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

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

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Peer reviewers for the third pre-public comment draft of the Toxicological Profile for 1,2-Dichloropropane were:

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Comments provided by Reviewer #1

GENERAL COMMENTS

COMMENT: This Toxicological Profile is well-written, follows in the tradition of previous profiles, and will be helpful to physicians and the general public. I found no significant deficiencies in the report, and specific changes in wording and minor issues have been noted directly in the document and in the answers to specific questions that were requested. The nature and extent of effects of 1,2-dichloro-propane on human health are detailed; included are effects on non-human animals, the nature of human exposures, and the environmental fate of the chemical. The relevance to public health in the larger sense is provided. Key literature has been assembled, assessed for validity, and succinctly reviewed with controversial data examined in detail. The health effects are helpfully categorized by occurrence for various organ systems. Toxicokinetics, susceptible populations, and biomarkers of exposure are characterized in detail. Consequences for children and populations that might be unusually susceptible to toxicity are adequately described. There is a detailed examination of the adequacy of the data and scientific conclusions in the literature for acute, intermediate, and chronic exposure including cancer. As appropriate and available, the medical tests for exposure are described. The chemical and physical nature of 1,2-dichloropropane and its concentrations in air and water, interaction with other chemicals, production amounts, and releases and fates in the environment are provided. Approximately 10 Figures and 19 Tables include novel formats to simply and forcefully depict complex information in a simplified manner that aids understanding. These tables include NOAELS, LOAELS, MRLS, and AGLES conveniently collected. An appendix is detailed and provides adequate explanation and justification for the described toxicities. Figure 6.1 is excellently formatted; however, there is an error in the title – it should be 1,2-dichloropropane.

RESPONSE: *The typographical error in Figure 6-1 was corrected.*

ATSDR Charge Questions and Responses

Chapter 1

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

COMMENT: Yes.

RESPONSE: *No response is necessary.*

QUESTION: Are the effects only observed in animals likely to be of concern to humans? Why or why not? If you do not agree, please explain.

COMMENT: Yes, effects only known to occur in animals are of concern; because it is desirable to have a "fail safe" position and because animal experiments are often done over a wider range of conditions and may show effects that could occur in humans.

RESPONSE: *No response is necessary.*

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

COMMENT: Yes.

RESPONSE: *No response is necessary.*

QUESTION: Do you believe the derived MRL values are justifiable? If you disagree, please explain. (see also Appendix A)

COMMENT: The MRL values appear to be derived according to traditional and accepted methods and therefore are acceptable and justifiable. I have reviewed the MRLs and provide details in comments made in my answers to questions for Appendix A.

RESPONSE: *No response is necessary.*

QUESTION: Do you agree that the data do not support derivation of MRLs?

COMMENT: No comment.

RESPONSE: *No response is necessary.*

Chapter 2

QUESTION: Do the health effect conclusions made in Chapter 2 adequately reflect the findings in the published literature for 1,2-Dichloropropane?

COMMENT: Yes.

RESPONSE: *No response is necessary.*

QUESTION: Were adequately designed human studies identified in the text (i.e., good exposure data, sufficiently long period of exposure to account for observed health effects, adequate control for confounding factors)? Were the major study limitations sufficiently described in the text without going into lengthy discussions? If study limitations were not adequately addressed, please suggest appropriate changes.

COMMENT: Yes.

RESPONSE: *No response is necessary.*

QUESTION: Were adequately designed animal studies identified in the text (i.e., adequate number of animals, good animal care, accounting for competing causes of death, sufficient number of dose groups,

and sufficient magnitude of dose levels)? If not, does the inadequate design negate the utility of the study? Please explain.

COMMENT: Yes.

RESPONSE: *No response is necessary.*

QUESTION: Were the animal species appropriate for the most significant toxicological endpoint of the study? If not, which animal species would be more appropriate and why?

COMMENT: Yes.

RESPONSE: *No response is necessary.*

QUESTION: Are you aware of any studies that are not included in the profile that may be important in evaluating the toxicity of 1,2-Dichloropropane? Please provide a copy of each study and indicate where in the text each study should be included.

COMMENT: I suggest three studies for consideration (attachments 3, 4, 5):

For inclusion under "Mechanisms of Cancer" p. 88 (copy provided as attachment 3, citation reference 1):
Spontaneous Production of Glutathione-Conjugated Forms of 1,2-Dichloropropane: Comparative Study on Metabolic Activation Processes of Dihaloalkanes Associated with Occupational Cholangiocarcinoma.
Toyoda Y; Takada T; Suzuki H.
Oxidative medicine & cellular longevity. 2017:9736836, 2017.
[Comparative Study. Journal Article]
UI: 28555163

For inclusion under "Mechanisms of Cancer" p. 88 (copy provided as attachment 4, citation reference 2):
1,2-Dichloropropane generates phosphorylated histone H2AX via cytochrome P450 2E1-mediated metabolism Tatsushi Toyookaa, *, Yukie Yanagibaa, Megumi Sudaa, Yuko Ibukib, Rui-Sheng Wanga a Industrial Toxicology and Health Effects Research Group, National Institute of Occupational Safety and Health, Japan bGraduate Division of Nutritional and Environmental Sciences, University of Shizuoka, Japan

For inclusion under 3.1.2 Distribution p 94 (Copy provided as attachment 5, citation reference 3):
Distribution of 1,2-dichloropropane in blood and other tissues of rats after oral administration.
Take M; Takeuchi T; Hirai S; Takanobu K; Matsumoto M; Fukushima S; Kanno J.
Journal of Toxicological Sciences. 42(2):121-128, 2017.
[Journal Article]
UI: 28321038
Authors Full Name
Take, Makoto; Takeuchi, Tetsuya; Hirai, Shigeyuki; Takanobu, Kenji; Matsumoto, Michiharu; Fukushima, Shoji; Kanno, Jun.

RESPONSE: *References were reviewed and added to the profile in the relevant sections (see below).*

Toyoda et al. (2017) was added in Section 2.19, in the Mechanisms of Cancer section:

> *"An in vitro study was conducted to evaluate potential differences in GSH conjugation of 1,2-dichloropropane and dichloromethane, which have both been implicated in the development of occupational CCA (Toyoda et al. 2017). This study showed that 1,2-dichloropropane spontaneously conjugates with GSH under physiological conditions, while dichoromethane shows very little spontaneous activity. However, GST T1-1 greatly enhanced GSH conjugation with dichloromethane, and only had a mild effect on GSH conjugation with 1,2-dichloropropane. Therefore, while both 1,2-dichloropropane and dichloromethane produce glutathione-conjugated reactive metabolites, there are differences in the metabolic activation processes."*

Toyooka et al. (2017) was in Section 2.9 (Hepatic) and the inhalation Levels of Significant Exposure (LSE) table:

> *"No changes in liver weight or clinical chemistry were observed in mice exposed to concentrations up to 400 ppm for 2 days (6 hours on day 1, 3 hours on day 2) (Toyooka et al. 2017)."*

Toyooka et al. (2017) was added to Section 2.20 (Genotoxicity) and Tables 2-5 and 2-6:

> *"In laboratory animals, DNA damage was also observed in the livers of mice following acute- or intermediate-duration inhalation exposure to concentrations ≥100 ppm (Suzuki et al. 2014; Toyooka et al. 2017)."*

> *"However, DNA damage was observed in cultured human hepatocytes and cholangiocytes exposed to 1,2-dichloropropane (Toyooka et al. 2017)."*

Toyooka et al. (2017) was not directly cited in Mechanisms of Cancer in Section 2.19, but results are covered in the first statement that refers readers to Section 2.20:

> *"The available evidence suggests that 1,2-dichloropropane is not a potent mutagen, but can cause DNA and chromosomal damage under certain conditions (see Section 2.20, Genotoxicity)."*

Take et al. (2017) was added to Section 3.1 (Toxicokinetics):

> *Section 3.1.1: "Take et al. (2017) reported peak blood concentrations of 1,2-dichloropropane in rats 1–3 hours after oral exposure."*

> *Section 3.1.2: "Take et al. (2017) evaluated distribution of ^{14}C-labeled 1,2-dichloro-propane in blood, abdominal fat, lung, liver, and kidneys following oral exposure to 62 or 125 mg/kg in rats, and reported a higher concentration in abdominal fat compared to blood and other tissues at both doses. Twenty-four hours after exposure, 1,2-DCP was only detectible in blood and abdominal fat of rats given 62 mg/kg, and was detected in the blood, liver, kidney, lung, and abdominal fat of rats given 125 mg/kg. These findings suggest that low levels of 1,2-DCP can remain in tissues for prolonged periods after exposure."*

Section 3.1.4: "Elimination half-life ($t_{1/2}$) values and area under the curve values over the first 1,440 minutes ($AUC_{0–1,440}$) were estimated in rats for blood and select organs following inhalation or oral exposure (Take et al. 2014, 2017). Values are presented in Tables 3-1 and 3-2, respectively. These values support that at low levels accumulation of 1,2-dichloropropane in the body is not expected; however, concentration in body fat is predicted if the metabolic capacity is exceeded following high-level inhalation or oral exposures."

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 1,2-Dichloropropane isomers?

COMMENT: No.

RESPONSE: *No response is necessary.*

QUESTION: Were all appropriate NOAELs and/or LOAELs identified for each study (both in the text and the Levels of Significant Exposure (LSE) tables and figures)? If not, did the text provide adequate justification for excluding NOAELs/LOAELs including, but not limited to, citing study limitations? Please suggest appropriate changes.

COMMENT: Yes, all appropriate NOAELs and/or LOAELs were identified; however, there were specific instances where these values (for specific end-points) were not found in cited papers and this was appropriately noted.

RESPONSE: *No response is necessary.*

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

COMMENT: Yes, I agree in principal that such distinction is appropriate as described on pp. 10-11 where these classifications have been defined. However, it is apparent that this subject deserves further evaluation and refinement. In particular, definitions need to be refined. The definitions lack specificity and clarity as shown by the statements: " 'Serious' effects are those that evoke failure of a biological system and can lead to morbidity or mortality (….). [and] 'Less serious' effects are those that are not expected to cause significant dysfunctions or death, or those whose significance to the organism is not entirely clear." In particular, morbidity and mortality covers about everything, and it is not clear that there is any distinction to be made between morbidity and "not expected to cause significant dysfunction or death". It is also a complication that the definition includes (lumps in) cases where "significance to the organism is not entirely clear". I agree with the statement to the effect that considerable judgment is required (will always be required). I agree that is a useful goal to separate effects this way.

RESPONSE: *The comment refers to boilerplate text. ATSDR will consider the Reviewer's suggestion in future versions of the profile guidance.*

QUESTION: Have all possible mechanisms of action been discussed within their relevant health effect section? If not, please explain.

COMMENT: I am not aware of any significant, adequately justified mechanisms that were omitted.

RESPONSE: *No response is necessary.*

QUESTION: Are the hazard identifications clear and justifiable based on ATSDR's systematic review (SR) process? (In other words, if you follow ATSDR's SR protocol from start to finish, would you come to the same hazard identification conclusions?) If not, discuss where in the process there was a deviation from the protocol.

COMMENT: No comment.

RESPONSE: *No response is necessary.*

Chapter 3

Toxicokinetics

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

COMMENT: For absorption: It was helpful to say that no human data were found but that data from rats was adequate except for no data for humans or animals for dermal exposure and explanations were provided for assumptions that it was absorbed to produce toxicity. For distribution: no human data for inhalation, but rat data was appropriate and adequate for oral exposure. No data were found for distribution following dermal exposure in animal or humans. For metabolism: no data was found for humans. There was a significant discussion of metabolism in animals. Figure 3-1. is a very useful depiction of metabolism. For excretion: No studies with humans were found, and the discussion of metabolism in animals is adequate.

RESPONSE: *No response is necessary.*

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

COMMENT: It is stated that "No chemical-specific PBPK models have been developed." There is a discussion of time-course metabolism from two papers which is probably about as good as can be done.

RESPONSE: *No response is necessary.*

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

COMMENT: No, for either question. These differences between humans and animals are very briefly discussed under 3.3.6. However, it is stated that no studies were located to evaluate these differences. It is explained in two sentences that species differences are observed but that the targets appear to be similar. They justify their one-paragraph discussion by saying "Available mechanistic data are inadequate to evaluate potential species differences." I suggest that the questions (see questions 3

[directly above]) are not adequately addressed in the document. I believe it would be helpful to provide information relating especially to the second question of item 3).

RESPONSE: *As noted in the profile, data are not available to adequately address these questions. In the absence of human toxicokinetics studies and the absence of any concrete reason to think that the animal studies do not apply to humans, the usual risk assessment default is to assume relevance of animal pharmacokinetic studies to humans. The following statement was added for clarity in Section 3.1.6:*

> *"In the absence of adequate human toxicokinetic studies, animal data are assumed relevant to humans.* ~~*However,*~~ *In addition, . . ."*

Children and Other Populations that are Unusually Susceptible

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

COMMENT: No.

RESPONSE: *No response is necessary.*

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

COMMENT: No; Yes. The discussion adequately addresses the state of knowledge today. This is incomplete because experiments have not addressed unusually susceptible populations. My opinion is that we do not know of susceptible populations that are not addressed by current data.

RESPONSE: *No response is necessary.*

Biomarkers of Exposure and Effect

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

COMMENT: They are not specific; however, this is the best available based on my understanding.

RESPONSE: *No response is necessary.*

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

COMMENT: They are not specific; however, this is the best available based on my understanding.

RESPONSE: *No response is necessary.*

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? P lease explain and provide any additional references.

COMMENT: There is adequate information about interactive effects including minimal human data. There is no discussion of any relationship to hazardous waste sites. I can provide no references for the latter.

RESPONSE: *No response is necessary.*

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: It is stated that "studies were not designed to evaluate potential interactions between the chemical components". I do not know of any papers that shed light on this.

RESPONSE: *No response is necessary.*

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: I found no errors; I have not authenticated every number from an original source.

RESPONSE: *No response is necessary.*

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

COMMENT: I am not certain how this question is to be interpreted. There is essentially only one form of the substance to be considered of concern. It does appear in various product mixtures and several of these have been identified in footnote 'a' for Table 4-1.

RESPONSE: *No response is necessary.*

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: I believe it to be complete and to provide the information that is likely to be required.

RESPONSE: *No response is necessary.*

QUESTION: Has the text appropriately traced the substance from its point of release to the environment until it reaches the receptor population? Does the text provide sufficient and technically sound information regarding the extent of occurrence at NPL sites? Do you know of other relevant information? Please provide references for added information.

COMMENT: Yes and yes; I am not aware of other, useful information not provided. However, the document does provide a caveat that data should be used with caution because only certain types of facilities are required to report (which appears to be appropriate).

RESPONSE: *No response is necessary.*

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: Adequate regarding transport and partitioning in air, water and soil (including half-lives, chemistry, and importance), and for fish and potatoes (briefly).

RESPONSE: *No response is necessary.*

QUESTION: Does the text provide information on levels monitored or estimated in the environment, including background levels? Are proper units used for each medium? Does the information include the form of the substance measured? Is there an adequate discussion of the quality of the information? Do you know of other relevant information? Please provide references for added information.

COMMENT: Yes, environmental levels were adequately provided for various media; however, the exact chemical form measured was not always provided (residues for 1,2-dichloropropane, p.114). I believe this is the best that can be done. I believe there is adequate information about quality of the data and appropriate units are used. I found it useful that indoor air monitoring data was included even though it was expected to be low and was low. There are many Tables and they improved the transmission of information in this section. I am not aware of other references of merit.

RESPONSE: *No response is necessary.*

QUESTION: Does the text describe sources and pathways of exposure for the general population and occupations involved in the handling of the substance, as well as populations with potentially high exposures? Do you agree with the selection of these populations? If not, why? Which additional populations should be included in this section?

COMMENT: Yes. As expected, human exposure is low, and selection of population for reporting is not critical for this agent; however, NOESS data were provided in considerable detail. I do not believe that additional population data is necessary.

RESPONSE: *No response is necessary.*

Chapter 6

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

COMMENT: I am not aware of studies that provide significant information for data gaps (which do exist). Figure 6-1 is remarkably well done and helpful; note, however, that in the title it should be 1,2-dichloropropane (not 1-Dichloropane).

RESPONSE: *The typographical error was fixed in Figure 6-1.*

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

COMMENT: Yes. There is a need for human data, as previously identified for exposures, specific toxicities, and for better understanding of metabolism.

RESPONSE: *No response is necessary.*

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

COMMENT: I detected no bias.

RESPONSE: *No response is necessary.*

Chapter 7

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

COMMENT: No.

RESPONSE: *No response is necessary.*

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

COMMENT: No.

RESPONSE: *No response is necessary.*

Appendix A – Minimal Risk Levels (MRLs)

QUESTION: Do you agree or disagree with the proposed MRL values? Explain. If you disagree, please specify the MRL value that you propose.

COMMENT: I agree. Based on review of information in Appendix A, there is sufficient, reliable data to identify the target effects for specific routes and durations of exposure. I also agree that there is insufficient information to permit derivation of MRLs for dermal exposure. I agree with the approach to use the most sensitive substance-induced toxic endpoint. I agree that it is necessary to use a conservative approach for assessing uncertainty factors. I agree that it is reasonable to base MRLs on animal data when appropriate human data is not available. It is necessary to assume that humans are more sensitive than animals to achieve the necessary conservative (fail safe) approach. For the acute inhalation MRL, the selection of the Nitschke and Johnson study (1983) is appropriate. Selection of olfactory mucosal degeneration in the rat is appropriate. The point of departure is appropriate and the adjusted intermittent exposure of 16 ppm is correct. I agree with the approach and calculations used to determine the human equivalent concentration. The uncertainty factor is appropriate.

The Minimal Risk Level (MRL) Worksheet for the intermediate duration exposure appears to have been carefully and correctly done. The intermediate-duration inhalation MRL appears to have been correctly done including selection of the critical effect, selection of the principal study, and calculation of benchmark dose. I could not independently validate the statistics in Table A-4, but found no basis to disagree with the results. The summary of the principal study appears to be appropriate. I agree with the use of hyperplastic lesions in the nasal mucosa as an adverse effect, and identification of the LOAEL with no NOAEL identified. The departure point was selected from a range of values based on the value with the highest statistical power which seems appropriate. The adjustments for intermittent exposure, human equivalent concentration, and uncertainty factor appear to be valid and the math is correct. Other studies were appropriately considered. The chronic-duration inhalation MRL was not derived due to lack of adequate data, and this appears to be a proper assessment. The MRL for acute-duration oral exposure was appropriately derived, based on appropriate selection of the critical effect, point of departure (based on increased maternal reticulocyte counts) adjustment for intermittent exposure, calculation of uncertainty factor. The statistical approach used was extensive and appears to be appropriate although I am unable to independently verify the statistics. Additional studies were described that supported the calculated MRL. The intermediate-duration oral MRL was appropriately derived based on proper selection of the critical effect (hematologic anemia), and each step in the process leading to MRL determination (as described above) was properly assessed (including careful statistical consideration). There was reported to be insufficient, adequate data to derive a chronic-duration oral MRL.

RESPONSE: *No response is necessary.*

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

COMMENT: I agree with the components of the uncertain factor as explained immediately above in the answer to 1).

RESPONSE: *No response is necessary.*

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

COMMENT: I believe the database assessment is appropriate as stated in detail immediately above in the answer to described in the answer to 1).

RESPONSE: *No response is necessary.*

Appendix B – Literature Search Framework

QUESTION: Does Appendix B provide a sufficiently clear documentation of ATSDR's health effects literature search strategy and inclusion/exclusion criteria?

COMMENT: Yes, the objective of locating the necessary literature to evaluate the potential for human exposure and the potential health hazards associated with inhalation oral exposure was provided. However, as the authors concluded, there were insufficient sources to permit assessment of the dermal/ocular exposure route.

RESPONSE: *No response is necessary.*

QUESTION: Does it provide enough transparency regarding ATSDR's implementation of its inclusion and exclusion criteria (e.g., how ATSDR chose the studies it included in the health effects chapter)?

COMMENT: Yes, I was satisfied with the focus on peer-reviewed articles without publication date or language restrictions and consideration of relevant non-peer-reviewed studies after peer-review "by at least three ATSDR-selected experts who have been screened for conflict of interest". Additionally, there was: Table B-1 which provided detailed inclusion criteria, Table B.1.1. that documented the databases that were searched, Table B-2 that provided further details about "Pre-Public" comment, and Table B-3 that detailed strategies were used to augment the literature search. Under subhead B.1.2., the methods used for literature screening were detailed and provide adequate assurance that the search was carefully and extensively done. Finally, Figure B-1. provided a colored summary "slide/diagram" that made it easy to see the results of the literature screening. This was greatly appreciated.

RESPONSE: *No response is necessary.*

Appendix C – Framework for ATSDR's Systematic Review of Health Effects Data

QUESTION: Does Appendix C provide a sufficiently clear documentation of ATSDR's systematic review of health effects data?

COMMENT: Yes; text and tables are used to provide more than adequate information.

RESPONSE: *No response is necessary.*

QUESTION: Do you agree with the SR framework as presented in Appendix B? Are there any steps that need to be revised? Please offer any suggestions to improve the utility, effectiveness, or clarity of the SR Framework.

COMMENT: Yes, I agree but do have a question: Why was the search restricted to exclude studies published prior to 1987? I found the SR Framework to be adequate; and was actually quite helpful

RESPONSE: *The current literature search was intended to update the existing toxicological profile for 1,2-dichloropropane, which was published in 1989. In order to capture literature published since the*

search was conducted for the 1989 profile, the current search included the 2 years prior to publication. The text in Section B.1.1. (Literature Search) was revised to include the text below for clarity:

> *"The current literature search was intended to update the existing toxicological profile for 1,2-dichloropropane (ATSDR 1989b); thus, the literature search was restricted to studies published between January 1987 to December 2016 to capture literature published since the search was conducted for the existing profile."*

Overall Usability of the Profile

QUESTION: Does the new chapter organization make it easier for you to find the information you need? For example, are you satisfied with the organization of the health effects chapter by organ system rather than exposure route?

COMMENT: The chapter organization was appropriate. I like the organization by organ system.

RESPONSE: *No response is necessary.*

QUESTION: Does the profile contain all of the information you need? Is there information you would like to see that is not currently included?

COMMENT: The Profile has an appropriate coverage of information likely to be needed by users. I recognized no significant deficiencies.

RESPONSE: *No response is necessary.*

QUESTION: If you have used the Toxicological Profiles before, which chapter(s) have you used the most and for what purpose?

COMMENT: Yes, I have both reviewed and used other Profiles. In my use of profiles, the summary of health effects, MRL values, the description of toxic symptoms, and the references provided were equally-valuable parts.

RESPONSE: *No response is necessary.*

QUESTION: Are the new tables and figures clear and useful? Do they make the toxicological profile easier to read?

COMMENT: Yes, I especially appreciated the extensive use of Figures and Tables. Compared to previous Profiles I found this Profile to be especially well-designed with regard to presentation of information in a user-friendly manner

RESPONSE: *No response is necessary.*

Comments provided by Reviewer #2

Front Matter

COMMENT: Version history appears to be incomplete. It omits reference to a previous Toxicological Profile published by ATSDR, U.S. Public Health Service *"in collaboration with the U.S. Environmental Protection Agency"* in December 1989. My (pdf) copy also indicates *"U.S. Government Printing Office 1999 – 535 – 152/."* The current draft Toxicological Profile should clarify its relationship, if any, with the previous Profile, such as whether it incorporates and updates the 1989 analysis (it apparently does). The current Profile *Forward* indicates that *"This toxicological profile is prepared in accordance with guidelines developed by the Agency for Toxic Substances and Disease Registry (ATSDR)* ***and the Environmental Protection Agency (EPA)"*** [emphasis added]. The phraseology *"in accordance with"* differs from *"in collaboration with."* The history, and basis for the change, should be explicated.

RESPONSE: *The version history was revised to include the 1989 profile. ATSDR will consider adding text discussing updated toxicological profiles in future versions of the profile guidance. The "in collaboration with the U.S. Environmental Protection Agency" is no longer included in profiles because toxicological profiles are now only prepared by ATSDR (early toxicological profiles were written in collaboration with the EPA).*

Chapter 1. Relevance To Public Health

COMMENT: I examined my archive of data, and found no document(s) that would add to the inventory of 1,2-dichloropropane health effects potentially posed to humans (or to animals) reported in the draft Toxicological Profile under review. I do suggest an additional source of such information. The Profile reports that 1,2-dichlopropane *"is now used in the United States only in research and industry."* The preparer therefore should identify research and industrial users of 1,2-dichloropropane, and contact them to request information about studies that may have been used to establish its safety, and required safety precautions to protect against its potential risk, for use in their operations, or that otherwise may have emerged from their experience.

RESPONSE: *As outlined in Appendix B, ATSDR conducted an extensive literature search to identify papers that have been published since the 1989 toxicological profile. This literature search includes a search of EPA's Toxic Substances Control Act (TSCA) database of industry studies submitted to EPA. Unpublished studies that were determined to be relevant to the profile were peer reviewed by at least three ATSDR-selected experts. ATSDR solicits unpublished studies when we are aware of their existence. Otherwise, ATSDR relies on the public comment period to obtain any additional studies that are not in the public domain. This request is published in the Federal Register Notice announcing the release of the profile for public comment.*

COMMENT: Along related lines, to acquire industrial and commercial information about 1,2-dichloropropane, I conducted a Google search using the descriptors *"1,2-dichloropropane AND MSDS OR "Safety Data Sheet,"* and found 12,400 results. I have not analyzed these results, except to note that multiple MSDS documents describing 1,2-dichloropropane are available. MSDSs (or, nowadays, SDSs) typically do not undergo external peer review, as might be arranged by the editor of an academic journal. They typically do undergo internal peer-review, however. Internal peer review may be at least as rigorous as external peer review, given corporate liability issues that must be addressed via completeness and accuracy of disclosure of subject-substance characteristics in a publically available SDS or MSDS.

RESPONSE: *MSDS/SDS documents are considered secondary sources. For most sections of the profile, it is not ATSDR's practice to use secondary sources. Additionally, it has been ATSDR's experience that most MSDS/SDS documents do not include citations that would allow for independent verification of the information.*

COMMENT: The Profile should clarify the passage quoted above: *"is now used in the United States only in research and industry." This* suggests a significant narrowing of the usage of 1,2-dichloropropane, whereas the subsequent clarification indicates only that it no longer is used in farming and *"some paint strippers, varnishes, and furniture finish removers."* This leaves the preponderance of potential categories of industrial use untouched, and suggests the potential fruitfulness of inquiring about health risks that might have motivated former industrial (and maybe also farm) users to cease using 1,2-dichloropropane.

RESPONSE: *The text in the overview regarding uses was simplified and clarified for the intended audience. The strike-out text was removed, and the underlined text was added:*

> *"1,2-Dichloropropane is ~~now~~ used in the United States as a chemical intermediate and in the manufacture of chlorinated and industrial solvents ~~only in research and industry~~. Before the early 1980s, 1,2-dichloropropane was used in farming as a soil fumigant ~~and was found in some paint strippers, varnishes, and furniture finish removers~~."*

COMMENT: Effects that have been observed only in animals are likely to be of concern to humans. The Profile appropriately states that such concern is *"presumed"* with respect to several health effect categories. When effects are observed *"only in animals,"* the presumption of concern is appropriate when the meaning of the phrase is that the effects were not *looked for* in humans. The presumption of concern is less appropriate if the effects indeed were looked for, but were not found, despite having been looked for, in humans.

RESPONSE: *As presented in Table C-18, the human data were considered inadequate for categorizing the level of evidence of most health outcomes (there were no developmental human data). Thus, the health effects conclusions were based on animal data. Upper respiratory, hematological, hepatic, central nervous system (CNS), and developmental effects were considered to be presumed effects in humans based on high levels of evidence in animal studies.*

COMMENT: Exposure conditions are described adequately for purposes of an executive summary. They are described more particularly elsewhere, in Chapter 5 and especially in Section 5.6. See my comments on the adequacy of description in Chapter 5.

RESPONSE: *No response is necessary.*

COMMENT: The derived inhalation and oral MRL values for acute- and intermediate-term exposure seem justifiable. However, the decision to derive no inhalation MRL and no oral MRL for chronic-duration exposure based upon database inadequacy seems premature. In this circumstance, the proper strategy is to seek literature on structurally similar substances, especially other chloropropane congeners, such as 2,2-dichloropropane… but no indication that this was done is included in the Profile, even though it cites two studies of structure-activity relationships (SARs).[1]

Application of available strategies such as analysis of SARs may generate only inadequate data for derivation of toxicity values… but this is irrelevant. The important criterion of due diligence is doing the diligent thing, which is to try untried strategies such as examining SARs, including qualitative and quantitative SARs.

I am unaware of specific studies that are not included in the profile that may be relevant to deriving MRLs for any of the 1,2-dichloropropane congeners. Even so, the Profile will support adequately the decision to derive, or not derive, MRL values only after feasible possibilities for doing so have been exhausted. In short, reasonable strategies should be followed, and the resulting decision explicated. My concern is that neither has been done, or done adequately.

[1] **Chroust K, Pavlova M, Prokop Z, *et al.*** *Quantitative structure-activity relationships for toxicity and genotoxicity of halogenated aliphatic compounds: Wing spot test of Drosophila melanogaster.* Chemosphere 67(1):152-159. 10.1016/j.chemosphere.2006.09.020, 2007;

Kawasaki, M. *Experiences with the test scheme under the chemical control law of Japan: An approach to structure-activity correlations.* Ecotoxicol. Environ. Safety, 4(4):444-54, 1980.

RESPONSE: *It is not current ATSDR practice to base MRLs on structurally related compounds. In some cases, known hazards for structurally related compounds may be reviewed to identify data needs for the profile compound.*

Chapter 2. Health Effects

COMMENT: The purpose of the *Health Effects* chapter is to provide *"a summary evaluation of the weight of evidence."* As a summary evaluation, Chapter 2 reflects adequately the findings in published literature. Indeed, the coverage is thorough and clear, and its graphical presentation is creative and communicative. As suggested above, however, it necessarily excludes any *unpublished* data evinced from inquiries of research and industry users of 1,2-dichloropropane, and of former farm and industry users, if such inquiries never were made.

RESPONSE*: ATSDR searched for unpublished industry-sponsored studies submitted to EPA under TSCA. Unpublished studies that were determined to be relevant to the profile were peer reviewed by at least three ATSDR-selected experts. ATSDR solicits unpublished studies when we are aware of their existence. Otherwise, ATSDR relies on the public comment period to obtain any additional studies that are not in the public domain. This request is published in the Federal Register Notice announcing the release of the profile for public comment.*

COMMENT: These represent a minority of studies considered. They include adequately designed studies, but human studies suffer generally from inherent limitations, regarding satisfaction of the criteria of causation in epidemiology (less of a problem for acute exposure). The human studies included in the Profile nonetheless are important standing alone. Because of the limitations of epidemiology studies, however, they also must be viewed in the broader context of the much larger number of animal studies that are controlled as human studies cannot (ethically) be controlled.

RESPONSE: *No response is necessary.*

COMMENT: The scope of animal studies reviewed in the Profile is broad. It includes many appropriate and adequately designed studies involving standard bioassay species (most notably rodents). It spans a broad range of investigated health endpoints.

An area where more lucid description would be desirable is in the immunological effects category. Description of these studies is somewhat unsatisfying in focusing more on morphological effects, for example on glands such as the thymus, but less on the consequence of exposure for endocrine and immune function. The statement is made that *"...it is not known if 1,2-dichloropropane caused an increased susceptibility to infections"* (page 74), which (if confirmed) would constitute an important effect on immune functioning. This issue deserves further attention and clarification in the Profile text.

RESPONSE: *After discussion of skin sensitization studies in Section 2.14, there is a statement–"No additional parameters of immunological function have been directly assessed following exposure to 1,2-dichloropropane in any available laboratory animal study." The following statement was added to emphasize the lack of immunological function assays:*

> *"Immune system evaluation in additional studies are limited to organ weight and/or histology, without evaluation of potential effects on immunological function."*

The statement quoted by this reviewer regarding susceptibility to infection refers to reduced survival in a mouse colony during a chronic study (in all exposure groups, with no apparent effect of 1,2-dichloropropane exposure). The statement was revised for clarity:

> *"However, available data is inadequate to determine if 1,2-dichloropropane caused an increased susceptibility to the infection observed in this study."*

COMMENT: The above issue of possible 1,2-dichloropropane effects on susceptibility to infection relates to the essential, broader issue of potential 1,2-dichloropropane effects on immune surveillance in animals and people. This issue is especially important, given the Profile statement that *"1,2-dichloropropane (and/or other chlorinated solvents) may increase the risk of developing CCA, a rare form of bile duct cancer"* (page 79). The text should clarify that CCA is cholangiocarcinoma.

Immune surveillance that protects against increased susceptibility to infections also may protect against cancer via distinguishing between 'self' vs. 'non-self '(foreign) tissue. When cells of the body become cancerous, a normal immune system would recognize them as foreign, and work to kill them. By suppressing the immune system, immunosuppressors may permit cancer development induced by carcinogens. These relationships should be elucidated more thoroughly, as should be the state of knowledge evinced from relevant (animal and human) studies.

RESPONSE: *No studies of immunological function following exposure to 1,2-dichloropropane that could inform potential changes in susceptibility to infection were identified. Therefore, data are inadequate to include a discussion of immune surveillance as a potential cancer mechanism for 1,2-dichloropropane. CCA was identified as cholangiocarcinoma at first mention (in Chapter 1); it is now also defined at first mention in Chapter 2.*

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

COMMENT: The issues of absorption, distribution, metabolism, and excretion of 1,2-dichloropropane are addressed only superficially in the Profile, in the sense that human studies were reported to be

unavailable, and animal studies instead were used to elucidate these toxicokinetic issues. However, the statement that human studies are unavailable is not entirely true, as indicated in the subsequent discussion of biomarkers: *"Kawai et al. (2015) showed significant correlation of 1,2-dichloropropane levels in workplace air with 1,2-dichloropropane levels in end-of-shift urine samples in print shop workers."* This statement constitutes strong evidence that humans excrete 1,2-dichloropropane via the urine. The exposure route would appear to be inhalation, or predominantly inhalation, unless significant absorption by the shift workers may be presumed to occur via ingestion or dermal exposure.

RESPONSE: *Kawai et al. (2015) was added to Section 3.1.4 (Excretion):*

> *"Data on excretion of 1,2-dichloropropane are limited to a biomarker study that reports a correlation between occupational 1,2-dichloropropane air levels and unmetabolized 1,2-dichloropropane levels in end-of-shift urine samples from exposed workers (Kawai et al. 2015). This indicates that urine is a route of excretion in humans following inhalation exposure. No additional studies were located regarding the rate or route of excretion of 1,2-dichloropropane following exposure in humans."*

COMMENT: As noted earlier, no attempt evidently was made to advance the toxicokinetics analysis via structure-activity relationships (SARs), for example, via literature that might be available regarding the closely related congener 2, 2-dichloropropane. Qualitative and quantitative SARs analysis, and SARS modeling, all might reveal little if any useful information regarding humans but, if available, SARs might elucidate possible differences between human and animal models. If such differences can be elucidated with respect to a congener, they might inform and improve extrapolation of 1,2-dichloropropane toxicokinetics from animals to humans. This is potentially very relevant regarding physiologically based pharmacokinetic (PBPK) modeling.

RESPONSE: *PBPK information that was available is presented in Section 3.1.5. Information regarding 2,2-dichloropropane could possibly be useful, but there would still be uncertainty in the extrapolation between the two congeners when developing the quantitative assessment.*

COMMENT: The Profile is inadequately informative regarding the possibly greater sensitivity of children to 1,2-dichloropropane. This issue must be viewed in the context of US EPA's longstanding special mandate regarding children's health, embodied by US EPA's *Children's Health Risk Initiative* (US EPA 2001)[2]. In 1997 the Office of Children's Health Protection was instituted within US EPA. Its mission was and remains "to make children's health protection a fundamental goal of public health and environmental protection…[by] ensuring strong standards that protect children's health." Commonly, a given airborne substance concentration will expose children more intensively than adults on a body-weight basis. Likewise, this may be the case with respect to ingestion, as in drinking water with a given substance concentration.

The Profile indicates that *"Populations at greater exposure risk to unusually high exposure levels to 1,2-dichloropropane are discussed in Section 5.7."* The issue of exposure risk based upon exposure levels differs from comparative exposure of children vs. adults where the same exposure concentration is involved. This distinction should be elucidated in the Profile. Similarly, the Profile states that *"[i]t is unclear if the developing fetus or neonate are* [sic] *uniquely susceptible to toxic effects of 1,2-dichloropropane, as all available studies report developmental effects at doses associated with parental toxicity."* This statement undermines the appropriate shift in the default assumption: that fetuses and neonates should be regarded as potentially more susceptible than members of the general population, at least based upon toxicokinetics, and in the absence of evidence to the contrary. This is a

subtle but critically important shift in the burden of proof arising from the weight of evidence of commonly greater susceptibility of fetuses, pregnant women, and children to potentially toxic substances. It should be reflected in the Profile text.

[2] **US EPA. 2001.** *Region 2's Management of Children's Health Risk Initiative and Related Projects.* Office of Inspector General Audit Report, Grant Management, Report No. 2001-P-00002. https://www.epa.gov/sites/production/files/2015-12/documents/kidshealth.pdf.

RESPONSE: *Based on available toxicity data, we cannot determine if the developing fetus or neonate are uniquely susceptible. Therefore, that statement has not been removed. It is not ATSDR practice to assume that children are more susceptible than adults are to the toxicity of the profiled substance. Susceptibility is assessed based on an evaluation of the chemical-specific toxicity data, as well as known differences in metabolism. ATSDR does recognize the general increased susceptibility of the young (e.g., employing default uncertainty factors for human variability in the development of MRLs); however, data are not specifically available. In response to a comment by another reviewer, a discussion on potential susceptibility due to metabolic differences between the developing fetus/neonate and the adult was added in Section 3.2:*

> *"Based on glutathione conjugation during metabolism of 1,2-dichloropropane (see Section 3.1.3), differences in glutathione metabolism due to life-stage and/or genotype may alter susceptibility" ... "differential expression of GST isoforms has been reported during developmental stages, compared to adults, which may alter the glutathione conjugating rate and capability (Raijmakers et al. 2001). Similar differences in hepatic cytochrome P450 expression have been reported throughout development (Hines 2007). These potential differences in age-related metabolism may infer differential susceptibility in the developing fetus, neonate, or child."*

COMMENT: The Profile is tentative with respect to interactions: *"Based on epidemiological studies in Japanese printers, there is some evidence to suggest a potential interaction between 1,2-dichloropropane and other chlorinated solvents."* Yet, organic solvents generally do exert at least additive effects. These effects may be deemed "interactions" in the sense that tolerance to one solvent (or its vapors) may be reduced (susceptibility increased) by the presence of another. This issue should be elucidated, and the Profile should elucidate relevant mechanism(s) producing additivity or, if applicable, synergism.

RESPONSE: *Available data are inadequate to elucidate the nature of the potential interactions, so further discussion of potential for increase susceptibility, additivity, and/or synergism would be inappropriate.*

Chapter 4. Chemical and Physical Information

COMMENT: Chemical and physical information is summarized appropriately, primarily in tabular form. Physical state is reported generally to be "liquid." This is true under STP: *standard temperature and pressure.* As the substance is volatile, however, it most definitely is not a liquid under all conditions. This caveat should be explicated.

RESPONSE: *The physical state reported in Table 4-2 is for standard temperature and pressure. This table also includes the vapor pressure, which would allow the reader to assess its volatility. Additionally, volatilization from environmental media is discussed in Section 5.4 of the profile.*

Chapter 5. Potential for Human Exposure

COMMENT: The subsection on production is poorly organized and difficult to comprehend. It encompasses in a single paragraph the topics of domestic production, global production, commercial sources, synthesis, and substances (such as pesticides) that contain 1,2-dichloropropane. A coterie of additional topics is included in the paragraph. These topics should be broken out and presented in a logical order, tracing the substance from its point of release to the environment until it reaches the receptor population(s). The discussion of domestic production trends should be separated from the subsequent discussion of global production, in separate paragraphs. Perhaps a tabular presentation (broader in scope than Table 5-1) would be helpful to augment the text.

RESPONSE: *Older data were consolidated, and the section was reorganized and broken down into paragraphs for clarity. The revised text is below:*

> *"In 1980–1984, the U.S. production of 1,2-dichloropropane was 59.8-77 million pounds (EPA 1995a; IARC 1986), of which >95% was used onsite as a captive chemical intermediate in the production of perchloroethylene and other chlorinated products (Dow Chem. Co. 1983; EPA 1986b). The 2012 Chemical Data Reporting (CDR) website updated in June 2014, which reports information on the production and use of chemicals manufactured or imported into the United States for 2010 and 2011, lists three companies as producing 1,2-dichloropropane, including Dow Chemical in Freeport, Texas, Dow Chemical in Midland, Michigan, and Dow Chemical in Plaquemine, Louisiana (EPA 2016d). Specific production volume data are listed as confidential business information (CBI), not available (N/A), or 0 for these companies. The 2016 CDR website, which reports information on the production and use of chemicals manufactured or imported into the United States for 2012, 2013, and 2014, listed two parent companies for 1,2-dichloropropane, The Dow Chemical Company with three facilities (Freeport, Texas; Midland, Michigan; Plaquemine, Louisiana) and Olin Corporation with two facilities (Freeport, Texas; Clayton, Missouri) (EPA 2017b). Aggregate production data for 1,2-dichloropropane during the years 2012 through 2015 are reported as 'withheld' in the 2016 CDR (EPA 2017b). Global production for 2001 has been reported as approximately 350 kilotonnes (OECD 2006)."*

> *"Dow Chemical discontinued production of soil fumigants containing 1,2-dichloropropane in 1991, and pesticide formulations containing this chemical are no longer available in the United States (EPA 1995a; IARC 2017; Meister 1987; OECD 2006). 1,2-Dichloropropane is no longer sold for consumer use in paint strippers, paint varnish, or furniture finish removers; the majority of this substance is used on-site or as a limited transport co-product/raw material for the production of other chlorinated compounds (Dow Chem. Co. 1983; EPA 1986b; OECD 2006)."*

> *"High-purity 1,2-dichloropropane is obtained commercially as a byproduct in the manufacture of propylene oxide in the chlorhydrin process. 1,2-Dichloropropane may also be obtained as a byproduct from the synthesis of allyl chloride (Langer et al. 2011). The high-purity product may also be obtained by the reaction of propylene and chlorine in the presence of an iron oxide catalyst at moderate temperature (45°C) and pressure (25–30 psia). Pesticide products that contain 1,2-dichloropropane were distillates of the chlorination of propylene (IARC 1986)."*

*"**Error! Reference source not found.** summarizes information on U.S. companies that reported the manufacture or use of 1,2-dichloropropane in 2016 (TRI16 2017). Toxics Release Inventory (TRI) data should be used with caution since only certain types of industrial facilities are required to report. This is not an exhaustive list."*

COMMENT: This subsection is deficient. It excludes information that was presented in the 1989 version of the Profile: *"Mobay Corporation imported 1 million lbs. of 1,2-dichloropropane from the German Federal Republic in 1986 (EPA 1987c). Mobay currently imports 1,2-dichloropropane from the German Federal Republic on an as-need basis on customer's request…"* Further, the Toxic Substances Control Act (TSCA) regulates chemicals in U.S. commerce, including chemicals that enter U.S. commerce via importation. TSCA includes reporting requirements. If information is unavailable, description of efforts to obtain it is necessary, along with reasons why the information was unavailable.

Further, if data were "withheld" from the Chemical Data Reporting (CDR) website, as apparently was the case with the Dow Chemical Company, non-web-based sources of the data should be sought. The EPA, for example, might provide aggregated data based upon reports received from multiple sources, all labeled *"confidential business information,"* much as epidemiologists must (code and) aggregate data for use in research reports without compromising individual patient privacy. None of these strategies was reported, and therefore appear not to have been applied. The abbreviations and acronyms table in Appendix G also should include and define 'CDR'.

RESPONSE: *Regarding Section 5.2.2, the Mobay import data were deleted in the updated profile because the information is over 30 years old and is no longer relevant. ATSDR relies on the CDR as the source of import/export data. As the focus of the toxicological profile is on health and toxicologic information, it is beyond the scope of the profile for ATSDR to identify why information was withheld in the CDR. Note that CDR is defined the first time it appears in the profile (Section 5.2.1) and was added to Appendix G.*

COMMENT: This subsection is deficient. It excludes information that was presented in the 1989 version of the Profile[3]. The 1989 information is out of date, but conceivably might constitute the most recent available information. The Profile, however, omits description of efforts to obtain data on use of 1,2-dichloropropane. The discussion of use requires thorough revision.

[3] Based on 1982 production data supplied by Dow (EPA 1986c), it has been estimated that over 95% of the isolated product manufactured by Dow Chemical is used on-site as a captive intermediate in the production of perchloroethylene and other chlorinated products by their 'per-tet' process (EPA 1986c, Dow Chem. Co. 1983). Approximately 3 million pounds per year of dichloropropane was marketed by Dow Chemical in 1982 for use as an industrial solvent for oils, fats, resins, waxes, and rubber, in ion exchange manufacture, in toluene diisocyanate (TDI) production, in photographic film manufacture, for paper coating, and for petroleum catalyst regeneration (HSDB 1988; IARC 1986; EPA 1986c). As of 1982, Dow Chemical no longer sold 1, 2-dichloropropane for use as a solvent in paint strippers, paint, varnish, and furniture finish removers as a low-cost alternative to methylene chloride. It had been a component of 10 of these products (EPA 1986c). By the end of 1983, its use as a solvent for film production was to be phased out in favor of l, l, l-trichloroethane (Dow 1983). According to Dow (1989), the phaseout of use of 1, 2-dichloropropane as a solvent for film production had not occurred as of June, 1989, although it is still planned. They further stated that the use of 34% in TDI production has now been discontinued, Outside of its use as a chemical intermediate, Dow Chemical Company's use pattern for 1, 2-dichloropropane in 1982 was 41% in ion exchange manufacturing, 34% in toluene diisocyanate (TDI) production, 19% in photographic film production, 4% in paper coating, and 2% in petroleum catalyst regeneration (Dow 1983).

An estimated 20 million pounds/year of dichloropropane were produced as a by-product in a mixture marketed as a soil fumigant which had been used in the cultivation of a variety of crops, including citrus fruits, pineapple, soya

beans, cotton, tomatoes, and potatoes (IARC 1986; HSDB 1988). Dow has discontinued production of soil fumigants containing 1, 2-dichloropropane, and pesticidal formulations containing this chemical are no longer available in the U.S. (Meister 1987). Other uses for 1,2-dichloropropane include an intermediate in the synthesis of carbon tetrachloride, lead scavenger in gasoline, textile stain remover, oil and paraffin extractant, scouring compound, and metal degreasing agent, especially prior to electroplating (IARC 1986). However, the largest manufacturer of 1, 2-dichloropropane, Dow Chemical Co. (1989), is not aware of its current uses as a lead scavenger in gasoline, textiles, stain remover, oil and paraffin extractant, scouring compound, and metal degreasing agent.

RESPONSE: *Regarding Section 5.2.3, in updating the toxicological profile, ATSDR deleted outdated information including use data from 1982. The profile does note that 1,2-dichloropropane is no longer used as a soil fumigant. Current uses of 1,2-dichloropropane are discussed in Section 5.2.3.*

COMMENT: This subsection is deficient. It excludes information that was presented in the 1989 version of the Profile[4]. The discussion of disposal requires thorough revision, with components similar to those described above.

[4]Incineration under controlled conditions appears to be the most viable method of disposal for 1, 2-dichloropropane (OHM-TADS 1988; HSDB 1988). It is reported that Dow Chemical incinerates 7 million pounds of 1,2-dichloropropane annually (EPA 1986c). Disposal through the use of a liquid injection incinerator requires a temperature range of 650 to 1600°C and residence time of 0.1 to 2 seconds. A rotary kiln incinerator requires a temperature range of 820 to 1600°C and a residence time of seconds. A fluidized bed incinerator requires a temperature range of 450 to 980°C and a residence time of seconds (HSDB 1988). Where land disposal of waste residue containing 1, 2-dichloropropane is sought, environmental regulatory agencies should be consulted on acceptable disposal practices (HSDB 1988). 1, 2-Dichloropropane may also be a constituent of wastewater streams.

RESPONSE: *Regarding Section 5.2.4, the information on the amount of 1,2-dichloropropene incinerated by Dow Chemical was deleted from the update profile because the information is over 30 years old and is not currently relevant.*

COMMENT: This subsection is more thorough than previous subsections described as 'deficient'.

RESPONSE: *No response is necessary to this comment on Section 5.3.*

COMMENT: This subsection is more thorough than previous subsections described as 'deficient'.

RESPONSE: *No response is necessary to this comment on Section 5.4.*

COMMENT: This subsection is more thorough than previous subsections described as 'deficient'.

RESPONSE: *No response is necessary to this comment on Section 5.4.2.*

COMMENT: This subsection is more thorough than previous subsections described as 'deficient'.

RESPONSE: *No response is necessary to this comment on Section 5.5.*

COMMENT: This subsection is more thorough than previous subsections described as 'deficient'.

RESPONSE: *No response is necessary to this comment on Section 5.6.*

COMMENT: This subsection is deficient. It apparently copies the discussion presented in the 1989 Profile. However, it omits other relevant data, for example on occupational exposure.

RESPONSE: *Workers were added as a population with potentially high exposures in Section 5.7:*

> *"Although industrial uses of 1,2-dichloropropane have decreased, workers who use 1,2-dichloropropane as a chemical intermediate (even in a "closed" system) are still considered a potentially high exposure group."*

Chapter 6. Adequacy of the Database

COMMENT: Chapter 6 summarizes the adequacy of the database and any "data needs," which are substance-specific informational needs that, if met, would reduce or eliminate uncertainties of the human health risk assessment. Footnotes in this peer review report present citations that may have been omitted from consideration, or considered in a narrower context than would be appropriate. That is, the issue of database adequacy depends upon recognition of the relevance of available data; if recognition is absent, apparent data needs increase.

As noted earlier, for example, two citations of studies used in the Profile address the issue of structure-activity relationships (SARs). That issue, however, was omitted from consideration in the Profile. A broader use of the cited studies, along with other studies on SARs, might contribute significantly to reducing uncertainties explicated in the Profile, and thereby increase its quality.

The profile highlights several areas of uncertainty, with the comment that additional studies would reduce uncertainty regarding those areas. Yet, some available studies do indeed inform some of those issue areas, but were not used to the fullest possible extent. A further example (in addition to SARs studies cited in the Profile) is excretion. As stated earlier*: "... the statement that human studies are unavailable is not entirely true, as indicated in the subsequent discussion of biomarkers: "Kawai et al. (2015) showed significant correlation of 1,2-dichloropropane levels in workplace air with 1,2-dichloropropane levels in end-of-shift urine samples in print shop workers." This statement constitutes strong evidence that humans excrete 1,2-dichloropropane via the urine. The exposure route would appear to be inhalation, unless the shift workers may be presumed to ingest or dermally absorb the substance."*

RESPONSE: *Regarding SAR citations mentioned by the reviewer (Chroust et al. 2006; Kawasaki 1980), both references contain compound-specific data, which is preferable to SAR-generated data due to increased uncertainty associated with SAR data. Therefore, compound-specific data are cited in Section 2.20 (Genotoxicity) from Chroust et al. (2006) and Section 5.4 (Environmental Fate) from Kawasaki (1980). In general, use of SAR data in toxicological profiles is limited. In some cases, known hazards for structurally related compounds may be reviewed to identify data needs for the profile compound. However, for 1,2-dichloropropane, available compound-specific data preclude the need for consideration of SARs for identification of potential hazards.*

Regarding Kawai et al. (2015), this paper was added to the discussion in Section 3.1.4. (Excretion) as suggested. However, this singular study identifying that 1,2-dichloropropane is excreted in the urine does not really address the toxicokinetic data needs in humans. No other potential routes of excretion

were evaluated, and no metabolites were evaluated. This study is of limited usefulness, particularly with regards to comparative toxicokinetics.

Chapter 7. Regulations and Guidelines

COMMENT: The chapter addresses broadly and appropriately the issue of applicable international and national regulations and guidelines. Table 7-1 cautions that the list is not exhaustive, *"and current regulations should be verified by the appropriate regulatory agency."* This statement suggests the possibility that highly relevant guidelines and/or regulations might be omitted. I agree that the list need not be "exhaustive," and that an encyclopedic presentation that might be of value for attorneys would be dense and impenetrable for most users of ATSDR Toxicological Profiles.

The Profile appropriately presents numerous guidelines and regulations up to the year 2017. I have one concern: that some of the most stringent guidelines or regulations might be among those missing. Some discussion should be included to assure readers that an attempt was made to identify systematically the most stringent toxicology-based guidelines and regulations nationally and internationally.

RESPONSE: *It is not possible to assess what guidelines/regulations would be highly relevant to a particular user. The purpose of the statement in Chapter 7 that the list is not exhaustive is to inform the reader that other guidelines/regulations may be available. Table 7-1 provides a list of guidelines/ regulations that ATSDR typically includes in a profile and may be used by health assessors; the table also states whether there are no values for a particular guideline/regulation. The Agency does not attempt to identify the most stringent guidelines/regulations; but, rather includes national guidelines/regulations that are most frequently used by its users.*

Chapter 8. References

COMMENT: My comments on references used and references cited are distributed in text, above.

RESPONSE: *See previous responses to comments, above.*

Appendix A. Minimal Risk Levels (MRLs)

COMMENT: Appendix A documents and explains how ATSDR derived its MRLs for **1,2-dichloropropane.** This discussion is encyclopedic. This level of detail is appropriate for the Appendix, conveniently providing in-document technical information for users requiring it. The encyclopedic coverage supports MRLs appropriately presented more generally in the main body of the Profile. My comments on specific MRLs, or their absence, are provided in text above, and will not be repeated here.

RESPONSE: *The Reviewer has provided comments on specific MRLs; as the Reviewer indicates, these comments (and the responses) are provided above.*

COMMENT: I do have concerns about the formalism, including mathematical formalism, applied in MRL derivations with respect to "uncertainty factors" (and beyond). Consider, for example, the MRL Worksheet relating to intermediate oral exposure (page A-33). The summary states ***"****Uncertainty Factor: 1,000 mg/kg/day."* Mathematically, the uncertainty factor should be dimensionless, as reflected in the

explanatory *MRL Summary* text beneath: *"a total uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human availability)."* This is correct, because it omits the superfluous and misleading dimension "mg/kg/d."

RESPONSE: *The units on the uncertainty factor were in error. They have been removed.*

COMMENT: The form of the dimension "mg/kg/d" also is mathematically ambiguous. A correct, unambiguous expression of this term is "mg/(kg d)." This distinguishes the term from the unintended "(mg d)/kg)," which also could be derived from "mg/kg/d" [via mg x 1/kg/d = mg x d/kg = (mg d)/kg)]. That is, day (d) belongs in the denominator, whereas the expression "mg/kg/d" can place it in the numerator or the denominator. This applies, of course, throughout the Profile, and all Profiles.

RESPONSE: *This is a standard reporting unit found in the published literature and used in ATSDR profiles.*

COMMENT: As a final comment, three "uncertainty factors" are explicated above, leaving open the issue of whether a *safety factor,* or *safety factors,* also should be applied. The answer may be 'no', but in that case, the formalism expressed above as *"uncertainty factor"* should be changed to *"safety and uncertainty factors,"* thereby clarifying that both parameters are encompassed within the derived MRL. A formal distinction between the concepts of safety factors and uncertainty factors should support such discussion.

RESPONSE: *The comment refers to boilerplate text. ATSDR will consider the Reviewer's suggestion in future versions of the profile guidance.*

Appendix B. Literature Search Framework for 1,2-Dichloropropane

COMMENT: Appendix B presents ATSDR's protocol for completing the literature search and screening for the health effects chapter of the Profile. The discussion is deficient in three respects:

--1. it is general, failing to describe separately the literature search strategy (or strategies) applied to each specific topic area,

--2. it is non-specific, omitting the cut-off date of the literature search generally, and with respect to the search in each topic area, and

--3. it is incomplete, omitting specific health effect topics, as well as topics outside of the health effect area (see below).

Appendix B fails to encompass the SARs issue highlighted earlier. The literature search nonetheless may encompass adequately the broad scope of health effects literature specifically related to 1,2-dichloropropane. Specific areas, some exemplified in earlier comments, suggest that the breadth of description in Appendix B might be overly broad for specific issues. As noted earlier, I found no discussion of the search strategy for international and national guidelines and regulations.

As a general comment, information search strategies should be described in more detail in connection with each specific (reasonably delineated) topic area, rather than merely broadly, to assure completeness of toxicological issue coverage. The cut-off date for literature searches should be specified.

Appendix B Table B-2 is useful but still inadequate in this regard. Table B-2, for example, reports access dates for PubMed (2016.12.20), Toxline (2016.12), and Toxcenter (2016.12). These dates are not tied to any specific topic area, and do not preclude other searches. Further, the query strings seem to be defined *a priori,* but that is not how searches typically are conducted. My own searches, for example, usually depend upon what I encounter, which is to say, they are not defined *a priori.* Finally, all three databases have search dates in the year 2016, whereas guidelines and regulations are tabulated into the year 2017, illustrating that Table B-2 cannot be used to infer cut-off dates for information searching in the draft Toxicological Profile for 1,2-dichoropropane.

RESPONSE: *ATSDR typically conducts one literature search to identify all relevant data for the profile. It clearly states in Section B.1.1 that the literature search was conducted in December 2016 and that the literature search was intended to update the existing toxicological profile and was restricted to January 1987 to December 2016.*

ATSDR disagrees with the Reviewer that the literature search strategy employed by ATSDR is not typical of how literature searches are conducted. ATSDR notes that other government agencies, such as EPA, use a similar approach to conducting literature searches for comprehensive documents on a particular compound. If necessary, ATSDR will conduct additional literature searches on very specific topics, these additional searches would also be documented in Appendix B. For 1,2-dichloropropane, additional searches were not conducted. Since ATSDR does not typically discuss structure activity relationships in detail, special searches on this topic were not included.

In Section B.1.1, ATSDR notes--Regulations applicable to 1,2-dichloropropane were identified by searching international and U.S. agency websites and documents—*given the amount of time needed to prepare the first draft of the profile, these databases were not searched until 2017.*

Appendix C. Framework for ATSDR's Systematic Review of Health Effects Data

COMMENT: The purpose of Appendix C is to present the protocol ATSDR that used to complete the systematic review for the health effects chapter of the profile, including identification of the most relevant endpoints, evaluation of the quality of the relevant studies, and integration of evidence to develop hazard identification conclusions. In this endeavor, Appendix C is highly successful. Two strengths deserve highlighting:

--1. It is generic, and
--2. The generic framework is filled in with Profile-specific data.

RESPONSE: *No response is necessary.*

Appendix G. Acronyms, Abbreviations, and Symbols

COMMENT: As noted earlier, Appendix G omits at least one acronym. In general, in a large document such as the Profile under review, readers should not be expected to peruse large numbers of prior pages to find the first mention, and the only definition, of an abbreviation, acronym, or symbol. Any abbreviation, acronym, or symbol appearing at least twice, undefined in text after the first mention, should be included in the appendix. As a general suggestion, a generic table of abbreviations, acronyms, and symbols commonly used in ATSDR Toxicological Profiles might be included in the current Profile, and in all Profiles.

RESPONSE: *ATSDR does include a list of commonly used acronyms in Appendix G. At the Reviewer's request, ATSDR added CDR to Appendix G.*

Overall Usability of the Profile

COMMENT: I have no problem with the overall formatting of the Profile. Further, the new tables and figures are creative and informative. Several comments made earlier relate to overall usability. For example, I expressed concerns about the formalism, including mathematical formalism, applied in MRL derivations with respect to "uncertainty factors" (and beyond). These comments were presented in the context of the subject Profile, but they also apply to Profiles generically.

Consider, for example, the MRL Worksheet relating to intermediate oral exposure (page A-33). The summary states *"Uncertainty Factor: 1,000 mg/kg/day."* Mathematically, the uncertainty factor should be dimensionless, as reflected in the explanatory *MRL Summary* text beneath: *"a total uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human availability)."* This is correct, because it omits the superfluous and misleading dimension "mg/kg/d." This correction applies to ATSDR Toxicological Profiles generically.

RESPONSE: *As stated in previous response, the mg/kg/day units on the uncertainty factors for the oral MRLs was in error and has been removed.*

COMMENT: The form of the dimension "mg/kg/d" also is mathematically ambiguous. A correct, unambiguous expression of this term is "mg/(kg d)." This distinguishes the term from the unintended "(mg d)/kg)," which also could be derived from "mg/kg/d" [via mg x 1/kg/d = mg x d/kg = (mg d)/kg)]. That is, day (d) belongs in the denominator, whereas the expression "mg/kg/d" can place it in the numerator or the denominator. This applies, of course, throughout the subject Profile, and all Profiles.

RESPONSE: *This is a standard reporting unit found in the published literature and used in ATSDR profiles.*

COMMENT: Further, "uncertainty factors" were applied in the subject Profile, leaving open the issue of whether a *safety factor,* or *safety factors,* also should be applied. The answer may be 'no', but in that case, the formalism expressed above as *"uncertainty factor"* should be changed to *"safety and uncertainty factors,"* thereby clarifying that both parameters are encompassed within the derived MRL. A formal distinction between the concepts of safety factors and uncertainty factors should support such discussion. This applies, of course, throughout the subject Profile, and all Profiles.

RESPONSE: *The comment refers to boilerplate text. ATSDR will consider the Reviewer's suggestion in future versions of the profile guidance.*

COMMENT: Additionally, I find that the title of the Toxicological Profile, and I believe of all Profiles, is awkward and even incorrect: *Toxicological Profile for 1,2-Dichloropropane.* Toxicological profiles are not "for" substances. They are profiles "of" substances. I suggest adopting a generic Profile title that is grammatically correct, such as (in the subject case): *Toxicological Profile of 1,2-Dichloropropane.*

RESPONSE: *ATSDR will consider the Reviewer's suggestion in future versions of the profile guidance.*

Comments provided by Reviewer #3

ATSDR Charge Questions and Responses and General Comments

Chapter 1

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

COMMENT: Yes, I agree with the human health effects reported in the text.

RESPONSE: *No response is necessary.*

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: Due to the observations that in accidental or intentional exposures to 1,2-dichloropropane (or mixtures), the profile of organ toxicities observed were similar to those exhibited in animals, therefore, I agree that the effects observed in animals are likely to be of concern to humans.

RESPONSE: *No response is necessary.*

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

COMMENT: Yes, I agree that the exposure conditions have been adequately described.

RESPONSE: *No response is necessary.*

QUESTION: Do you believe the derived MRL values are justifiable? If you disagree, please explain. (see also Appendix A)

COMMENT: Yes, I agree that the derived MRL values are justifiable. The derivations are adequately described in appendix A.

RESPONSE: *No response is necessary.*

QUESTION: Do you agree that the data do not support derivation of MRLs?

COMMENT: Yes, the available data is sufficient to derive MRLs for 1,2-dichloropropane based on the findings of upper respiratory effects following inhalation exposures, and hematological, CNS, hepatic and developmental toxicities following oral exposures for acute and intermediate exposures, however, for chronic studies, the available data is not sufficient to support the derivation of chronic MRLs for 1,2-dichloropropane.

RESPONSE: *No response is necessary.*

COMMENT: Figures 1-1 and 1-2 – both figures indicate the observation of cancer as a chronic effect. This might be more informative if the figure include in which organ cancer was observed.

RESPONSE: *Organ systems affected at the cancer effect level (CEL) were added to Figures 1-1 and 1-2 (lung for inhalation, liver for oral).*

COMMENT: While it is recognized that the dermal studies that was performed did not yield any toxicity data that should be included in the summary of observations, perhaps a statement reflecting that comment could be included.

RESPONSE: *Inhalation and oral data are the focus of this review because dermal MRLs are not derived. The hazard identification paragraph in Chapter 1 was revised to emphasize that only oral and inhalation data were included in the systematic review (new text is underlined):*

> *"As illustrated in Figures 1-1 and 1-2, the most sensitive effects in laboratory animals <u>following inhalation or oral exposure</u> appear to be upper respiratory tract (nasal) damage, liver damage, anemia, central nervous system (CNS) depression, and delayed ossification in fetuses."*

COMMENT (page4, lines 1-2, and 18-21): – for clarity, indicating that these effects were observed in human exposures might be helpful

RESPONSE: *Text was revised to clarify that effects were observed in humans (new text is underlined):*

> *"Limited data from chemical spill accident reports indicate that exposure to high concentrations of 1,2-dichloropropane can cause respiratory tract irritation <u>in humans</u> (ACGIH 2014; Rubin 1988)."*
>
> *"Hemolytic anemia as well as incidences of disseminated intravascular coagulation have been reported <u>in humans</u> following accidental or intentional acute exposure to high levels of 1,2-dichloropropane, some of which were fatal (Di Nucci et al. 1988; Fiaccadori et al. 2003; Lucantoni et al. 1991, 1992; Perbellini et al. 1985; Pozzi et al. 1985)."*

Chapter 2

QUESTION: Do the health effect conclusions made in Chapter 2 adequately reflect the findings in the published literature for 1,2-Dichloropropane?

COMMENT: Yes, I agree with the conclusions made in chapter 2; the most sensitive effects in laboratory animals appear to be upper respiratory tract (nasal) damage, liver damage, anemia, central nervous system (CNS) depression, and developmental toxicity (delayed ossification in fetuses).

RESPONSE: *No response is necessary.*

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: Human exposure studies were identified and described in the profile. However, these were not adequately designed, they were not controlled human exposure studies, and largely did not (or could not) control for confounding factors such as co-exposure to other chlorinated solvents, lack of exposure data, etc. The limitations of these studies were sufficiently described in the text. Further, the process used for scientific review of the literature and the outcome of the data analysis (as described in Appendices B &C) support that while the human exposure studies identified endpoints of toxicological significance, the studies were weighted as having a high risk of bias, and a low overall confidence in the study. I agree with those conclusions.

RESPONSE: *No response is necessary.*

QUESTION: Were adequately designed animal studies identified in the text (i.e., adequate number of animals, good animal care, accounting for competing causes of death, sufficient number of dose groups, and sufficient magnitude of dose levels)? If not, does the inadequate design negate the utility of the study? Please explain.

COMMENT: Yes, adequately designed animal studies were identified and described in the text. As noted in the response to the above question, the process used for scientific review of the literature and the outcome of the data analysis (as described in Appendices B &C) thoroughly evaluated the appropriateness of the existing scientific literature and determined the overall confidence in each study. I agree with those conclusions.

RESPONSE: *No response is necessary.*

QUESTION: Were the animal species appropriate for the most significant toxicological endpoint of the study? If not, which animal species would be more appropriate and why?

COMMENT: Yes, I agree with the selection of the principal studies and the species selected.

RESPONSE: *No response is necessary.*

QUESTION: Are you aware of any studies that are not included in the profile that may be important in evaluating the toxicity of 1,2-Dichloropropane? Please provide a copy of each study and indicate where in the text each study should be included.

COMMENT: I am not aware of additional studies that should be included in the profile that are relevant to evaluating the health effects of 1,2-dichloropropane.

RESPONSE: *No response is necessary.*

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 1,2-Dichloropropane isomers?

COMMENT: I am not aware of additional studies that would assist in deriving MRLs for 1,2-dichloropropane.

RESPONSE: *No response is necessary.*

QUESTION: Were all appropriate NOAELs and/or LOAELs identified for each study (both in the text and the Levels of Significant Exposure (LSE) tables and figures)? If not, did the text provide adequate justification for excluding NOAELs/LOAELs including, but not limited to, citing study limitations? Please suggest appropriate changes.

COMMENT: I agree that appropriate NOAELs (when available) and LOAELs were identified for each study and were accurately written in tables and figures. As noted in other sections of this review, the process used for scientific review of the literature and the outcome of the data analysis (as described in Appendices B &C) thoroughly evaluated the appropriateness of the existing scientific literature and determined the overall confidence in each study, a process that included evaluating the appropriateness of NOAELs and/or LOAELs. I have no changes to suggest for this section of the profile.

RESPONSE: *No response is necessary.*

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

COMMENT: As noted in the profiles document, LOAELs have been categorized into "less serious" or "serious" effects. "Serious" is defined as effects that elicit alteration of a biological system that can lead to morbidity or mortality whereas "Less serious" is defined as effects that are not expected to cause significant dysfunction or death. While it is acknowledged that this is not a quantitative classification, but rather a categorization based on judgement and knowledge of biological processes, I agree with this classification and feel that these descriptors have been appropriately cited in the LSE tables included in this chapter.

RESPONSE: *No response is necessary.*

QUESTION: Have all possible mechanisms of action been discussed within their relevant health effect section? If not, please explain.

COMMENT: A section on possible mechanisms of action was included following the discussion of many, but not all, of the organ/system toxicity data sections included in chapter 2. In general, no specific mechanism(s) for the observed toxicity has been proposed largely due to a lack of data concerning mechanism(s) of action for 1,2-dichloropropane . Glutathione depletion was listed as a common mechanism proposed for most of the organ/system toxicities observed (respiratory, hemolytic anemia, renal, liver). In support of this proposed mechanism, a mechanistic studies demonstrated that pre-treatment with N-acetylcysteine reduced 1,2-dichloropropane renal and hepatic toxicities. I agree, given that glutathione conjugation is a major detoxification pathway for 1,2-dichloropropane, this is a possible mechanism for the observed toxicity. Due to the paucity of mechanistic research conducted with 1,2-dichloropropane, I feel that this section adequately describes potential plausible mechanisms for toxicity.

RESPONSE: *No response is necessary.*

QUESTION: Are the hazard identifications clear and justifiable based on ATSDR's systematic review (SR) process? (In other words, if you follow ATSDR's SR protocol from start to finish, would you come to the same hazard identification conclusions?) If not, discuss where in the process there was a deviation from the protocol.

COMMENT: Yes, I agree that the hazard identifications were presented in a logical, clear and justifiable manner. The systematic review process used by ATSDR for the preparation of this toxicological profile was comprehensive and provided a balanced approach to assessing the validity, strengths, weaknesses and biases of each study included in the document. Irrespective of a few comments and questions provided in response to questions concerning derivation of MRLs and application of uncertainty factors (described later in this review), I feel that I would arrive at similar hazard identification conclusions described in this profile.

RESPONSE: *No response is necessary.*

COMMENT (page 54, line 22): while the profile described how the literature that was selected for inclusion in this document was evaluated (peer-review, etc.), it is questions whether the abstract of Matsumoto et al (1982) contained sufficient details to include in this document.

RESPONSE: *ATSDR may opt to include an abstract in a toxicological profile when it addresses a data gap. Matsumoto et al. (1982) is the only study reporting an oral LD_{50} in mice. The LSE entry was revised to indicate that this study is an abstract only for transparency. However, the Matsumoto et al. (1982) abstract was deleted from the hepatic section and the systematic review of the hepatic endpoint due to points brought up by this Reviewer. Additionally, Matsumoto et al. (1982) was erroneously cited in the immune section instead of Matsumoto et al. (2013). This error has been corrected.*

COMMENT (page P55, lines 7-9): information appears to be lacking. For example, how many animals were studied? how many death occurred?

RESPONSE: *The requested information is not available in Smyth et al. (1969) study, which reported acute toxicity data for 200 compounds in tabular format.*

COMMENT (page 62, line 25): typo? "rats exposed once to a gavage doses up to …"

RESPONSE: *The typographical error was corrected to read "rats exposed once to a gavage dose up to . . .".*

COMMENT (Section 2.19 – Cancer): As noted elsewhere in this review, this reviewer feels that much of the human exposure data for the Japanese print workers reviewed in this document should be interpreted with caution as 1,2-dichloropropane was not the only chlorinated solvent (and/or or other unknown chemicals) to which the individuals were exposed. Conclusions on the relationship of 1,2-dichloropropane to CCA risk based on these data should be tempered to balance this major limitation.

RESPONSE: *ATSDR does not make weight-of-evidence statements regarding cancer data, so no conclusions on the relationship of 1,2-dichloropropane to CCA were made. Throughout the text and tables in the Section 2.19, it is clearly noted when multiple exposures occurred. However, the summary in Chapter 1 (Section 1.3) was revised to emphasize exposure to additional solvents (and exposure ranges where available) to address this Reviewer's concern (new text underlined):*

> *"Actual air levels of chlorinated solvents were not measured, but based on quantities of chemicals reportedly used, some studies estimated that print shop workers were exposed to 1,2-dichloropropane at concentrations ranging from 5 to 346 ppm (Kumagai et al. 2013, 2016; Yamada et al. 2014, 2015a, 2015b). Most workers were also exposed to other chlorinated solvents, including dichloromethane (15–360 ppm) and/or 1,1,1-trichloroethane (exposure levels not estimated)."*

COMMENT (page 85, lines 6-8): the document indicates that the incidence was significantly elevated, it would be useful to include the background (general population) rate in the text.

RESPONSE: *The expected incidence rate based on the general population was added in Section 2.19 as requested:*

> *"When considering these four plants together, the CCA incidence was 17/95 (18%), which was significantly elevated compared with the incidence expected based on the rates in the general Japanese population (0.02%), both in workers exposed to 1,2-dichloropropane only or both 1,2-dichloropropane and dichloromethane (Kumagai et al. 2016)."*

COMMENT (page 85, lines 10-13): It would be useful to include the relative risk and confidence intervals that are reported in Table 2-4 at this point in the body of the text.

RESPONSE: *The text was revised to refer the reader to Table 2-4, which is on the previous 5 pages. The relative risk (RR) and confidence interval (CI) values were not re-reported, consistent with ATSDR format guidance.*

> *"Further analysis reported a statistically significant increase in relative risk across cumulative exposure to 1,2-dichloropropane (see Table 2-4)."*

COMMENT (page 92, line 19): typo? "occupational exposure to 1,2-dichloropropane"?

RESPONSE: *The typographical error (missing "to") was corrected on pg. 92, line 29.*

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: There are limited studies that have been conducted concerning the ADME of 1,2-dichloropropane. Those that are available are adequately described in this section. This section did

not include any information on PK parameter such as biological half-life, volume of distribution, bioavailability. Please confirm that this information does not exist in the available scientific database.

RESPONSE: *Biological half-life and AUC values in rats following inhalation or oral exposure from Take et al. (2014, 2017) were added in Section 3.1.4 (Excretion). Volume of distribution and bioavailability data were not available in identified sources.*

> *"Elimination half-life ($t_{1/2}$) values and area under the curve values over the first 1,440 minutes ($AUC_{0–1,440}$) were estimated in rats for blood and select organs following inhalation or oral exposure (Take et al. 2014, 2017). Values are presented in Tables 3-1 and 3-2, respectively. These values support that at low levels accumulation of 1,2-dichloropropane in the body is not expected; however, concentration in body fat is predicted if the metabolic capacity is exceeded following high-level inhalation or oral exposures."*

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

COMMENT: PBPK models for 1,2-dichloropropane have not been developed. The document did provide information from a one-compartment PK model for 1,2-dichloropropane that provided limited data blood clearances.

RESPONSE: *No response is necessary.*

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: Toxicokinetic information for 1,2-dichloropropane are limited. As such, little discussion of differences between animals and humans can be included in this section. The document does include a statement, that, in general, the toxicity targets of 1,2-dichloropropane that have been identified in animal studies have been reported in case studies of human exposures to 1,2-dichloropropane. I agree with that statement.

RESPONSE: *No response is necessary.*

COMMENT (page 94, lines 12-17): This statement implies that skin absorption occurs based on a single case report in which human exposure resulted in systemic toxicity. This appears an overstatement as the exposure was not exclusively to 1,2-dichloropropane, but rather a mixture that also contained a high percentage of toluene. Thus, the observed effects may or may not be attributed to 1,2-dichloropropene. I suggest revising this section to reflect this uncertainty.

RESPONSE: *The statement in Section 3.1.1 was revised to reflect that observed effects may be attributable to 1,2-dichloropropane and/or toluene:*

> *"Systemic toxicity (acute renal failure, impaired liver function, acute hepatocellular necrosis, rhabdomyolysis, and severe disseminated intravascular coagulation) in a human case report following prolonged dermal exposure (~5 hours) to a commercial fixative containing 30–40% 1,2-dichloropropane and 33–38% toluene (Fiaccadori et al.*

2003) may also be attributable to dermal absorption of 1,2-dichloropropane and/or toluene."

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

COMMENT: I am not aware of any additional data concerning the effect of 1,2-dichloropropane on children's health or developmental toxicity that should be included in this document.

RESPONSE: *No response is necessary.*

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: As noted in the profile, no populations with unusual/increased susceptibility have been described in the available scientific literature. I agree that the developing fetus or neonate could be a uniquely susceptible population. As CYP2E1 is proposed as being involved in the toxification of 1,2-dichloropropane and this P450 exhibits ontogenic expression, (Hines RN, J Biochem Mol Toxicol. 2007;21(4):169-75. Ontogeny of human hepatic cytochromes P450), and further, GSH levels and GST isoforms are also different during development versus adult (M.T.M. Raijmakers E.A.P. Steegers W.H.M. Peters. Glutathione S-transferases and thiol concentrations in embryonic and early fetal tissues Human Reproduction, 2001; 16 (11): 2445–2450), differences in metabolism between early life-stage and adult exposure might be expected.

I agree that other potentially susceptible populations could be those carrying variant GST phenotypes.

RESPONSE: *Section 3.2 has been expanded to included suggested references and discuss differences in metabolism at different life-stages, and the potential effects on susceptibility:*

"Based on glutathione conjugation during metabolism of 1,2-dichloropropane (see Section 3.1.3), differences in glutathione metabolism due to life-stage and/or genotype may alter susceptibility" . . . "differential expression of GST isoforms has been reported during developmental stages, compared to adults, which may alter the glutathione conjugating rate and capability (Raijmakers et al. 2001). Similar differences in hepatic cytochrome P450 expression have been reported throughout development (Hines 2007). These potential differences in age-related metabolism may infer differential susceptibility in the developing fetus, neonate, or child."

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

COMMENT: Yes, unmetabolized 1,2-dichloropropane in urine is specific to exposure, dichloropropane glutathione conjugates would also be relatively specific biomarkers for exposure to 1,2-dichloropropane.

RESPONSE*: No response is necessary.*

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

COMMENT: No, biomarkers of effect for exposure to 1,2-dichloropropane would not be specific for exposure to this chemical, but would likely be common among other chlorinated solvents.

RESPONSE: *No response is necessary.*

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

COMMENT: This section of the profile includes statements indicating that there is some evidence for the interaction of 1,2-dichloropropane with other chlorinated solvents in the increased CCA observed in studies of Japanese printers. I disagree with this statement. Since the chemical exposure was to mixtures, it is equally as likely that the other chemicals were causal to cancer induction. Further, as noted in this document, in other human populations exposed to 1,2-dichloropropane, an increase in CCA was not observed. This section might be drafted to better reflect this uncertainty.

The remainder of this section describes the limited number of studies that have experimentally tested the interaction of 1,2-dichloropropane with other chemicals in animals.

RESPONSE: *The section on chlorinated solvents in Section 3.4 was revised to soften the language regarding the evidence for a potential interaction as well as to point out the uncertainty mentioned by this reviewer. The strike-out text was removed, and the underlined text was added:*

> *pg. 104 – "Based on epidemiological studies in Japanese printers, there ~~is some evidence to suggest a potential~~ may be an interaction between 1,2-dichloropropane and other chlorinated solvents (e.g., dichloromethane) with regard to the development of CCA (Kubo et al. 2014a, 2014b; Kumagai et al. 2013, 2014, 2016; Sobue et al. 2015; Yamada et al. 2014, 2015a, 2015b). However, available data are inadequate to determine the existence and/or nature of the potential interaction (e.g., one chemical may induce CCA on its own, regardless of co-exposure with additional chlorinated solvents)."*

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: For the few studies that have evaluated chemical interactions with 1,2-dichloropropane, the text described the interactions as additive (or not greater than additive).

RESPONSE: *No response is necessary.*

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: There is nothing missing/incorrect that I am aware of in this section.

RESPONSE: *No response is necessary.*

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

COMMENT: The physical and chemical properties of 1,2-dichloropropane are presented in this section.

RESPONSE: *No response is necessary.*

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: I To my knowledge, the information on production, import/export, use and disposal is complete. I am not aware of additional references that should be included in this section.

RESPONSE: *No response is necessary.*

QUESTION: Has the text appropriately traced the substance from its point of release to the environment until it reaches the receptor population? Does the text provide sufficient and technically sound information regarding the extent of occurrence at NPL sites? Do you know of other relevant information? Please provide references for added information.

COMMENT: Yes, information on the presence of 1,2-dicholropropane from its point of release through point of human contact appear adequately detailed for air water, and soil routes of transport.

RESPONSE: *No response is necessary.*

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: While environmental chemistry is not my area of expertise, this section appears to adequately describe the transport, partitioning, transformation, and degradation of 1,2-dichloropropane in air, soil and water. I am not aware of additional information that should be included in this section.

RESPONSE: *No response is necessary.*

QUESTION: Does the text provide information on levels monitored or estimated in the environment, including background levels? Are proper units used for each medium? Does the information include the form of the substance measured? Is there an adequate discussion of the quality of the information? Do you know of other relevant information? Please provide references for added information.

COMMENT: Yes, information on levels of 1,2-dichloropropane that were monitored or estimated in the environment were included in this section of the document. The document referred to the quantitation of 1,2-dicholorpropane as the form of the chemical measured throughout this section. I

believe that there was adequate discussion of the quality of the information provided. I am not aware of additional information that should be included in this section.

RESPONSE: *No response is necessary.*

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: This section contains information on general population exposures, including results from NHANES, and drinking water surveys, as well as occupational exposures studies conducted by NIOSH, as well as other occupational sources.

Concerning populations with potentially high concentrations, I agree that individuals consuming contaminated drinking water would have a high potential for 1,2-dichloropropane exposure (such as the Philadelphia population described in the document). I also agree that populations living in close proximity to waste sites in which 1,2-dichloropropane has been disposed should be considered a potentially high exposure population. Although industrial uses have decreased and the industries suggest that 1,2-dicholorpropane is used in "closed" systems, occupational exposures should still be considered a potentially high exposure group.

RESPONSE: *In Section 5.7, workers have been added as a potentially high exposure group:*

> *"Although industrial uses of 1,2-dichloropropane have decreased, workers that use 1,2-dichloropropane as a chemical intermediate (even in a "closed" system) are still considered a potentially high exposure group."*

COMMENT (page 111, line 20): can an alternate wording for "the carbon filter was reportedly spent" be used in the document?

RESPONSE: *In Section 5.3.2, the word "spent" was replaced with the word "saturated" for clarity.*

COMMENT (page 128, line 22): space is needed "machinery(except…")

RESPONSE: *A space was added.*

Chapter 6

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

COMMENT: I am unaware of any other study that would satisfy any data gaps that were identified in the document.

RESPONSE: *No response is necessary.*

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

COMMENT: Yes, I agree with the data needs that were identified. In particular, for the derivation of chronic MRLs, sufficient chronic studies evaluating health effects at low doses are currently lacking, thus precluding derivation of chronic toxicity values. Further, the potential for 1,2-dichloropropane to elicit developmental toxicity has not sufficiently been addressed as the existing studies cannot preclude that the resulting effects were due to parental toxicity (for both oral and inhalation routes of exposure).

Human dosimetry, epidemiology – as noted in this section, the existing epidemiology studies did not control for confounding effects of other chlorinated chemical exposure in the populations. This is a major limitation of these studies. Further evaluation of occupationally exposed populations appears necessary.

ADME- some work has been done, however, as it is noted that dermal absorption may occur, additional studies are warranted. In addition, information concerning the biological half-life of 1,2-dichloropropane was not identified in this document.

I agree that a potentially susceptible population is children. While it is noted that CYP2E1 is fully developed in children, this enzyme exhibits ontogenic expression having the fetal isoform present during developmental stages. Whether its activity on 1,2-dichloropropane is similar during developmental stages is not known, therefore, studies evaluating early life-stage exposures in animals appear critical and would help address this data gap.

Toxicokinetics – modeling of this chemical is sparse. Information across species is limited and would be useful for assessing human health risk.

As production and usage has changed significantly, the identified data gaps concerning environmental fate, bioavailability from environmental media, bioaccumulation, and exposure levels in environmental media appear warranted. Similarly, since 1,2-dichloropropane's usage is now greatly reduced, human exposure patterns may have shifted from individuals exposed occupationally exposures to population exposed in locations in close proximity to waste sites, human exposure measurements should be updated – in particular to gather exposure data and heath assessment information on those living near 1,2-dichloropropane contaminated waste sites.

RESPONSE: *Biological half-life data were added to the document from Take et al. (2014, 2017) in Section 3.1.4:*

> *"Elimination half-life ($t_{1/2}$) values and area under the curve values over the first 1,440 minutes ($AUC_{0–1,440}$) were estimated in rats for blood and select organs following inhalation or oral exposure (Take et al. 2014, 2017). Values are presented in Tables 3-1 and 3-2, respectively. These values support that at low levels accumulation of 1,2-dichloropropane in the body is not expected; however, concentration in body fat is predicted if the metabolic capacity is exceeded following high-level inhalation or oral exposures."*

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

COMMENT: Data needs were presented in a neutral manner, no biases were noted in the text.

RESPONSE: *No response is necessary.*

Chapter 7

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

COMMENT: I am not aware of other regulations or guidelines that should be included in this section

RESPONSE: *No response is necessary.*

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

COMMENT: There is not any information that I am aware of that should be removed from this Chapter..

RESPONSE*: No response is necessary.*

Appendix A

QUESTION: Do you agree or disagree with the proposed MRL values? Explain. If you disagree, please specify the MRL value that you propose.

COMMENT: I agree with the MRLs proposed. Following the systematic evaluation of the literature, the critical effects were selected from appropriate animal studies that were determined to have an overall high confidence in the study. I agree that the following MRLs were derived from the most appropriate study and were based on:

Inhalation (acute) – a LOAEL of 100 ppm for nasal lesions in a 2 week inhalation exposure study in rats;

Inhalation (intermediate) – a LOAEL of 15 ppm for nasal lesions in a 13 week inhalation exposure study in rats;

Oral (acute) – a LOAEL of 100 mg/kg/day for maternal anemia following oral dosing on GD 7-19 in NZ rabbits; and

Oral (intermediate) – a LOAEL of 100 mg/kg/day for hemolytic anemia in a 13 week oral dosing study in rats.

Comments on the appropriateness of dosimetric adjustments and BMD analyses performed on LOAELs are provided in the response to question 2 below.

RESPONSE*: No response is necessary.*

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: As defined in Appendix D – Users guide, MRLs are not meant to support regulatory action, but rather to acquaint health professionals with exposure levels that are intended to be safe for human exposures. When deriving MRLs for a chemical, uncertainty factors of 10 should be applied for human variability, when using a LOAEL instead of a NOAEL, and for extrapolation from animal to human (composite of 1000). In The uncertainty factors applied for the derivation of acute and intermediate MRLs for 1,2-dichloropropane deviated from this approach. In all cases, NOAELs were not available and LOAELs were used, however, doses were adjusted for exposure duration (inhalation), and allometric scaling (HED adjustments) were calculated. Further, when possible, benchmark dose analysis was performed yielding BMDL10 values as the point of departure. As such, the use of the lower UFs are mostly justified in the derivation of MCLs for 1,2-dichloropropane by both inhalation and oral routes of exposure.

Inhalation (acute); UF = 90 was suggested – 10 for human variation, 3 for extrapolation from animal to human (after dosimetric adjustment) and 3 for use of a minimal LOAEL. The latter UF was not adequately described. As such, it is questioned why a UF of 10 was not applied as a LOAEL was used instead of a NOAEL.

Inhalation (intermediate); UF of 30 was suggested – benchmark dose analysis was used in this calculation and derived that value as the point of departure (in lieu of a NOAEL or LOAEL),10 for human variation, and 3 for extrapolation from animal to human (after dosimetric adjustment). I agree with this approach.

Oral (acute); UF of 100 was suggested, benchmark dose analysis was used in this calculation and derived that value as the point of departure (in lieu of a NOAEL or LOAEL),10 for human variation, and 10 for extrapolation from animal to human. I agree with this approach.

Oral (intermediate); UF of 1000 was suggested, benchmark dose analysis was attempted, however, none of the models applied resulted in an adequate fit for any of the effects observed in the study. Therefore, a UF of 10 was applied as the LOAEL was used as the point of departure, 10 for human variation, and 10 for extrapolation from animal to human. I agree with this approach.

RESPONSE: *For the acute-duration inhalation MRL, an uncertainty factor of 3 for the use of a LOAEL was selected instead of the full-factor of 10 due to the slight severity of the lesion at the point of departure (POD). The text in the Uncertainty Factor section of the MRL worksheet was revised for clarity (see below).*

> *"3 for use of a minimal LOAEL. The dose was considered a minimal LOAEL because the severity of the lesions was graded as slight."*

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

COMMENT: I have no specific comments that I feel need to be addressed concerning the MRL assessment

RESPONSE: *No response is necessary.*

Appendix B

QUESTION: Does Appendix B provide a sufficiently clear documentation of ATSDR's health effects literature search strategy and inclusion/exclusion criteria?

COMMENT: Yes, the search strategy and inclusion/exclusion criteria was clearly documented.

RESPONSE*: No response is necessary.*

QUESTION: Does it provide enough transparency regarding ATSDR's implementation of its inclusion and exclusion criteria (e.g., how ATSDR chose the studies it included in the health effects chapter)?

COMMENT: Yes, how exclusion/inclusion criteria were used to select the studies described in the profile were made clear to the reader.

RESPONSE: *No response is necessary.*

Appendix C

QUESTION: Does Appendix C provide a sufficiently clear documentation of ATSDR's systematic review of health effects data?

COMMENT: Yes, this section is very well presented and sufficiently clear. This section described the very thorough and transparent approach that was used to systematically evaluate the selected scientific literature and categorization of health effects elicited by 1,2-dichloropropane.

RESPONSE: *No response is necessary.*

QUESTION: Do you agree with the SR framework as presented in Appendix B? Are there any steps that need to be revised? Please offer any suggestions to improve the utility, effectiveness, or clarity of the SR Framework.

COMMENT: I agree with this framework, as stated above, this is a thorough and systematic approach to evaluate the literature. I do not feel that any step requires revision at this time, nor can I offer suggestions that would improve the scientific review process that was followed.

RESPONSE: *No response is necessary.*

Overall Usability of the Profile

QUESTION: Does the new chapter organization make it easier for you to find the information you need? For example, are you satisfied with the organization of the health effects chapter by organ system rather than exposure route?

COMMENT: Yes, I find the chapter organization easier to navigate, and the overall flow of the document is logical and easy to navigate. I do prefer chapter 2 organized by organ systems rather than route of exposure. It makes it easier to read the health effects tables as well.

RESPONSE: *No response is necessary.*

QUESTION: Does the profile contain all of the information you need? Is there information you would like to see that is not currently included?

COMMENT: All information that I am aware of is included in this document. It presents a comprehensive scientific review of 1,2-dichloropropane

RESPONSE: *No response is necessary.*

QUESTION: If you have used the Toxicological Profiles before, which chapter(s) have you used the most and for what purpose?

COMMENT: Yes, I have used Toxicological Profiles previously. As a Toxicologist, I most often use the health effects chapter to gain an overview of various chemicals toxicity profiles, doses, etc. I also use these documents in classroom exercises (undergraduate and graduate toxicology courses) as these are an excellent resource for understanding effects of chemicals.

RESPONSE: *No response is necessary.*

QUESTION: Are the new tables and figures clear and useful? Do they make the toxicological profile easier to read?

COMMENT: Yes.

RESPONSE: *No response is necessary.*