2.9 given the lack of evidence that chloroethane exposure results in hepatic toxicity, and the inclusion of these studies in Table 2-1. The Reviewer's point is valid regarding the title of this paragraph. Given the lack of hepatic toxicity, changes in ATP, glutathione, and non-protein sulfhydryl concentrations are most likely adaptive. ATSDR believes that this information is important to include in the profile; therefore, the title of this paragraph was changed to "Adaptive Responses" and the first sentence was changed to:*

> Changes in adenosine triphosphate/adenosine diphosphate (ATP/ADP) ratio and GSH depletion were investigated as possible adaptive measures occurring in the liver following chloroethane exposure.

The studies in the referenced paragraph do not include toxicologically relevant endpoints and were not included in the LSE table (Table 2-1) or figure (Figure 2-2).

In Section 2.11, Dermal, the Reviewer suggests a qualifying statement be added to explain that studies were not included in summary tables and figures because an effective dose was not reported. As suggested, the following sentence was added after the first paragraph in Section 2.11:

> These studies were not included in the LSE table because the effective dose of chloroethane was not reported.

In section 2.16, Reproductive, the Reviewer was unclear as to what effect and which study the following statement was referring to: "At 22.7 ppm, the effect subsided after the exposure period ended, but at 216 ppm, no recovery occurred during the month after exposure." This sentence was removed from the profile. It is a legacy sentence from a study (Toshina 1966) that was removed from the profile due to inability to verify findings.

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: Yes, I agree that the available human studies were presented in the text. Study limitations and confounding were sufficiently presented, yet the descriptions were not excessive in length.

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, I agree that the adequately designed animal studies were presented in the text. In cases where the studies had limitations (small group size, limited dosing, no control group, meeting abstract), they were adequately described in this section. Studies that were selected to derive MRLs represented adequately designed studies.

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, the animal species were appropriate to detect the toxicological endpoints in both studies.

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 agree that attention was given to dose response relationships for chloroethane for both animal and human data. For most human studies, dose-response data was not available, and this was adequately noted in the document.

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: I am unaware of any additional studies that are related to the toxicity of chloroethane that should be included in the profile. The literature review and search strategy were very thorough. The summary figures and tables provided aided greatly in enhancing the readability of this document.

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: I am unaware of any additional studies that would be relevant to the derivation of an MRL for any of the chloroethane that should be included in the profile.

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: I agree that the appropriate NOAELs and LOAELs were identified for each study and were clearly shown I the text, and LSE tables and figures.

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: As described in this chapter, "Serious" effects were listed for LOAELs that evoke failure in a biological system and can lead to morbidity or mortality whereas, "Less serious" effects were ascribed in instances where a LOAEL was for effects that were not expected to cause significant dysfunction or death, or whose significance to the organism was not clear. I agree with the designations used in the LSE tables.

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: Limited mechanistic data is available for chloroethane. To my knowledge, all possible mechanisms of action for chloroethane were included in this chapter of the profile.

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: I agree that the conclusions presented for were appropriate.

RESPONSE: *No response needed.*

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

Toxicokinetics

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

COMMENT 19: I agree that there was adequate discussion of the available data for the absorption, distribution, metabolism and elimination of chloroethane.

RESPONSE: *No response needed.*

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

COMMENT 20: There are two PBPK models for chloroethane (Gargas et al. 1990, 2008) but were not used to derive MRLs. The first was based on a rat dosimetry study (gas uptake) and the second expanded and refined the initial model to allow for species comparisons and evaluate the potential carcinogenic mode of action for chloroethane. The limitations of these models were also adequately presented.

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: The profile does contain some information on toxicokinetic differences between animals and humans, and the relevance of animal toxicokinetic data to humans. However, limited human data are available, therefore there is not an extensive discussion in the document. Further while a PBPK model was developed to compare the dosimetry of chloroethane between rodents and humans, as presented in the document, the human model has not adequately been validated due to limited data.

RESPONSE: *No response needed.*

Children and Other Populations that are Unusually Susceptible

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

COMMENT 22: I am not aware of any other relevant data concerning children's health or developmental effects that should be included in the profile.

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 limited discussion concerning potentially susceptible populations. As stated in the document, no populations have been identified that are unusually susceptible to toxic effects resulting from chloroethane exposure. I am not aware of any publications concerning other populations that might be considered at higher risk for toxicity and agree with that conclusion.

RESPONSE: *No response needed.*

Biomarkers of Exposure and Effect

QUESTION: Are the biomarkers of exposure specific for the substance?

COMMENT 24: The measurement of chloroethane in breath may serve as a potentially reliable biomarker of exposure, as it would be specific to chloroethane exposure. As stated, the metabolites of chloroethane (GSH conjugates and acetaldehyde) are not specific to chloroethane exposure.

RESPONSE: *No response needed.*

QUESTION: Are the biomarkers of effect specific for the substance?

COMMENT 25: As written in the profile, the effects that occur following chloroethane exposure also occur following exposure to many chemicals, thus they would not serve as useful biomarkers for chloroethane exposure.

RESPONSE: *No response needed.*

Interactions with Other Chemicals

QUESTION: Is there adequate discussion of the interactive effects with other substances? Does the discussion concentrate on those effects that might occur at hazardous waste sites?

COMMENT 26: The profile does include information concerning the interaction of chloroethane with other chemicals, however, little data is available. The discussion is not limited to effects that might occur at hazardous waste sites. I am not aware of additional information that should be included in this section.

RESPONSE: *No response needed.*

QUESTION: If interactive effects with other substances are known, does the text discuss the mechanisms of these interactions?

COMMENT 27: This section of the document does provide examples of interactive effects between chloroethane and other substances. As noted above, data on chemicals interactions is limited. Some discussion of the mechanism(s) of these interactions is included. I am not aware of other studies that should be included in this section.

RESPONSE: *No response needed.*

Chapter 4. Chemical and Physical Information

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

COMMENT 28: To my knowledge, the information provided for the chemical and physical properties of chloroethane are correct.

RESPONSE: *No response needed.*

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

COMMENT 29: Information on one chemical form of chloroethane is provided.

RESPONSE: *No response needed.*

Chapter 5. Potential for Human Exposure

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

COMMENT 30: In general, the information in this section appears complete. Concerning inport/export, some information was included for 1978-1988, and for 2016-2019, no other import/export information was included. However, I am not aware of any additional information related to the production, import/export, use or disposal of chloroethane that should be included in this profile.

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: Yes, adequate information on release into the environment and potential routes of human contact is included in chapter 5 of the profile. This section describes the number of hazardous wasted sites in which chloroethane has been identified, but also states that the number of sites in which chloroethane has been evaluated is not known. I am not aware of other information that could be included in this section of the profile.

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: Yes, this chapter of the profile contained an adequate summary of the available information on the transport, partitioning, transformation and degradation of chloroethane in all media. I am not aware of any additional data that can be added to this section of the profile.

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: Yes, monitoring data for chloroethane has been collected and a thorough summary of the monitoring for chloroethane in air, water and sediment/soil, as well as other media is presented in Chapter 5 of the profile. Comprehensive summary tables are also provided in this section. It appears that proper units were used for each medium for chloroethane. Further, there appears to be an adequate discussion of the quality of the data. I am not aware of any other studies or information that should be included in this section.

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?

COMMENT 34: Yes, chapter 5 of the profile adequately describes sources and pathways of exposure for the general population, those who were occupationally exposed, and other populations with potentially high exposures. In the latter category, workers who work at facilities that produce, process, or use chloroethane were considered populations with potentially high exposures. In addition, medical personnel who use chloroethane to anaesthetize the skin, people who self-administer chloroethane for muscle or joint pain and people who abuse chlorohexane may also have a higher potential for exposure than the general population. I agree with the selection of these populations.

RESPONSE: *No response needed.*

Chapter 6. Adequacy of the Database

QUESTION: Do you know of other studies that may fill a data gap?

COMMENT 35: I am not aware of any additional studies that have been performed and would fill in a data gap.

RESPONSE: *No response needed.*

QUESTION: Do you agree with the identified data needs?

COMMENT 36: The database for chloroethane is limited, however the toxicological profile for chloroethane was very thorough and chapter 6 identified studies that are missing that preclude the development of a chronic-duration inhalation MRL, and oral MRLs. Also, the studies described to fill the data gaps would provide information on the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites, occupational settings and the general population.

RESPONSE: *No response needed.*

QUESTION: Are the data needs presented in a neutral, non-judgmental fashion?

COMMENT 37: Yes, I agree that the data needs section is presented in a neutral, non-biased manner.

RESPONSE: *No response needed.*

Chapter 7. Regulations and Guidelines

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

COMMENT 38: I am not aware of any additional regulations or guidelines for chloroethane that should be included in this section.

RESPONSE: *No response needed.*

QUESTION: Are there any that should be removed?

COMMENT 39: Nothing noted.

RESPONSE: *No response needed.*

Appendices

COMMENT 40: Appendices A - G were well organized and concise. The overall presentation style in the document and appendices makes the document easy to follow, readable, and contained pertinent information for the various audiences that may read the profile.

RESPONSE: *ATSDR appreciates the comment from the Reviewer.*

Unpublished Studies

Breslin et al., 1988

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

COMMENT 41: Yes, the group size was adequate to identify statistical differences, and the study was performed utilizing good laboratory practices (GLP). The animal care described in the document was adequate.

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

COMMENT 42: Early death due to chlorethane exposure did not occur in this study.

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

COMMENT 43: Only one dose group of chlorethane was included in this study. I do not feel that this study design is adequate as it precludes identifying if the chemical elicited dose-related changes on the estrous cycle.

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

COMMENT 44: Although only one dose was evaluated, this was a GLP study and was described in good detail.

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

COMMENT 45: Yes, this was a straightforward study that evaluated the effect of chlorethane on length of the estrous cycle in mice with accompanying histopathology and used appropriate statistical methods.

Dow 1941

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

COMMENT 46: In this report, studies were conducted in rats, rabbits, and a monkey. In general, the number of animals used was not adequate. In the rat study, 6 male, and 6 female rats were exposed to only 1 dose of chlorethane for 6.5 months, however, 2 males died early, leaving a group size of only 4 rats. For the rabbit inhalation study 1 dose was evaluated, and the group size was n=4 – the sex of these animals was not stated in the text. In the monkey study, 1 animal was exposed to chlorethane, and no control animal was evaluated. The animals were bred in-house and the health status of the animals at the beginning of the study does not appear to be documented. Some details of animal care were provided, and in general it seems that appropriate husbandry was provided.

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

COMMENT 47: Early deaths did occur in the male rat control group, the study authors did not clearly state the cause. Since the deaths were in the control group, they were not caused by chlorethane.

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

COMMENT 48: Aside from the oral exposure study in rabbits, only 1 dose was evaluated in the other studies. I do not feel that this study design is adequate as it precludes identifying if the chemical elicited dose-related changes on the endpoints assessed.

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

COMMENT 49: The design and reporting of the studies in this report somewhat diminish any utility of this report. At the time these studies were conducted, this report was one of the first (if not the first) to evaluate repeated dosing of chlorethane, however, the small group sizes and limited doses evaluated lower the significance of these studies.

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

COMMENT 50: Yes, I agree with the conclusions drawn, but the confidence I have in the results is low due to the limitations noted above.

Williams, 1983

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

COMMENT 51: This report described results for DNA damage (genotoxicity) in mouse and rat hepatocytes. Eleven chemicals including chloroethane were evaluated. The report indicates that hepatocytes were isolated from rats and mice then used to conduct the assay, at least three times. It is unclear whether the replicated were from the same or different animals. Only mouse data is provided, as there was high background in the rat hepatocyte assays. Animal care is not discussed in detail. However, the author hypothesized that the rat hepatocyte study that could not be interpreted was due to contamination by microorganisms indigenous to the animals in some of our later animal shipments, leading one to question the health of the animals used in this study.

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

COMMENT 52: Not applicable for this study (in vitro)

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

COMMENT 53: Yes, although some of the higher concentrations tested were unusable as theu produced cytotoxicity, the study author tested the highest non lethal concentrations of chlorethane in the assay.

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

COMMENT 54: I feel that the study was adequately designed.

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

COMMENT 55: Yes, I agree with the conclusions made by the author.

Dow, 1985

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

COMMENT 56: Yes, the sample group sizes were adequate and and nimal care provided was adequate and well described in the document.

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

COMMENT 57: No early deaths occurred in this study.

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

COMMENT 58: Yes, 3 dose groups and a control group were evaluated, spaning a relatively broad range of doses.

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

COMMENT 59: I agree that this study was adequately designed and reported.

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

COMMENT 60: Yes, I agree with the conclusions of the author.

Dow, 1992

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

COMMENT 61: This study was composed of three phases, with each evaluating different endpoints and scientific questions. In general, the group sizes were smalle (n = 3-5 animals per group). Given that these many of these studies were administering radiolabeled compound for toxicokinetic analyses, and that that it was a GLP study the group sizes may be appropriate. The animal care was adequate and well described in the report.

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

COMMENT 62: No early deaths were observed in these studies.

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

COMMENT 63: Yes, given the experimental questions and endpoints that were being addressed in these studies, there were a sufficient number of dose groups (and magnitude, when applicable) used in this study.

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

COMMENT 64: I agree that this study was adequately designed and reported.

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

COMMENT 65: Yes, I agree with the conclusions of the author.

Dow, 1995

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

COMMENT 66: This report included 2 studies, phase I being a 7 day oral palatability study of chloroethane, and the second a standard 14 day oral exposure study. The group sizes were adequate for these studies. The animal care was adequate and well described in the report.

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

COMMENT 67: No early deaths were observed in these studies.

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

COMMENT 68: One treatment group and one control group were included in these studies. Given that the stated purpose of these studies were to satisfy the Office of Drinking Water Chemicals Final Test Rule, requiring evaluation of the 14-day oral toxicity of ethyl chloride when administered *via* drinking water to rats, and that the authors tested the highest dose possible (practical saturation) this experimental design is adequate.

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

COMMENT 69: I agree that this study was adequately designed and reported.

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

COMMENT 70: I agree with the conclusions of the author.

Comments provided by Reviewer #3

ATSDR Charge Questions and Responses and Reviewer Comments

GENERAL COMMENTS

COMMENT 1: Overall, I thought that this was a good profile and nearly ready for publication.

RESPONSE: *ATSDR appreciates the comment from the Reviewer.*

Chapter 1. Relevance to Public Health

QUESTION: Do you agree with those effects known to occur in humans as reported in the text?

COMMENT 2: Yes

QUESTION: 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 3: N/A

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 4: Yes, mostly. Most of the phenomena are straightforward, except the anxiety in female mice. I am not sure about the uterine cancer, but the work is clearly described.

RESPONSE: *No response needed.*

QUESTION: Have exposure conditions been adequately described?

COMMENT 5: Yes

RESPONSE: *No response needed.*

Minimal Risk Levels (MRLs)

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

COMMENT 6: Yes. With several of the endpoints, there is simply not enough data.

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. Do you agree/disagree with each component of the total uncertainty factor?

COMMENT 7: Yes. These were done in proper order.

RESPONSE: *No response needed.*

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

COMMENT 8: Although there may not be enough data in this case, a shift form NOAEL calculations to BMDL would be in order, perhaps in the future (not sure there will be enough interest in this compound, though).

RESPONSE: *ATSDR agrees with the Reviewer that BMDL modeling to determine MRL is preferred over the use of a NOAEL or LOAEL. Unfortunately, the data available on chloroethane did not lend themselves to BMDL modeling.*

Chapter 2. Health Effects

QUESTION: Do the health effect conclusions made in Chapter 2 adequately reflect the findings in the published literature?

COMMENT 9: 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)?

COMMENT 10: Yes, although the human studies were older and very limited.

RESPONSE: *No response needed.*

QUESTION: Were the major study limitations sufficiently described in the text without going into lengthy discussions?

COMMENT 11: Yes

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)?

COMMENT 12: Yes

RESPONSE: *No response needed.*

QUESTION: Were the animal species appropriate for the most significant toxicological endpoint of the study?

COMMENT 13: Probably Yes

RESPONSE: *No response needed.*

QUESTION: If not, which animal species would be more appropriate and why?

COMMENT 14: The species tested were not exhaustive but I do not think more animal testing is in order.

RESPONSE: *No response needed.*

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

COMMENT 15: Yes. See MRL calculations. Hard to say much about human doses in light of the limited data.

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?

COMMENT 16: 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?

COMMENT 17: 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)?

COMMENT 18: No

RESPONSE: *No response needed.*

QUESTION: If not, did the text provide adequate justification for excluding NOAELs/LOAELs including, but not limited to, citing study limitations?

COMMENT 19: Yes

RESPONSE: *No response needed.*

QUESTION: Do you agree with the categorization of "less serious" or "serious" for the effects cited in the LSE tables?

COMMENT 20: Yes

RESPONSE: *No response needed.*

QUESTION: Have all possible mechanisms of action been discussed within their relevant health effect section?

COMMENT 21: Yes –metabolism is pretty straightforward for this compound.

RESPONSE: *No response needed.*

QUESTION: Are the conclusions appropriate given the overall database?

COMMENT 22: Yes

RESPONSE: *No response needed.*

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

Toxicokinetics

QUESTION: ***Is there adequate discussion of absorption, distribution, metabolism, and excretion of the substance?***

COMMENT 23: Yes

RESPONSE: *No response needed.*

QUESTION: ***Have all available pharmacokinetic/pharmacodynamic models and supporting data been presented?***

COMMENT 24: Yes , as much as possible

RESPONSE: *No response needed.*

QUESTION: Is there adequate discussion of the differences in toxicokinetics between humans and animals?

COMMENT 25: There is really not enough human data available to do this well.

RESPONSE: *No response needed.*

QUESTION: Is there adequate discussion of the relevance of animal toxicokinetic information for humans?

COMMENT 26: Not enough human data available.

RESPONSE: *No response needed.*

Children and Other Populations that are Unusually Susceptible

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

COMMENT 27: Not really-very limited data.

RESPONSE: *No response needed.*

QUESTION: Is there a discussion of populations at higher risk of susceptibility?

COMMENT 28: Yes but very limited data.

RESPONSE: *No response needed.*

QUESTION: Do you agree with the choice of populations?

COMMENT 29: Yes

RESPONSE: *No response needed.*

Biomarkers of Exposure and Effect

QUESTION: Are the biomarkers of exposure specific for the substance?

COMMENT 30: Only the mercapturic acid, which may not be that specific.

RESPONSE: *No response needed.*

QUESTION: Are the biomarkers of effect specific for the substance?

COMMENT 31: Sort of, but not great. Useful at high exposure but I would be suspect at low levels.

RESPONSE: *No response needed.*

Interactions with Other Chemicals

QUESTION: Is there adequate discussion of the interactive effects with other substances?

COMMENT 32: Yes, especially ethanol.

RESPONSE: *No response needed.*

QUESTION: Does the discussion concentrate on those effects that might occur at hazardous waste sites?

COMMENT 33: I am not sure that is all that relevant, in light of the volatile nature of the compound.

RESPONSE: *No response needed.*

QUESTION: If interactive effects with other substances are known, does the text discuss the mechanisms of these interactions?

COMMENT 34: Yes, in terms of P450 2E1 induction.

RESPONSE: *No response needed.*

Chapter 4. Chemical and Physical Information

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

COMMENT 35: No.

RESPONSE: *No response needed.*

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

COMMENT 36: Yes, as liquid & gas (bp 12 °C)

RESPONSE: *No response needed.*

Chapter 5. Potential for Human Exposure

QUESTION: Is the information on production, import/export, use, and disposal of the substance complete?

COMMENT 37: 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?

COMMENT 38: Yes

RESPONSE: *No response needed.*

QUESTION: Does the text provide sufficient and technically sound information regarding the extent of occurrence at NPL sites?

COMMENT 39: Yes

RESPONSE: *No response needed.*

QUESTION: Do you know of other relevant information?

COMMENT 40: No

RESPONSE: *No response needed.*

QUESTION: Does the text cover pertinent information relative to transport, partitioning, transformation, and degradation of the substance in all media?

COMMENT 41: Yes

RESPONSE: *No response needed.*

QUESTION: Do you know of other relevant information?

COMMENT 42: No

RESPONSE: *No response needed.*

QUESTION: Does the text provide information on levels monitored or estimated in the environment, including background levels? Yes Are proper units used for each medium?

COMMENT 43: Yes

RESPONSE: *No response needed.*

QUESTION: Does the information include the form of the substance measured?

COMMENT 44: Yes

RESPONSE: *No response needed.*

QUESTION: Is there an adequate discussion of the quality of the information?

COMMENT 45: Yes

RESPONSE: *No response needed.*

QUESTION: Do you know of other relevant information?

COMMENT 46: No

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?

COMMENT 47: Yes

RESPONSE: *No response needed.*

QUESTION: Do you agree with the selection of these populations?

COMMENT 48: Yes

RESPONSE: *No response needed.*

Chapter 6. Adequacy of the Database

QUESTION: Do you know of other studies that may fill a data gap?

COMMENT 49: Not really

RESPONSE: *No response needed.*

QUESTION: Do you agree with the identified data needs?

COMMENT 50: Yes. Section 6.2 is very good on this.

RESPONSE: *No response needed.*

QUESTION: Are the data needs presented in a neutral, non-judgmental fashion?

COMMENT 51: Yes

RESPONSE: *No response needed.*

Chapter 7. Regulations and Guidelines

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

COMMENT 52: No. The use of this chemical has been considerably reduced.

RESPONSE: *No response needed.*

QUESTION: Are there any that should be removed?

COMMENT 53: Not really

RESPONSE: *No response needed.*

Appendices

COMMENT 54: These were good. I like the color shading and the "Initial study confidence" entries.

RESPONSE: *ATSDR appreciates the comment from the Reviewer.*

Unpublished Studies

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

COMMENT 55: Varies-not some of the older ones

RESPONSE: *No response needed.*

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

COMMENT 56: Generally yes

RESPONSE: *No response needed.*

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

COMMENT 57: Generally yes

RESPONSE: *No response needed.*

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

COMMENT 58: Possibly, in some older studies The "Initial study confidence" entries are useful in this regard.

RESPONSE: *No response needed.*

QUESTION: Do you agree with the conclusions of the author?

COMMENT 59: Yes, in general, and insofar as it was possible with the data available.

RESPONSE: *No response needed.*

Annotated Comments

The Reviewer provided annotated comments on the toxicological profile. Many of these comments are identical or nearly identical to specific comments above. This section focuses on comments not previously addressed.

COMMENT 60: (Section 3.2, page 71, line 18) The word at the end of line 4 should be "less" not "more." Acetylation of an amine will make it less polar. The correct citation for this is not Amdur et al. 1991, it is I. G. Sipes & A. J. Gandolfi as authors of that chapter. Amdur, Doull, & Klaassen are the editors of the book.

RESPONSE: *The reference, Amdur et al. (1991), in Section 3.2 was changed to the correct citation of Sipes and Gandolfi (1991):*

> During the process of metabolism, NAT enzymes may convert the chloroethane conjugate to a less hydrophilic form, allowing it to be excreted (Sipes and Gandolfi 1991).

COMMENT 61: (Section 3.4, page 74, line 14) The statement is made that "chloroethane enhanced the effects of ethanol in rats." This implies synergism. How do we know that the effects on liver enzymes were simply not additive? Did chloroethane exposure alone also change the enzyme levels? I do not have access to the two references, and they are in German.

RESPONSE: *This paragraph was removed from the profile based on poor reporting of findings. ATSDR could not verify the effects of chloroethane exposure alone on hepatic enzyme levels. Furthermore, the aim of this section is to discuss the influence other substances have on the toxicity of chloroethane. The paragraph, as written, discusses the effect chloroethane has on ethanol toxicity. Since data on chloroethane alone are not available, the influence ethanol has on chloroethane toxicity cannot be determined.*