DISPOSITION OF PEER REVIEW COMMENTS FOR TOXICOLOGICAL PROFILE FOR VINYL CHLORIDE

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

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Comments provided by Peer Reviewer #1

General Comments

COMMENT 1: Whether neurological effects should be a presumed or a suspected human health effect.

There are 20 human and 14 animal studies that examined neurological effects of vinyl chloride (Fig 2.1). In Chap. 1.2 Summary of Health Effects, it is described that neurological effects were reported or observed in multiple human studies with no weakness or limitations indicated (pg. 6 line 4-16). Furthermore, Table 2-5 (Chap 2.15) presents that 6 out of 7 human studies summarized in this table reported the associations between neurological outcomes and the exposure. More studies were described in the text, with no major shortness pointed out, and the results seem to be consistent. However, in Appendix C (Table C-18), the body of evidence was adjust from Moderate in Initial Confidence to Low in Final Confidence due to -1 risk of bias. The risk of bias and thus the low confidence in the body of evidence should be mentioned in Chap 1.2 and further explained in Chap 2.15. Vinyl chloride has been "known" to cause neurological effects, as indicated in the Vinyl Chloride - ToxFAQs™ that states "Breathing high levels of vinyl chloride for short periods of time can cause dizziness, sleepiness, unconsciousness, and at extremely high levels can cause death" (https://www.atsdr.cdc.gov/toxfaqs/tfacts20.pdf). If the revised Toxicological Profile is going to classify vinyl chloride as a suspected human health effect, more clear explanations on limitations in human studies reporting neurological effects are needed in relevant sections throughout the document.

RESPONSE: *Neurological effects were characterized as a suspected health effect in error (i.e., should be a presumed health effect). The initial confidence rating for human studies should <u>not</u> have received a -1 for risk of bias, because most studies were in the risk of bias first tier. The error was corrected in Tables C-18, C-19, C-20, and C-21, and in the text in Sections 1.2, 2.1, and C.8.*

COMMENT 2: Whether development effects is a presumed or a suspected human health effect – there are inconsistencies throughout the document.

- Table C-18 indicates the final confidence in the body of evidence for developmental outcome is Low for human studies and High for animal studies. However, in the end of Appendix C (page C-37), it says developmental outcome has "Inadequate evidence in humans" but "Moderate level of evidence in animals." According to the framework (Appendix C) and especially Figure C-1, moderate level of evidence in animals and inadequate evidence in humans should be classified as "Suspected."
- Chap1.2 says that developmental effects are a suspected health effect for humans
- Chap 2.1 and Appendix C developmental effects are classified as a presumed health effect for humans.
- Table C-21 lists developmental outcome as "Suspected health effect."

RESPONSE: *The inconsistencies in the document were corrected to describe developmental effects as a Suspected health effect throughout the profile. In Section C.7, the <u>low</u> confidence in the body of evidence in humans was translated to <u>inadequate</u> level of evidence for the health effect, because of the absence of demonstrated effects in a small number of very limited studies (see Table C-20). In animals, the level of evidence for developmental effects is <u>high</u> based on the effects occurring at low concentrations in several inhalation studies. The bulleted text in Section C.8 was corrected to reflect the <u>high</u> level of evidence in animals. Because the high level of evidence in humans is not supported by adequate human studies, developmental effects are considered suspected and not presumed.*

COMMENT 3: Cancer should be listed as one of the bullet points at the beginning of Chap 1.2 as it is discussed in Chap 1.2 Summary of Health Effects.

RESPONSE: *The bulleted list in Section 1.2 refers to the list of noncancer endpoints evaluated using a systematic review process in the profile. For cancer, ATSDR relied on the weight-of-evidence classifications from NTP (2016), IARC (2012), and EPA (2000). This information is provided at the end of Section 1.2. For clarity, the 2nd paragraph of Section 1.2 was revised to list cancer as a sensitive effect and the sentence prior to the bulleted list was revised to indicate that the systematic review was performed for noncancer endpoints only. Cancer details were added to the bulleted list in Section 2.1.*

COMMENT 4: Although the number of human studies is comparable to that of animal studies, there are only two human studies listed Table 2.1. A footnote should be added if this is because other human studies are listed in the subsequent tables, e.g. Table 2-3, 2-4, 2-5, 2-6, and 2-7.

RESPONSE: *The following sentence was added to footnote [a]: "The only human studies included in this table are controlled exposure studies. Other epidemiological studies are described in text and Tables 2-3 through 2-8 in the health effect sections below."*

COMMENT 5: "PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL" is an independent chapter that is separated from "POTENTIAL FOR HUMAN EXPOSURE" in the toxicological profile for other compounds such as tetrachloroethylene and trichloroethylene. I wondered why for vinyl chloride the "PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL" becomes a sub-chapter (Chap 5.2) of the chapter 5, "POTENTIAL FOR HUMAN EXPOSURE." I think it would be better to keep them separated.

RESPONSE: *The organization of Chapter 5 is consistent with the latest version of the ATSDR Guidance for the Preparation of Toxicological Profiles. The guidance can be found here: https://www.atsdr.cdc.gov/toxprofiles/guidance/profile_development_guidance.pdf. ATSDR will consider this Reviewer's comments in future revisions of the profile guidance.*

ATSDR Charge Questions and Responses Reviewer Comments

Chapter 1

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

COMMENT 6: Yes, I agree.

RESPONSE: *No response needed.*

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

COMMENT 7: I agree with the analysis presented in the document.

RESPONSE: *No response needed.*

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

COMMENT 8: I made some minor revisions in the document.

RESPONSE: *The suggested revisions to Sections 1.1 were retained in the document. Added: "Community members living on or near hazardous waste sites may experience long-term exposure to low levels of vinyl chloride as it has been found in many National Priority List (NPL) sites identified by the U.S. Environmental Protection Agency (EPA)."*

Minimal Risk Levels

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

COMMENT 9: Yes, I agree

RESPONSE: *No response needed.*

QUESTION: If MRLs have been derived, do you agree with the proposed MRL values? Explain. If you disagree, please specify the MRL value that you would propose. 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 10: Yes, I agree.

RESPONSE: *No response needed.*

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

COMMENT 11: I believe the process of deriving MRL is solid.

RESPONSE: *No response needed.*

Chapter 2

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

COMMENT 12: Although they were consistently reported or observed in human studies, neurological effects were classified as a suspected human health effect. Given no sufficient information was

provided on the major limitations in the human studies, I would like to consider to classify the neurological effects as a presumed human health effect.

RESPONSE: *Neurological effects were classified as a presumed health effect as suggested. The characterization as a suspected health effect was an error in the draft profile.*

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 13: No major study limitations for neurological effects were sufficiently described in the text. In Appendix C (Table C-18), the body of evidence for neurological effects was adjust from Moderate in Initial Confidence to Low in Final Confidence due to -1 risk of bias. It was not explained what the risk of bias was.

RESPONSE: *Neurological effects were characterized as a suspected health effect in error (i.e., should be a presumed health effect). The initial confidence rating for human studies should <u>not</u> have received a -1 for risk of bias, because most studies were in the risk of bias first tier. The error was corrected in Tables C-18, C-19, C-20, and C-21, and in the text in Sections 1.2, 2.1, and C.8.*

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 14: I believe yes.

RESPONSE: *No response needed.*

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

COMMENT 15: It is hard for me to answer this question, as I am not a toxicologist.

RESPONSE: *No response needed.*

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

COMMENT 16: yes

RESPONSE: *No response needed.*

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

COMMENT 17: No.

RESPONSE: *No response needed.*

QUESTION: Are you aware of any studies that are not included in the profile that may be relevant to deriving MRLs for any of the substance isomers? Please provide a copy if this is a new reference.

COMMENT 18: No.

RESPONSE: *No response needed.*

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

COMMENT 19: Yes.

RESPONSE: *No response needed.*

QUESTION: Do you agree with the categorization of "less serious" or "serious" for the effects cited in the LSE tables? If not, please explain why and suggest appropriate changes.

COMMENT 20: Yes, I agree

RESPONSE: *No response needed.*

QUESTION: Have all possible mechanisms of action been discussed within their relevant health effect section? If not, please explain. If citing a new reference, please provide a copy if available.

COMMENT 21: Yes

RESPONSE: *No response needed.*

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

COMMENT 22: Yes

RESPONSE: *No response needed.*

Chapter 3

Questions:

- Is there adequate discussion of absorption, distribution, metabolism, and excretion of the substance? If not, suggest ways to improve the text.
- Have all available pharmacokinetic/pharmacodynamic models and supporting data been presented? If not, please explain.
- 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?
- 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.
- 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.
- Are the biomarkers of exposure specific for the substance? Please explain.
- Are the biomarkers of effect specific for the substance? Please explain.
- 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.
- 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 23: Due to the time constraints and being an exposure scientist, I mainly focused on Chap 1-2 and 4-6 and skipped Chap 3.

RESPONSE: *No response needed.*

Chapter 4

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

COMMENT 24: No.

RESPONSE: *No response needed.*

Chapter 5

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

COMMENT 25: Yes

RESPONSE: *No response needed.*

QUESTION: Has the text appropriately traced the substance from its point of release to the environment until it reaches the receptor population? Does the text provide sufficient and technically sound

information regarding the extent of occurrence at NPL sites? Do you know of other relevant information? Please provide references for added information.

COMMENT 26: The descriptions in the text is appropriate.

RESPONSE: *No response needed.*

QUESTION: Does the text cover pertinent information relative to transport, partitioning, transformation, and degradation of the substance in all media? Do you know of other relevant information? Please provide references for added information.

COMMENT 27: I wish the chemical reaction equations can be provided in this sub-sections. I was especially interested in the photochemical reaction in the air but could not find the relevant information.

RESPONSE: ATSDR considers the inclusion of the chemical reaction equations beyond the scope of Chapter 5.

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 28: The answer is positive for the first 4 questions. I am not aware of other relevant information that is not included in the document.

RESPONSE: *No response needed.*

QUESTION: Does the text describe sources and pathways of exposure for the general population and occupations involved in the handling of the substance, as well as populations with potentially high exposures?

COMMENT 29: Yes.

RESPONSE: *No response needed.*

QUESTION: Do you agree with the selection of these populations? If not, why?

COMMENT 30: Yes.

RESPONSE: *No response needed.*

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

COMMENT 31: No.

RESPONSE: *No response needed.*

Chapter 6

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

COMMENT 32: I am not aware of any other studies that should be included to fill a data gap.

RESPONSE: *No response needed.*

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

COMMENT 33: Yes, I agree.

RESPONSE: *No response needed.*

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

COMMENT 34: Yes. Not noted.

RESPONSE: *No response needed.*

Chapter 7

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

COMMENT 35: I am not aware of any additional regulations.

RESPONSE: *No response needed.*

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

COMMENT 36: Not noted.

RESPONSE: *No response needed.*

Annotated Comments on the Toxicological Profile

COMMENT 37: Regarding Section 1.1, the Reviewer suggests adding the following sentence after the first sentence in the fourth paragraph—Community members living on or near hazardous waste sites may experience long-term exposure to low levels of vinyl chloride as it has been found in many National Priority List (NPL) sites identified by the Environmental Protection Agency (EPA)—and commented "It

"has been found in at least 616 of the 1,662 National Priority List (NPL) sites identified by the Environmental Protection Agency (EPA)," according to Vinyl Chloride - ToxFAQs™ https://www.atsdr.cdc.gov/toxfaqs/tfacts20.pdf."

RESPONSE: *The suggested addition was retained.*

COMMENT 38: Regarding the statement in Section 1.2—Neurological effects are a suspected health effect for humans—the Reviewer commented "Based on the evidence presented in Ch 2 and the summary description in Ch 6, neurological effects seems to be a presumed health effect for human."

RESPONSE: *Neurological effects were characterized as a suspected health effect in error (i.e., should be a presumed health effect). The initial confidence rating for human studies should not have received a -1 for risk of bias, because most studies were in the risk of bias first tier. The error was corrected in Tables C-18, C-19, C-20, and C-21, and in the text in Sections 1.2, 2.1, and C.8.*

COMMENT 39: Regarding the statement in Section 1.2—Developmental effects are a suspected health effect for humans—the Reviewer commented "This contradicts what described in Section 2.1 (page 12 Line 21), where developmental effects are determined as a presumed health effect for humans "based on strong evidence from acute inhalation exposures in mice and rabbits."

RESPONSE: *The inconsistencies in the document were corrected to describe developmental effects as a Suspected health effect throughout the profile. In Section C.7, the low confidence in the body of evidence in humans was translated to inadequate level of evidence for the health effect, because of the absence of demonstrated effects in a small number of very limited studies (see Table C-20). In animals, the level of evidence for developmental effects is high based on the effects occurring at low concentrations in several inhalation studies. The bulleted text in Section C.8 was corrected to reflect the high level of evidence in animals. Because the high level of evidence in humans is not supported by adequate human studies, developmental effects are considered suspected and not presumed.*

COMMENT 40: Regarding Section 1.2, the Reviewer added *Cancer effects are …* to the bulleted list and commented "I think cancer effects should be listed here with a hazard identification conclusion as it is discussed below in this sub-section."

RESPONSE: *The bulleted list in Section 1.2 refers to the list of noncancer endpoints evaluated using a systematic review process in the profile. For cancer, ATSDR relied on the weigh-of-evidence classifications from NTP (2011), IARC (2008), and EPA (2000). This information is provided at the end of Section 1.2. For clarity, the 2nd paragraph of Section 1.2 was revised to list cancer as a sensitive effect and the sentence prior to the bulleted list was revised to indicate that the systematic review was performed for noncancer endpoints only.*

COMMENT 41: Regarding the statement under Hepatic Effects in Section 1.2—Occupational studies have identified a consistent group of liver effects resulting from vinyl chloride exposure, including hypertrophy, hyperplasia of hepatocytes and sinusoidal cells, portal fibrosis, sinusoidal dilation, and focal cellular degeneration (Berk et al. 1975; Falk et al. 1974; Gedigke et al. 1975; Ho et al. 1991; Jones and Smith 1982; Lilis et al. 1975; Liss et al. 1985; Marsteller et al. 1975; NIOSH 1977; Popper and Thomas 1975; Suciu et al. 1975; Tamburro et al. 1984; Vihko et al. 1984)—the Reviewer commented "Can exposure ranges be provided here?"

RESPONSE: *Section 1.2 provides a summary of the health effects observed and does not generally include exposure information for epidemiology studies. In addition, many of the older studies listed in the Reviewer's comment are occupational health surveys that do not provide exposure data. When available, exposure information is provided for each study in Table 2-3 of Section 2.9 (Hepatic).*

COMMENT 42: Regarding the human studies under Neurologic Effects in Section 1.2, the Reviewer commented "Suggest to add any limitations in the aforementioned human studies here."

RESPONSE: *Study limitations were not added here, because the neurological effects were characterized as a suspected health effect in error (i.e., should be a presumed health effect).*

COMMENT 43: Regarding the last paragraph under Cancer in Section 1.2, the Reviewer commented "What is ATSDR's hazard identification conclusion on cancer for vinyl chloride?"

RESPONSE: *According to ATSDR guidance, toxicological profiles should report HHS, EPA, and IARC classifications for cancer and should not present an independent weight-of-evidence analysis for cancer studies. The guidance can be found here:*
https: //www.atsdr.cdc.gov/toxprofiles/guidance/profile_development_guidance.pdf.

COMMENT 44: Regarding the statement in Section 2.1—Animal inhalation studies are presented in Table 2-1 and Figure 2-2, and animal oral studies are presented in Table 2-2 and Figure 2-3; no dermal data were identified for vinyl chloride—the Reviewer commented "Two human studies are included in Table 2-1."

RESPONSE: *The introductory text was revised to indicate that controlled human exposure studies are included in Table 2-1.*

COMMENT 45: Regarding the statement in Section 2.1—Neurological effects are a suspected health effect for humans based on limited information including neurological symptom reporting and a single report of peripheral neuropathy in humans—the Reviewer commented "Base on the summary discussion in Ch 6, neurological effects should be a presumed effect."

RESPONSE: *Neurological effects were characterized as a suspected health effect in error (i.e., should be a presumed health effect). Section 2.1 was revised to describe neurological effects as a presumed health effect.*

COMMENT 46: Regarding the statement in Section 2.1—Developmental effects are a presumed health effect for humans based on strong evidence from acute inhalation exposures in mice and rabbits—the Reviewer commented "This contradicts what states in Section 1.2 Summary Health Effects (page 2 line 21), where Developmental effects are determined as a suspected health effect for humans."

RESPONSE: *The inconsistencies in the document were corrected to describe developmental effects as a suspected health effect throughout the profile. Section 2.1 was revised accordingly.*

COMMENT 47: Regarding Levels of Significant Exposure Table 2-1, the Reviewer commented "Only two human studies are listed in Table 2-1, while there are roughly equal amount of human and animal studies listed in Figure 2-1 – 98% of them are inhalation studies. It would be very helpful to include human inhalation studies in this table."

RESPONSE: *According to ATSDR guidance, human observational epidemiology studies are reported in separate tables in Chapter 2. The LSE tables are used for experimental studies where exposure is controlled (i.e., animals studies or controlled-exposure human studies). The guidance can be found here: https: //www.atsdr.cdc.gov/toxprofiles/guidance/profile_development_guidance.pdf.*

COMMENT 48: Regarding the statement in Section 2.4 (Respiratory)—However, adverse respiratory effects were reported in cohort and case-control studies (Lloyd et al. 1984; Wong et al. 1991; Zhu et al. 2005a) and several occupational health studies, which often had no exposure measurements or comparison group (Lilis et al. 1975, 1976; Suciu et al. 1975; Walker 1976)—the Reviewer changed *group* to *groups* and commented "I suggest to remove "or comparison group," as studies cited in the following sentence discussing increased incidence of emphysema and decreased pulmonary functions did have comparison groups."

RESPONSE: *The phrase "or comparison group" was deleted as suggested.*

COMMENT 49: Regarding the statement in Section 2.5 (Cardiovascular)—Most of the evidence pertaining to Raynaud's phenomenon in vinyl chloride workers is derived from case reports and occupational health studies, which often had no exposure measurement and no comparison group—the Reviewer changed *measurement* to *measurements* and *group* to *groups.*

RESPONSE: *Revised as suggested.*

COMMENT 50: Regarding the statement under Mechanisms in Section 2.5 (Cardiovascular)—Cardiac sensitization by halogenated hydrocarbons generally occurs at very high air concentrations (0.5–90%) (Brock et al. 2003)—the Reviewer added *when the compounds were tested as anesthetic agents in experimental studies.*

RESPONSE: *Revised as suggested.*

COMMENT 51: Regarding the statement in Section 2.7 (Hematological)—Slight-to-severe thrombocytopenia in workers exposed to vinyl chloride was reported in several occupational health studies, which often had no exposure measurements or comparison group (Marsteller et al. 1975; Micu et al. 1985; Veltman et al. 1975)—the Reviewer changed *comparison group* to *a comparison group*.

RESPONSE: *Revised as suggested.*

COMMENT 52: Regarding the statement in Section 2.8 (Musculoskeletal)—Case reports and occupational health studies, which often had no exposure measurements or comparison group, reported that acroosteolysis, or resorption of the terminal phalanges of the finger, was observed in a small percentage of workers occupationally exposed to vinyl chloride (Dinman et al. 1971; Lilis et al. 1975;

Marsteller et al. 1975; Sakabe 1975; Veltman et al. 1975; Wilson et al. 1967)—the Reviewer changed *group* to *groups*.

RESPONSE: *Revised as suggested.*

COMMENT 53: Regarding the statement in Section 2.9 (Hepatic)—A potential association between vinyl chloride exposure and liver toxicity was evaluated in eight cohort studies, nine cross-sectional studies, four case-control studies (Table 2-3), and many occupational health study case reports and case series (i.e., studies of vinyl chloride workers with no exposure measurements or relative to a comparison group) (not tabulated)—the Reviewer removed *study*.

RESPONSE: *Revised as suggested.*

COMMENT 54: Regarding the statement in Section 2.11 (Dermal)—Case reports and occupational health studies, which often had no exposure measurements or comparison group, indicated that exposure to vinyl chloride resulted in scleroderma-like skin changes on the hands of a small percentage of exposed workers (Freudiger et al. 1988; Lilis et al. 1975; Marsteller et al. 1975; Suciu et al. 1975; Veltman et al. 1975; Walker 1976)—the Reviewer removed *, which often had no exposure measurements or comparison group* and commented *"*I suggest this is discussed in the general discussion sections rather than being brought up every time occupational studies are presented."

RESPONSE: *Revised as suggested.*

COMMENT 55: Regarding the statement in Section 2.14 (Immunological)—The potential association between vinyl chloride exposure and immunological toxicity was evaluated in five cross-sectional studies, three case-control studies (Table 4), and many occupational health studies, case reports, and case series, which often had no exposure measurements or comparison group (not tabulated)—the Reviewer removed *, which often had no exposure measurements or comparison group.*

RESPONSE: *Revised as suggested.*

COMMENT 56: Regarding Table 2-4 in Section 2.14 (Immunological), the Reviewer commented "If being listed in Table 2-3 and 2-4 is the reason for these human studies not being listed in Table 2-1, I think it would be helpful to add a footnote in Table 2-1 to indicate this. I was confused earlier why there were so few human studies listed in Table 2-1."

RESPONSE: *The following sentence was added to footnote [a]: "The only human studies included in this table are controlled exposure studies. Other epidemiological studies are described in text and tables in the health effect sections below."*

COMMENT 57: Regarding the statement in Section 5.6 (General Population Exposure)—Estimates provided by EPA (1985a) indicate that 0.9% of the U.S. population is exposed to levels of vinyl chloride in drinking water ≥1 µg/L, and 0.3% of the population is exposed to levels >5 µg/L—the Reviewer added *while the EPA MCL is 2 µg/L.*

RESPONSE: *Revised as suggested.*

COMMENT 58: Regarding Section 5.6 (General Population Exposure), the Reviewer moved the paragraph "Individuals located near or downwind of production…is exposed to." and the paragraph "Cigarette smoke and smoke from…chloride than nonsmokers." from Section 5.7 (Populations with Potentially High Exposures) before the last paragraph in this section.

RESPONSE: *Revised as suggested.*

COMMENT 59: Regarding Section 5.7 (Populations with Potentially High Exposures), the Reviewer moved the paragraph, "The National Occupational Exposure Survey (NOES) …(0.011–1.096 ppb) (Bloomdahl et al. 2014)." and paragraph, "In the United States, vinyl chloride … conforming to OSHA standards." from Section 5.6 (General Population Exposure) to this section.

RESPONSE: *Revised as suggested.*

COMMENT 60: Regarding the Developmental Toxicity paragraph in Section 6.2 (Identification of Data Needs), the Reviewer commented "This shows that developmental effects should be determined as a suspective effect, consistent with what states in Ch 1.1. Determination in Ch 2.1 should be correct, which is inconsistent with what's in Ch 1.1."

RESPONSE: *The inconsistencies in the document were corrected to describe developmental effects as a Suspected health effect throughout the profile.*

COMMENT 61: Regarding the Developmental paragraph in Section C.8 in Appendix C (Identification of Data Needs), the Reviewer commented "Should inadequate (which is equivalent to Low, right?) + moderate yield a Suspected human effect?"

RESPONSE: *In Section C.7, the <u>low</u> confidence in the body of evidence in humans was translated to <u>inadequate</u> level of evidence for the health effect, because of the absence of demonstrated effects in a small number of very limited studies (Table C-20). In animals, the level of evidence for developmental effects is <u>high</u> based on the effects occurring at low concentrations in several inhalation studies. The bulleted text in Section C.8 was corrected to reflect the <u>high</u> level of evidence in animals. Because the high level of evidence in humans is not supported by adequate human studies, developmental effects are considered suspected and not presumed.*

Comments provided by Peer Reviewer #2

ATSDR Charge Questions and Responses Reviewer Comments

Chapter 1

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

COMMENT 1: Yes, the effects that are reported and then selected are appropriate.

RESPONSE: *No response needed.*

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

COMMENT 2: There are few of this kind and the lack of human evidence is due to easily explainable reasons – doses unattainable, effects and endpoints impossible to measure, etc. There are no reasons to expect that VC would operate by different mechanisms in animals and humans.

RESPONSE: *No response needed.*

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

COMMENT 3: See comments on Tables 2-3 through 2-6. Text is fine, but the tables need to be standardized.

RESPONSE: *Tables 2-3 through 2-7 follow a standard format used for epidemiology studies in ATSDR Toxicological Profiles. ATSDR will consider this Reviewer's suggestions in future revisions of the profile guidance. Exposure metrics are based on information provided in the primary study and it is not possible to standardize exposure metrics across studies. The order of studies in each table is based on publication year (most recent to oldest).*

Minimal Risk Levels

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

COMMENT 4: Yes, I agree

RESPONSE: *No response needed.*

QUESTION: If MRLs have been derived, do you agree with the proposed MRL values? Explain. If you disagree, please specify the MRL value that you would propose. 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 5: Yes the reasoning is concise and clear and all the information is presented in sufficient detail.

RESPONSE: *No response needed.*

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

COMMENT 6: No further comment

RESPONSE: *No response needed.*

Chapter 2

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

COMMENT 7: Yes, the effects that are reported and then selected are appropriate.

RESPONSE: *No response needed.*

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

COMMENT 8: Yes, some minor edits are suggested in text.

RESPONSE: *Revised as suggested.*

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

COMMENT 9: Yes, the text is fine

RESPONSE: *No response needed.*

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

COMMENT 10: No concerns.

RESPONSE: *No response needed.*

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

COMMENT 11: Yes.

RESPONSE: *No response needed.*

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

COMMENT 12: See minor edits on the text itself.

RESPONSE: *See annotated comments for responses.*

QUESTION: Are you aware of any studies that are not included in the profile that may be relevant to deriving MRLs for any of the substance isomers? Please provide a copy if this is a new reference.

COMMENT 13: No, studies are okay.

RESPONSE: *No response needed.*

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

COMMENT 14: No changes.

RESPONSE: *No response needed.*

QUESTION: Do you agree with the categorization of "less serious" or "serious" for the effects cited in the LSE tables? If not, please explain why and suggest appropriate changes.

COMMENT 15: Yes, these are rather typical and similar to other ATSDR reports.

RESPONSE: *No response needed.*

QUESTION: Have all possible mechanisms of action been discussed within their relevant health effect section? If not, please explain. If citing a new reference, please provide a copy if available.

COMMENT 16: See comments in text on the liver mechanisms

RESPONSE: *A modified version of the figure from Rusyn et al. (2021) was inserted and the text was revised as suggested. See annotated comments for responses.*

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

COMMENT 17: Yes, appropriate. Everything is pretty well established for VC.

RESPONSE: *No response needed.*

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 18: Yes, no concerns.

RESPONSE: *No response needed.*

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

COMMENT 19: Yes, no concerns.

RESPONSE: *No response needed.*

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

COMMENT 20: Yes, no concerns.

RESPONSE: *No response needed.*

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

COMMENT 21: No concerns. seems comprehensive and accurate

RESPONSE: *No response needed.*

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

COMMENT 22: Please comments on the text. In few places the text seems overly speculative and unnecessarily alarmist. The paragraphs in Section 3.2 "Very high levels of vinyl chloride…concentrations of vinyl chloride." and "Vinyl chloride has been shown…impairment of the circulation." were considered speculative and unnecessarily alarmist by the Reviewer.

RESPONSE: *Text was deleted as suggested. See annotated comments for more details and responses.*

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

COMMENT 23: Looks good, see minor edits in text.

RESPONSE: *No edits were found in Section 3.3.1. No response needed.*

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

COMMENT 24: See comments on the text much what is written is non-specific to VC and shall be removed. The paragraphs in Section 3.3.2 "Mocci and Nettuno (2006) …(Devivo et al. 1994)."; "Detection of serum …and hepatocellular carcinoma."; and "serum can be used to …exposure to other compounds." were considered not specific to vinyl chloride.

RESPONSE: *Text was deleted as suggested. See annotated comments for more details and responses.*

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 25: See comments in the text. The paragraph in Section 3.4 "The results of recent…(Lang et al. 2019)." was considered co-morbidity and not other chemicals.

RESPONSE: *The paragraph* "The results of recent…(Lang et al. 2019)." was moved to the susceptibility section (Section 3.2).

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 26: Reads well.

RESPONSE: *No response needed.*

Chapter 4

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

COMMENT 27: No concerns.

RESPONSE: *No response needed.*

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

COMMENT 28: No concerns.

RESPONSE: *No response needed.*

Chapter 5

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

COMMENT 29: Very comprehensive, no further comments.

RESPONSE: *No response needed.*

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

COMMENT 30: Very comprehensive, no further comments.

RESPONSE: *No response needed.*

QUESTION: Does the text cover pertinent information relative to transport, partitioning, transformation, and degradation of the substance in all media? Do you know of other relevant information? Please provide references for added information.

COMMENT 31: Very comprehensive, no further comments.

RESPONSE: *No response needed.*

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

COMMENT 32: Very comprehensive, no further comments.

RESPONSE: *No response needed.*

QUESTION: Does the text describe sources and pathways of exposure for the general population and occupations involved in the handling of the substance, as well as populations with potentially high

exposures? Do you agree with the selection of these populations? If not, why? Which additional populations should be included in this section?

COMMENT 33: I agree with the choices made.

RESPONSE: *No response needed.*

Chapter 6

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

COMMENT 34: Many studies are ingoing but not sure they will make a difference for the MRL.

RESPONSE: *No response needed.*

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

COMMENT 35: Yes, standard data needs – "more research MIGHT be helpful"… but there is enough data to derive MRLs now.

RESPONSE: *No response needed.*

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

COMMENT 36: Looks fine.

RESPONSE: *No response needed.*

Chapter 7

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

COMMENT 37: Not aware of any additional ones. Perhaps may list earlier IARC monographs, not just 100F (2012).

RESPONSE: *No response needed.*

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

COMMENT 38: No.

RESPONSE: *No response needed.*

Appendices

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

COMMENT 39: Appendices look good and comprehensive

RESPONSE: *No response needed.*

Annotated Comments on the Toxicological Profile

COMMENT 40: Regarding the statement in Section 1.1—Vinyl chloride is a volatile compound used almost exclusively in the United States by the plastics industry for the production of polyvinyl chloride (PVC) and several copolymers—the Reviewer commented "Please revise as it implies that US is the place of "almost exclusive use" of VC…"

RESPONSE: *Revised to: "Vinyl chloride is a volatile compound used almost exclusively by the plastics industry for the production of polyvinyl chloride (PVC) and several copolymers in the United States."*

COMMENT 41: Regarding the statement in Section 1.1—Segments of the general population living in the vicinity of emission sources may be exposed to vinyl chloride by inhalation of contaminated air—the Reviewer commented "(e.g., plastic manufacturing facilities)."

RESPONSE: *Added "(e.g., plastic manufacturing facilities)" as suggested*.

COMMENT 42: Regarding the statement in Section 1.1—Workers involved in the handling and processing of PVC resins are exposed to lower levels of vinyl chloride than employees at vinyl chloride and PVC manufacturing facilities since fabricated products contain only minute quantities of vinyl chloride present as residual monomer—the Reviewer replaced *minute* with *trace*.

RESPONSE: *Revised as suggested*

COMMENT 43: Regarding the statement in Section 1.1—Since the early 1970s, improvements in manufacturing facilities, engineering controls, and workplace practices have substantially reduced workplace exposures in the United States and most other industrialized countries that manufacture vinyl chloride and produce or fabricate PVC products—the Reviewer commented "mention that the ban on use of VC in consumer products in 1970s resulted in considerable reduction of possible exposures in the general population?

RESPONSE: *The following sentence was added to the end of Section 1.1: "The 1974 ban on use of vinyl chloride in U.S. consumer products resulted in a reduction in possible exposures in the general population (IARC 2008)."*

COMMENT 44: Regarding the statement in Section 1.2—As shown in Figures 1-1 and 1-2, the most sensitive effects appear to be liver damage, enhanced immune response, and delayed fetal ossification—

the Reviewer added replace effects with non-cancer (?) effects, replaced *enhanced* with *exacerbated*, and commented "'enhanced' may be perceived as 'good'."

RESPONSE: *The word "enhanced" was replaced with "exacerbated." In response to a comment from another reviewer, "and carcinogenicity" was inserted after liver damage and "noncancer" was inserted in the last sentence before the bulleted list.*

COMMENT 45: Regarding the statement in Section 1.2—The hazard identification conclusion was that insulin resistance was not classifiable due to a low level of evidence in both human and animal studies, the Reviewer replaced *low* with *insufficient*.

RESPONSE: *Revised as suggested.*

COMMENT 46: Regarding Hepatic Effects in Section 1.2, the Reviewer commented "the most recent study cited here is from 2002, but a few excellent more contemporary studies by Cave and McClain are not cited…"

RESPONSE: *The reference list for hepatic effects in Section 1.2 was revised as follows: "Occupational studies have identified a consistent group of liver effects resulting from vinyl chloride exposure, including hypertrophy, hyperplasia of hepatocytes and sinusoidal cells, sinusoidal dilation, focal cellular degeneration, steatohepatitis, portal fibrosis, and cirrhosis (Berk et al. 1975; Cave et al. 2010; Du and Wang 1998; Falk et al. 1974; Fedeli et al. 2019a; Gedigke et al. 1975; Ho et al. 1991; Hsiao et al. 2004; Hsieh et al. 2007; Jones and Smith 1982; Lilis et al. 1975; Liss et al. 1985; Maroni et al. 2003; Marsteller et al. 1975; Mastrangelo et al. 2004; Mundt et al. 2017; NIOSH 1977; Popper and Thomas 1975; Suciu et al. 1975; Tamburro et al. 1984; Vihko et al. 1984; Ward et al. 2001; Zhu et al. 2005a)."*

COMMENT 47: Regarding the statement in Section 2.1—Hepatic effects are a presumed health effect for humans based on evidence of fibrosis, cirrhosis, and steatosis in vinyl chloride workers following chronic inhalation exposure—the Reviewer replaced *steatosis* with *steatohepatitis*.

RESPONSE: *Revised as suggested.*

COMMENT 48: Regarding Table 2-3 in Section 2.9 (Hepatic), the Reviewer commented "The comments below pertain to Tables 2-3 through 2-7. Please consider updating all of these.

1. The references in these tables are listed first, unlike in Tables 2.1-2. This is confusing
2. exposure metrics need to be standardized. please list ranges of exposure concentrations and durations of exposure, do not list exposure-years.
3. What is the order of studies in these tables? random? Consider listing by year or first author (alphabetically)

RESPONSE: *Tables 2-3 through 2-7 follow a standard format used for epidemiology studies in ATSDR Toxicological Profiles. ATSDR will consider this Reviewer's suggestions in future revisions of the profile guidance. Exposure metrics are based on information provided in the primary study and it is not possible to standardize exposure metrics across studies. The order of studies in each table is based on publication year (most recent to oldest).*

COMMENT 49: Regarding the statement in Section 2.9 (Hepatic)—Hepatic lesions in workers exposed to vinyl chloride generally include the following features: hypertrophy and hyperplasia of hepatocytes, activation and hyperplasia of sinusoidal lining cells, fibrosis of the portal tracts and the septa and intralobular perisinusoidal regions, sinusoidal dilation, and focal areas of hepatocellular degeneration (Berk et al. 1975; Falk et al. 1974; Gedigke et al. 1975; Ho et al. 1991; Jones and Smith 1982; Lilis et al. 1975; Liss et al. 1985; Marsteller et al. 1975; NIOSH 1977; Popper and Thomas 1975; Suciu et al. 1975; Tamburro et al. 1984; Vihko et al. 1984).—the Reviewer commented "These were evaluated how? Histopath from a biopsy or post-mortem? Ultrasound? please be more specific."

RESPONSE: *Information was added to indicate that the lesions were identified by liver biopsy.*

COMMENT 50: Regarding the text on Mechanisms in Section 2.9 (Hepatic), the Reviewer commented "This whole section may be reduced t one short paragraph and a figure from Rusyn et al (2021) PMID: 34105804"

RESPONSE: *Revised as suggested.*

COMMENT 51: Regarding the statement in Section 2.10 (Renal)—An ecological study evaluating residential exposure to vinyl chloride contaminated groundwater reported an increased risk of decreased estimated glomerular filtration rate (GFR) and increased proteinurea in highly-polluted villages compared to a non-polluted village in Taiwan (Chen and Wu 2017)—the Reviewer commented "This is a rather awkward wording… "highly polluted" with VC? How do you know there were no other pollutants…? Please re-write for clarity."

RESPONSE: *This section was revised for clarity as follows: "An ecological study evaluating residential exposure to contaminated groundwater reported an increased risk of decreased estimated glomerular filtration rate (GFR) and increased proteinurea in residents living near a PVC plant in Taiwan (Chen and Wu 2017). Groundwater was contaminated with vinyl chloride and other chlorinated solvents including trichloroethylene, 1,1-dichloroethylene, 1,1-dichloroethane, 1,2-dichloroethane, and cis-1,2-dichloroethene."*

COMMENT 52: Regarding the statement in Section 2.17 (Developmental)—Additional work by Infante (1976) and Infante et al. (1976b) examined the occurrence of congenital malformations among populations exposed to emissions from PVC polymerization facilities—the Reviewer replaced Infante (1976) with Infante (1976a?).

RESPONSE: *Infante (1976) was the correct reference.*

COMMENT 53: Regarding the statement in Section 2.17 (Developmental)—Furthermore, another study that examined the incidence of malformations in one of the cities studied by Infante (1976) concluded that, although the city had statistically increased incidences of congenital malformations, no correlation existed based on parental proximity to the polymerization plant or with parental employment at the plant (Edmonds et al. 1975)—the Reviewer replaced Infante (1976) with Infante (1976a?).

RESPONSE: *Infante (1976) was the correct reference.*

COMMENT 54: Regarding the statement in Section 2.17 (Developmental)—The study authors concluded that exposure to vinyl chloride did not correlate with changes in sex ratio, birth weight or height, perinatal mortality, or the incidence of congenital abnormalities—the Reviewer changed *birth weight or height* to *birth weight or body length*.

RESPONSE: *Revised as suggested.*

COMMENT 55: Regarding Section 2.18, Other Noncancer (Insulin Resistance), the review changed the subheading to *Other Noncancer Effects? (Insulin Resistance)*.

RESPONSE: *Change was not incorporated as numbered Section and Chapter names follow the standard outline in the ATSDR Guidance for the Preparation of Toxicological Profiles: https://www.atsdr.cdc.gov/toxprofiles/guidance/profile_development_guidance.pdf.*

COMMENT 56: Regarding the Table 2-9 Frameshift mutation row in Section 2.20 (Genotoxicity), the Reviewer commented "No reference here… delete this row?"

RESPONSE: *Row was deleted.*

COMMENT 57: Regarding the Table 2-10 Human lymphocytes row in Section 2.20 (Genotoxicity), the Reviewer commented "Please specify that these were studies in "exposed humans" – the terminology is critically important in IARC monographs now since 2019 revisions to the Preamble."

RESPONSE: *Revised as suggested.*

COMMENT 58: Regarding the Table 2-10 Rat (inhalation) DNA adduct row in Section 2.20 (Genotoxicity), the Reviewer commented "What tissues? or cell types?"

RESPONSE: *The tissue was added for each reference evaluating DNA alkylation, DNA damage, or DNA adducts in experimental animals.*

COMMENT 59: Regarding the paragraph in Section 2.20 starting with—The role of etheno-adducts in the carcinogenesis of vinyl chloride was reviewed by a number of researchers (Albertini et al. 2003; Barbin 1998, 1999, 2000; Gros et al. 2003; Kielhorn et al. 2000; Laib 1986; Nivard and Vogel 1999; Whysner et al. 1996)—the Reviewer commented "studies on 13C-VC need to be added here. Overall, this paragraph doesn't seem to have been updated. Please add at least the Mutlu et al 2010 study from Swenberg's lab."

RESPONSE: *Revised as suggested. A brief description of the stable isotope method (Mutlu et al. 2010, 2012; Swenberg et al. 2011) was added to the end of the paragraph. These studies were also described in the Section 3.3.2 (Biomarkers of Effect).*

COMMENT 60: Regarding Figure 3-1, the Reviewer commented "This figure seems to be missing formation of glycol aldehyde from 2-chloroethylene oxide (see IARC vol 100F schematic)."

RESPONSE: *The metabolism figure was revised as suggested.*

COMMENT 61: Regarding the last paragraph in Section 3.1.6 (Animal-to-Human Extrapolations) "There appears . . . animal species (John et al. 1977, 1981).", the Reviewer commented "Please mention VC at least once in this paragraph…"

RESPONSE: *Added vinyl chloride to the text of paragraph "There appears to be a correlation… animal species (John et al. 1977, 1981)."*

COMMENT 62: Regarding the paragraphs in Section 3.2 (Children and Other Populations that are Unusually Susceptible), "Very high levels of vinyl chloride…high concentrations of vinyl chloride." and "Vinyl chloride has been shown to produce… impairment of the circulation.", the Reviewer commented "These are highly speculative statements and are unnecessary for the purpose of this document. Consider deleting."

RESPONSE: *Text was deleted as suggested.*

COMMENT 63: Regarding the third paragraph in Section 3.3.2 (Biomarkers of Effect), the Reviewer commented "This paragraph needs some serious updating with more contemporary studies from Swenberg lab in 2000s and 2010s… The methods mentioned here are not in use for several decades…"

RESPONSE: *Section 3.3.2, paragraph "The intermediary metabolites, 2 chloroethylene…" has been updated as suggested and several references were added (Mutlu et al. 2010, 2012; Pottenger et al. 2014; Swenberg et al. 2011; Yun et al. 2020).*

COMMENT 64: Regarding the seventh, eighth, and ninth paragraphs in Section 3.3.2 (Biomarkers of Effect), the Reviewer commented "I am okay with aberrations and micronucleus staying here as long as studies did exposure measurement/reconstruction, but p53 and p21 stuff is completely non-specific as far as biomarkers of effect are concerned."

RESPONSE: *We agree that oncogene data are not specific for vinyl chloride and the paragraphs "Mocci and Nettuno (2006)… but not in controls (DeVivo et al. 1994)."; "Detection of serum anti-p53… hepatocellular carcinoma."; and "Serum can be used to immunologically… exposure to other compounds." were deleted.*

COMMENT 65: Regarding the last four paragraphs in Section 3.3.2 (Biomarkers of Effect), the Reviewer commented "I am also dubious as to why these disease states are listed as biomarkers. They are exposure outcomes, not biomarkers "before" the disease is apparent… Consider deleting."

RESPONSE: *Paragraphs with text: "Angiosarcoma of the liver …may not be justified."; "Exposure to vinyl chloride…vinyl chloride disease (Black et al. 1983, 1986)."; "Some of the symptoms… vascular endothelium (Ward 1976)."; and "The occurrence of vinyl chloride disease… may not be the most helpful." were deleted as suggested.*

COMMENT 66: Regarding the statement in Section 3.4 (Interactions with Other Chemicals) "This report (ATSDR 2007) indicated that are no direct data available to characterize health hazards (and dose-response relationships) from mixtures containing all four components.", the Reviewer changed *that are no direct data* to *that no direct data are*.

RESPONSE: *Changed "that are no direct data" to "that no direct data" as suggested.*

COMMENT 67: Regarding the second paragraph in Section 3.4 (Interactions with Other Chemicals), the Reviewer commented "This is co-morbidity, not "other chemicals"."

RESPONSE: *The paragraph: "The results of recent studies…subsequent oxidative stress (Lang et al. 2019)." was adapted to "Mice fed a high-fat diet… subsequent oxidative stress (Lang et al. 2019)… high-fat diet mice exposed to vinyl chloride (Chen et al. 2019)." and moved to the section on susceptibility (Section 3.2).*

Comments Provided by Peer Reviewer #3

ATSDR Charge Questions and Responses Reviewer Comments

Chapter 1

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

COMMENT 1: Generally yes. I had a few updates. See details in my annotations in the document.

RESPONSE: *Revised as suggested.*

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

COMMENT 2: Yes, if appropriate controls and sufficient endpoints were included. This was mostly the case, unless it was stated otherwise.

RESPONSE: *No response needed.*

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

COMMENT 3: Yes

RESPONSE: *No response needed.*

Minimal Risk Levels

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

COMMENT 4: Yes, I agree.

RESPONSE: *No response needed.*

QUESTION: If MRLs have been derived, do you agree with the proposed MRL values? Explain. If you disagree, please specify the MRL value that you would propose. 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 5: This is not my area of expertise, so I don't feel confident in providing any alternative information.

RESPONSE: *No response needed.*

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

COMMENT 6: Again, not my area of expertise, however I was surprised that only one or two older references were used to assess the MRLs.

RESPONSE: *No response needed.*

Chapter 2

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

COMMENT 7: Generally yes. However, I had a few updates. See details in my annotations in the document.

RESPONSE: *Revised as suggested.*

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

COMMENT 8: Generally yes. However, I had a few updates. See details in my annotations in the document.

RESPONSE: *Revised as suggested.*

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

COMMENT 9: Yes, adequately designed animal studies identified in the text.

RESPONSE: *No response needed.*

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

COMMENT 10: Yes.

RESPONSE: *No response needed.*

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

COMMENT 11: Yes.

RESPONSE: *No response needed.*

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

COMMENT 12: Yes, there are several studies. For details, see annotations in the manuscript.

RESPONSE: *Studies were added as requested by the Reviewer*

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

COMMENT 13: No. There were a few in the "hepatic effects section" that I don't agree with. For details see annotations in the manuscript.

RESPONSE: *The data presented in the LSE table are for mice fed a normal diet only. Data in high-fat diet mice pertain to susceptibility to liver toxicity and these data are discussed in Section 3.2. A brief summary of studies using high-fat diet mice was included in Section 1.2 as requested by the Reviewer, with the addition of text "Mice fed a high-fat diet (not included in Levels of Significant Exposure, LSE Tables)… Hong et al. 1981; Maltoni et al. 1981).".*

QUESTION: Do you agree with the categorization of "less serious" or "serious" for the effects cited in the LSE tables? If not, please explain why and suggest appropriate changes.

COMMENT 14: Yes, I agree.

RESPONSE: *No response needed.*

QUESTION: Have all possible mechanisms of action been discussed within their relevant health effect section? If not, please explain. If citing a new reference, please provide a copy if available.

COMMENT 15: No, they have not. I have added a few mechanisms in the annotations, including an explanation and the appropriate references.

RESPONSE: *Revisions and additions to existing text were largely made as suggested. See the annotated comments and responses for more details. The mechanisms of liver toxicity section was replaced with a summary from Rusyn et al. (2021).*

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

COMMENT 16: Mostly. However, for the missing mechanisms and especially for the NOAEL/LOAEL justifications that I don't agree with I have added explanations in the annotations. This is especially the case for the hepatic effects and cancer sections. There have been several new studies recently that were not addressed in the text. I have included them in the annotations.

RESPONSE: *New studies were added as requested. See the annotated comments and responses for more details. The data presented in the LSE table are for mice fed a normal diet only and were not changed. Data in high-fat diet mice pertain to susceptibility to liver toxicity and these data are discussed in Section 3.2.*

Chapter 3

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

COMMENT 17: Mostly! Acetaldehyde dehydrogenase 2 (metabolism) was not discussed, however. I made annotations in the document. Additionally I added some information on urinary biomarkers.

RESPONSE: *Revised as suggested. See the annotated comments and responses for more details.*

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

COMMENT 18: Generally, yes! However, this not a strong area of expertise for me.

RESPONSE: *No response needed.*

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

COMMENT 19: Yes, but I also included a couple of updates in the annotations.

RESPONSE: *Revised as suggested. See the annotated comments and responses for more details.*

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

COMMENT 20: Yes, I included the potential update in the annotations

RESPONSE: *Revised as suggested. See the annotated comments and responses for more details.*

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

COMMENT 21: Yes there is. However, I also made some updates.

RESPONSE: *Revised as suggested. See the annotated comments and responses for more details.*

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

COMMENT 22: Yes. There are some that are not exclusive for vinyl chloride, however the limitations have been stated in the manuscript.

RESPONSE: *No response needed.*

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

COMMENT 23: Yes, mostly. Limitations have been stated in the manuscript. I have made also an update in the annotations.

RESPONSE: *Existing text was revised as suggested; however, information on disease processes was deleted based on comment from another Reviewer. See the annotated comments and responses for more details.*

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

COMMENT 24: There is adequate discussion. It does not exclusively concentrate on hazardous waste sites, but they are included.

RESPONSE: *No response needed.*

QUESTION: If interactive effects with other substances are known, does the text discuss the mechanisms of these interactions? Please explain and provide any additional references.

COMMENT 25: Mostly, I have made some updates and also asked for clarification (explanation provided) in the annotations.

RESPONSE: *The paragraph: "The results of recent studies…subsequent oxidative stress (Lang et al. 2019)." was adapted to "Mice fed a high-fat diet… subsequent oxidative stress (Lang et al. 2019)… high-fat diet mice exposed to vinyl chloride (Chen et al. 2019)." and moved to the section on susceptibility (Section 3.2). See the annotated comments and responses for more details.*

Chapter 4

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

COMMENT 26: I am not aware of missing information. I asked for clarification on one point. However, I do not know the information on that specific point.

RESPONSE: *No comments were made in Chapter 4; no response was needed.*

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

COMMENT 27: Yes.

RESPONSE: *No response needed.*

Chapter 5

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

COMMENT 28: Yes.

RESPONSE: *No response needed.*

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

COMMENT 29: Yes.

RESPONSE: *No response needed.*

QUESTION: Does the text cover pertinent information relative to transport, partitioning, transformation, and degradation of the substance in all media? Do you know of other relevant information? Please provide references for added information.

COMMENT 30: Yes.

RESPONSE: *No response needed.*

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

COMMENT 31: Yes.

RESPONSE: *No response needed.*

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

COMMENT 32: Yes. I have no additional information.

RESPONSE: *No response needed.*

Chapter 6

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

COMMENT 32: No.

RESPONSE: *No response needed.*

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

COMMENT 33: Yes. However, I included a few more on Exposure levels in environmental media and in humans.

RESPONSE: *The requested information on private drinking water supplies and the impact of plants in reducing exposure (Section 6.2, Identification of Data Needs, Exposure Levels in Environmental Media) is not consistent with standard methodology as outlined in the ATSDR Guidance for the Preparation of Toxicological Profiles: https://www.atsdr.cdc.gov/toxprofiles/guidance/profile_development_guidance.pdf. ATSDR will consider this Reviewer's comments in future revisions of the profile guidance. See annotated comments and responses for more details.*

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

COMMENT 34: Yes.

RESPONSE: *No response needed.*

Chapter 7

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

COMMENT 35: No.

RESPONSE: *No response needed.*

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

COMMENT 36: No.

RESPONSE: *No response needed.*

Annotated Comments on the Toxicological Profile

COMMENT 37: Regarding first two sentences in Section 1.1—Vinyl chloride is a volatile compound used almost exclusively in the United States by the plastics industry for the production of polyvinyl chloride (PVC) and several copolymers. Much of the vinyl chloride produced at manufacturing facilities gets converted to PVC and vinyl chloride derived copolymers on-site—the Reviewer moved the reference to the United states from the middle of the first sentence to the end, and had the following comment "I moved this because it sounded as if VC was almost exclusively used in the US and not other countries" In addition, the Review changed *Much* to *The Majority* and *gets* to *is* in the second sentence.

RESPONSE: *Revised to: "Vinyl chloride is a volatile compound used almost exclusively by the plastics industry to produce polyvinyl chloride (PVC) and several copolymers in the United States." "The majority…on-site.".*

COMMENT 38: Regarding the statement under Hepatic Effects in Section 1.2—Centrilobular hypertrophy and fatty liver changes resulted from intermediate-duration inhalation exposures of 10 and 50 ppm, respectively (Sokal et al. 1980; Thornton et al. 2002; Wisniewska-Knypl et al. 1980)—the Reviewer replaced *fatty liver changes* to *steatosis (fatty liver) and steatohepatitis (inflammation)* and had the following comments: (1) "Thornton 2002 showed basophilic and acidophilic foci, indicating inflammation;" (2) "This chapter (at the beginning) would benefit from a definition of what acute, intermediate and chronic means in this context. I know it is specified in Chapter 2, but the reader won't know that at this point;" and (3) "These are the newest data in this section. Much has been added over the last 10-15 years on hepatic effects of VC. I think these data should be incorporated. Cave 2010 (PMID: 19902480) was the first to describe toxicant-associated steatohepatitis caused by VC, demonstrating for the first time that even non-workers (office staff etc.) at those facilities develop steatohepatitis, fibrosis, etc. Also, a study on occupational exposures has demonstrated that occupational VC generated a distinct plasma metabolome, demonstrating significantly altered energy and amino acid metabolism in these subjects (PMID: 27765658). Further, recent intermediate exposure animal studies (that are referred to later in the document) should also be mentioned here as they show for the first time hepatic effects (intracellular/organelle effects that sensitize the liver, making them more vulnerable to other cytotoxic stimuli) at sub-OSHA standard levels: PMID: 29507902, PMID: 31026768, PMID: 31984951."

RESPONSE: *(1) Text was revised as suggested. (2) Text was revised to define acute-duration, intermediate-duration, and chronic-duration at first occurrence in Section 1.2. (3) Cave et al. (2010) (PMID 19902480), Guardiola et al. (2016) (PMID 27765658), Lange et al. (2018, 2020) (PMIDs 29507902, 31984951), and Chen et al. (2019) (PMID 31026768) as identified by the Reviewer were added to Hepatic Effects.*

COMMENT 39: Regarding Developmental Effects in Section 1.2, the Reviewer commented "Data from Thornton 2002 should be included here PMID: 12075123."

RESPONSE: *The Reviewer comment was addressed by adding: " No adverse effects were noted in an inhalation embryo-fetal developmental study in rats exposed to vinyl chloride at concentrations up to 1,100 ppm (Thornton et al. 2002).".*

COMMENT 40: Regarding the use of *lengthy* in the statement under Cancer in Section 1.2—The latency period for the development of hepatic angiosarcoma is lengthy (24–56 years in workers exposed prior to 1974) (Collins et al. 2014)—I think 'jargon' should be avoided and this word should be replaced."

RESPONSE: *Revised to: "The latency period for the development of hepatic angiosarcoma was 24–56 years in workers exposed prior to 1974 (Collins et al. 2014)."*

COMMENT 41: Regarding the critical effect of increased incidence of centrilobular hypertrophy for the Thornton et al. (2002) study in Table 1-1, the Reviewer commented "Expand! Inflammation, steatosis, organelle injury" and "Expand. PMIDs in comment on p. 5, line 12."

RESPONSE: *The critical effect for the intermediate-duration MRL is the effect occurring at the lowest concentration (i.e., centrilobular hypertrophy at 10 ppm). Other effects occurring at higher concentrations (e.g., steatohepatitis indicated by acidophilic and basophilic foci at 100 ppm) are not included in MRL tables. No change was made.*

COMMENT 42: Regarding the statement in the Introduction (Section 2.1) to Chapter 2—These data are discussed in terms of route of exposure (inhalation, oral, and dermal) and three exposure periods: acute (≤14 days), intermediate (15–364 days), and chronic (≥365 days)—the Reviewer commented "This definition is also needed in Chapter 1. It would be beneficial to repeat it throughout the document in chapters discussing these periods."

RESPONSE: *The exposure duration definitions were added at first occurrence in Chapter 1. The request to repeat the definitions throughout the profile is not consistent with standard profile format (https://www.atsdr.cdc.gov/toxprofiles/guidance/profile_development_guidance.pdf). ATSDR will consider this Reviewer's suggestion in future revisions of the profile guidance.*

COMMENT 43: Regarding the Levels of Significant Exposure (LSE) Table 2-1 in Section 2.1—the Reviewer commented "This table is confusing as the author names/dates are at the bottom of the respective row. I have the same comment for Table 2-2. It is also inconsistent with subsequent tables 2-3, 2-4, 2-5 and 2-6, where the names are at the top of the row. The format of 2-3, 2-4, 2-5 and 2-6 is preferred!"

RESPONSE: *The Reviewer's request is not consistent with standard LSE Table format as outlined in the ATSDR Guidance for the Preparation of Toxicological Profiles: https://www.atsdr.cdc.gov/toxprofiles/guidance/profile_development_guidance.pdf. ATSDR will consider this Reviewer's comments in future revisions of the profile guidance.*

COMMENT 44: Regarding hepatic no-observed-adverse-effect level (NOAEL) of 0.85 ppm under Figure key #34 (Chen et al. 2019)in LSE Table 2-1, the Reviewer commented "This should be moved to "Less serious LOAEL"! There are indeed hepatic effects at this concentration. This is already specified in comment on p. 5, line 12." and "The effects should be added here" (as a Serious lowest-observed-adverse-effect level [LOAEL]).

RESPONSE: *The data presented in the LSE table are for mice fed a normal diet only. Data in high-fat diet mice pertains to susceptibility to liver toxicity and these data are discussed in Section 3.2. A brief summary of studies using high-fat diet mice was included in Section 1.2 as requested by the Reviewer. Under hepatic effects in Section 1.2, ATSDR added "(not include in Levels of Significant Exposure, LSE, Tables)" to the high fat study sentence.*

COMMENT 45: Regarding hepatic NOAEL of 0.85 ppm under Figure key #38 (Lang et al. 2018) in LSE Table 2-1, the Reviewer commented "Same as previous comment (for Figure key 34)" and "Same as before" (regarding Serious LOAEL).

RESPONSE: *The data presented in the LSE table are for mice fed a normal diet only. Data in high-fat diet mice pertain to susceptibility to liver toxicity and these data are discussed in Section 3.2. A brief summary of studies using high-fat diet mice was included in Section 1.2 as requested by the Reviewer. Under hepatic effects in Section 1.2, ATSDR added "(not include in Levels of Significant Exposure, LSE, Tables)" to the high fat study sentence.*

COMMENT 46: Regarding hepatic NOAEL of 0.85 ppm under Figure key #39 (Lang et al. 2020) in LSE Table 2-1, the Reviewer commented "Same as previous comment" and "Same as before" (regarding Serious LOAEL).

RESPONSE: *The data presented in the LSE table are for mice fed a normal diet only. Data in high-fat diet mice pertain to susceptibility to liver toxicity and these data are discussed in Section 3.2. A brief summary of studies using high-fat diet mice was included in Section 1.2 as requested by the Reviewer. Under hepatic effects in Section 1.2, ATSDR added "(not include in Levels of Significant Exposure, LSE, Tables)" to the high fat study sentence.*

COMMENT 47: Regarding hepatic NOAEL of 0.85 ppm under Figure key #47 (Wahlang et al. 2020) in LSE Table 2-1, the Reviewer commented "Same as previous comments about the less serious LOAEL (males only)" and "Same as before (males only)" (regarding Serious LOAEL).

RESPONSE: *The data presented in the LSE table are for mice fed a normal diet only. Data in high-fat diet mice pertain to susceptibility to liver toxicity and these data are discussed in Section 3.2. A brief summary of studies using high-fat diet mice was included in Section 1.2 as requested by the Reviewer. Under hepatic effects in Section 1.2, ATSDR added "(not include in Levels of Significant Exposure, LSE, Tables)" to the high fat study sentence.*

COMMENT 48: Regarding LSE Figure 2-2, the Reviewer commented "I disagree with the assessment about 34M, 38M, 39M and 47M in terms of hepatic effects. See comment in table 2-1."

RESPONSE: *The data presented in the LSE figure are for mice fed a normal diet only. Data in high-fat diet mice pertain to susceptibility to liver toxicity and these data are discussed in Section 3.2.*

COMMENT 49: Regarding the statement in Section 2.2 (Death)—In female hamsters exposed to 200 ppm, two strains of female mice exposed to 50 ppm, and female rats exposed to 100 ppm for 12 months, a higher death rate was observed when 2-month-old animals were exposed than when 8- or 14-month-old animals were exposed—the Reviewer commented "Confusing. Needs to be reworded."

RESPONSE: *For clarity the text was revised as follows: "Drew et al. (1983) examined the influence of age on survival of female mice, rats and hamsters exposed to 50, 100, or 200 ppm vinyl chloride, respectively. For a 12-month exposure duration (6 hours/day, 5 days/week), mortality was highest in younger animals where exposure began at 2 months of age compared to animals that were first exposed at 8 or 14 months of age. All animals were maintained for up to 24 months; therefore, the post-exposure period was considerably longer for the younger animals."*

COMMENT 50: Regarding the statement in Section 2.2 (Death)—All animals were maintained on study for up to 24 months; therefore, the post-exposure period was considerably longer for the younger animals—the Reviewer replaced *study* with *this regimen*.

RESPONSE: *For clarity, the term "on study" was deleted.*

COMMENT 51: Regarding the statement in Section 2.2 (Death)—Tumors incidence was higher in younger animals, suggesting that mortality may be related to carcinogenesis in this study (see Section 2.19 Cancer)—the Reviewer changed *Tumors* to *Tumor*.

RESPONSE: *Revised as suggested.*

COMMENT 52: Regarding the statement in Section 2.3 (Body Weight)—Body weight was increased in mice fed a high-fat diet in these studies; however, this change was not related to vinyl chloride exposure, as body weight was also increased in the high-fat diet controls (Chen et al. 2019; Lang et al. 2018, 2020; Liang et al. 2018; Wahlang et al. 2020)—the Reviewer changed *related to further affected by* and removed*, as body weight was also increased in the high-fat diet controls*.

RESPONSE: *Revised as suggested. ATSDR added: "(not include in Levels of Significant Exposure, LSE, Tables)" to Section 2.3, Body Weight, Animal Studies sentence, above.*

COMMENT 53: Regarding Human Studies in Section 2.4 (Respiratory), the Reviewer commented "A study by Scarnato et al 2017 (PMID: 29119762) should be included here, in which they demonstrate that the excess in mortality for lung cancer is statistically significant for and with cumulative exposure higher."

RESPONSE: *It is standard ATSDR practice to limit retrieval and professional translation of foreign language studies to those essential for hazard identification and/or MRL derivation. Since Scarnato et al. (2017) does not fall into either of those categories, it was not retrieved or translated for the profile.*

COMMENT 54: Regarding Animal Studies in Section 2.5 (Cardiovascular), the Reviewer commented "A new study by Zelko IN (PMID: 34717031) on cardiometabolic toxicity caused by VC should be included here."

RESPONSE: *Added sentence: "*Exposure of LDL receptor-knockout … innominate artery (Zelko et al. 2022)."

COMMENT 55: Regarding Mechanisms in Section 2.5 (Cardiovascular), the Reviewer commented "Same comment as previous. PMID: 34717031."

RESPONSE: *See response to Comment 54.*

COMMENT 56: Regarding Section 2.9 (Hepatic), the Reviewer commented "Rusyn I et al 2021 is an important new study on toxicants including VC as human hepatotoxicants, that should be included PMID: 34105804."

RESPONSE: *Rusyn et al. (2021) was referenced and a figure from the publication added as Figure 2-4 in the Mechanisms of Liver Toxicity portion of Section 2.9*.

COMMENT 57: Regarding the statement in Section 2.9 (Hepatic)—Steatohepatitis (i.e., fatty liver) was also observed in studies of exposed workers (Cave et al. 2010; Hsiao et al. 2004; Maroni et al. 2003; Zhu et al. 2005a)—the Reviewer commented "This is incorrect. Steatosis is defined as fatty liver. Steatohepatitis is fatty liver with an inflammatory component and by definition more severe than just 'fatty liver'."

RESPONSE: *The text was revised for clarity as follows: Steatosis (i.e., fatty liver) and steatohepatitis (i.e., fatty liver with inflammatory changes) was also observed in studies of exposed workers (Cave et al. 2010; Hsiao et al. 2004; Maroni et al. 2003; Zhu et al. 2005a).*

COMMENT 58: Regarding the statement in Section 2.9 (Hepatic)—For example, the values obtained in several standard biochemical liver function tests (e.g., activities of serum alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], gamma-glutamyltransferase [GGT]) from workers with biopsy or ultrasonographic evidence of vinyl chloride-associated liver damage were not significantly higher than those from unexposed controls (Cave et al. 2010; Hsiao et al. 2004; Liss et al. 1985)—the Reviewer commented "While Cave showed that transaminases were unchanged, he did demonstrate a significant increase in CK-18. This is reflected in table 2-3, but it is not mentioned in the text of this section and should be added."

RESPONSE: *Added: "Cytokeratin 18 (CK-18) was elevated in vinyl chloride workers with steatohepatitis (Cave et al. 2010)."*

COMMENT 59: Regarding Animal Studies in Section 2.9 (Hepatic), the Reviewer commented "This section should be updated with additional newer references. There have been several studies with low concentrations of VC, demonstrating changes such as dysregulated hepatic energy metabolism, hepatic mitochondrial dysfunction etc: PMID: 29507902, PMID: 31026768, PMID: 31984951."

RESPONSE: *Corresponding with the PMIDs identified for Lang and Chen, ATSDR added "Mice fed a high-fat diet experienced enhanced liver damage, neutrophil infiltration, apoptosis, and oxidative and endoplasmic reticulum stress compared to mice fed a normal or low-fat diet (Chen et al. 2019; Fujiwara 2018; Lang et al. 2018, 2020; Liang et al. 2018; Wahlang et al. 2020)."*

COMMENT 60: Regarding the statement in Section 2.9 (Hepatic)—The molecular mechanism for hepatocellular necrosis was investigated in HepG2 cells exposed to increasing concentrations of chloroacetaldehyde (Beier et al. 2012)—the Reviewer commented "This is a poster abstract that led to a peer-reviewed publication and should be replaced by that: Anders et al PMID: 26962056."

RESPONSE: *In response to a comment from another Reviewer, the mechanisms section for liver toxicity was replaced by the figure and discussion text from Rusyn et al. (2021). Therefore, the Anders reference was not added.*

COMMENT 61: Regarding the statement in Section 2.9 (Hepatic)—Depletion of protein thiols and inhibition of mitochondrial respiration preceded liver cell death and were suggested as the primary mechanism of toxicity in these cells—the Reviewer commented "Ref PMID: 26962056."

RESPONSE: *In response to a comment from another Reviewer, the mechanisms section for liver toxicity was replaced by the figure and discussion text from Rusyn et al. (2021). Therefore, no response to this comment was needed. The Anders reference (PMID 26962056) was not added.*

COMMENT 62: Regarding the statement in Section 2.9 (Hepatic)—Metabolomics analysis of plasma samples from highly exposed vinyl chloride workers and healthy volunteers demonstrated an increase in plasma free fatty acids and lipid peroxidation products that may promote inflammation (Cave et al. 2012; Kirpich et al. 2013)—the Reviewer commented "This has also been shown in animals, which would lend weight to this section : PMID: 29507902, PMID: 31026768, PMID: 31984951."

RESPONSE: *In response to a comment from another Reviewer, the mechanisms section for liver toxicity was replaced by the figure and discussion text from Rusyn et al. (2021). The following sentence was added to account for animal studies with PMIDs identified in Comments 71 and 72: "Many of the same mechanisms have been noted in animal studies (Lang et al. 2018, 2020; Chen et al. 2019; Anders et al. 2019)."*

COMMENT 63: Regarding the statement in Section 2.9 (Hepatic)—Exposure of HepG2 cells to the lipid peroxidation products seen in the plasma of vinyl chloride workers produced mitochondrial dysfunction and endoplasmic reticulum stress (Kirpich et al. 2013)—the Reviewer commented "This has also been shown in animals, which would lend weight to this section: PMID: 29507902, PMID: 31026768, PMID: 31984951" and "This is a poster abstract that led to a peer-reviewed publication and should be replaced by that: PMID: 27765658."

RESPONSE: *In response to a comment from another Reviewer, the mechanisms section for liver toxicity was replaced by the figure and discussion text from Rusyn et al. (2021) obviating the need to refer to Guardiola et al. (2016) (PMID27765658). The following sentence was added to account for animal studies with PMIDs identified by the Reviewer: "Many of the same mechanisms have been noted in animal studies (Lang et al. 2018, 2020; Chen et al. 2019; Anders et al. 2019)."*

COMMENT 64: Regarding the statement in Section 2.9 (Hepatic)—Experiments with primary rat hepatocytes exposed to chloroacetaldehyde suggested that effects on both lysosomes (decreased membrane integrity) and mitochondria (respiratory chain disruption) may contribute to the liver cell toxicity (Pourahmad et al. 2012)—the Reviewer commented "This has also been shown in animals (with VC), which would lend weight to this section: PMID: 29507902" and "Also cite: Anders et al PMID: 26962056 Demonstrating that chloroacetaldehyde has rendered HepG cells to cytotoxic cell death caused by TNFalpha."

RESPONSE: *In response to a comment from another Reviewer, the mechanisms section for liver toxicity was replaced by the figure and discussion text from Rusyn et al. (2021). The following sentence was added to account for animal studies with PMIDs identified: "Many of the same mechanisms have been noted in animal studies (Lang et al. 2018, 2020; Chen et al. 2019; Anders et al. 2019)."*

COMMENT 65: Regarding the statement in Section 2.9 (Hepatic)—Kaiser et al. (2012) further suggested that insulin resistance, impaired hepatic lipid secretion, and increased cytokine production may play a role in the induction of steatosis in vinyl chloride-exposed workers—the Reviewer commented "Cite Cave 2010 and Guardiola 2016 PMID: 27765658."

RESPONSE: *In response to a comment from another Reviewer, the mechanisms section for liver toxicity was replaced by the figure and discussion text from Rusyn et al. (2021). Therefore, no references were added.*

COMMENT 66: Regarding the paragraph ending with the statement in Section 2.9 (Hepatic)—Increased CYP2E1 gene expression in peripheral blood lymphocytes in vinyl chloride-exposed workers was associated with increased risk of liver abnormalities, defined as ALT levels >40 units (U) and/or a defect observed by hepatic ultrasound (Wang et al. 2008)—the Reviewer commented "This paragraph should also include a discussion on the following mechanism: Another enzyme involved in VC metabolism is ALDH2. Chen 2019 has shown that activation of ALDH2 with agonist Alda-1 has protected from injury caused by VC. Moreover, VC metabolite directly inhibits ALDH2 enzyme, which can be partially rescued by Alda-1. PMID: 31026768."

RESPONSE: *In response to a comment from another Reviewer, the mechanisms section for liver toxicity was replaced by the figure and discussion text from Rusyn et al. (2021). A description of Chen et al. (2019) was included in Section 3.1.3 (as requested by the Reviewer).*

COMMENT 67: Regarding Human Studies in Section 2.10 (Renal), the Reviewer commented "There is a human study that includes VC at Camp Lejeune by Bove 2014 (PMID: 25115749) that should be added."

RESPONSE: *Bove et al. (2014) was added to Section 2.10 with the following text:* "A retrospective mortality…from kidney disease (Bove et al. 2014).".

COMMENT 68: Regarding Section 2.18 (Other Noncancer (Insulin Resistance)), the Reviewer changed the section title to *Other Noncancer (Insulin Resistance/and Metabolic Dyshomeostasis).*

RESPONSE: *Change was not incorporated as numbered Section and Chapter names follow the standard outline in the ATSDR Guidance for the Preparation of Toxicological Profiles: https://www.atsdr.cdc.gov/toxprofiles/guidance/profile_development_guidance.pdf.*

COMMENT 69: Regarding Human Studies in Section 2.18 (Other Noncancer), the Reviewer commented "Include the metabolomics study by Guardiola 2016 PMID: 27765658."

RESPONSE: *Added: "Plasma metabolomics analysis in vinyl chloride workers showed alterations in lipid and amino acid metabolites, which may contribute to the steatohepatitis (Guardiola et al. 2016).".*

COMMENT 70: Regarding the statement in Section 2.19 (Cancer)—Other liver tumors, including hepatocellular carcinoma and cholangiocellular carcinoma, were also associated with occupational exposure to vinyl chloride—the Reviewer commented "More commonly referred to as 'colangiocarcinoma'."

RESPONSE: *Added "(commonly referred to as colangiocarcinoma)" to sentence as suggested.*

COMMENT 71: Regarding Human Studies in Section 2.19 (Cancer), the Reviewer commented "PMID: 34065028, Gueardiola should be included here. It is a study on potential biomarkers and on metabolic changes in hepatic angiosarcoma."

RESPONSE: *Added: "Plasma metabolomics analysis of vinyl chloride workers who developed angiosarcoma showed upregulation of taurocholate, bradykinin, and fibrin degradation product 2 (Guardiola et al. 2021)." to Section 2.19. Table 2-8 was updated to include Guardiola et al. (2021).*

COMMENT 72: Regarding the Cancer type—Liver and biliary (angiosarcoma, hepatocellular carcinoma, cholangiocarcinoma)—Table 2-8 (Marsh et al. 2007a, 2007b), the Reviewer commented "PMID: 34065028, Guardiola should be included here. It is a study on potential biomarkers and on metabolic changes in hepatic angiosarcoma."

RESPONSE: *Guardiola et al. (2021) was added to Table 2-8.*

COMMENT 73: Regarding the statement in Section 2.19 (Cancer)—Hepatocarcinoma, hepatic angiosarcoma, and neuroblastoma were increased in treated animals compared to controls—the Reviewer commented "More commonly referred to as "hepatocellular carcinoma."

RESPONSE: *Replaced hepatocarcinoma with hepatocellular carcinoma as suggested.*

COMMENT 74: Regarding Mechanisms of Cancer in Section 2.19 (Cancer), the Reviewer commented "This section seems a little bit outdated with the newest reference from 2003. It should be updated. For

example (but not limited to): Chappell 2016 PMID: 27234561, Guengerich 2021 PMID: 34130743, Guardiola 2016 PMID: 34065028, Pan 2021 PMID: 33973497, etc."

RESPONSE: *Added: "Epigenetic processes that may contribute to vinyl chloride induced cancer formation include aberrant DNA methylation (Chappell et al. 2016) and cell cycle deregulation (Pan et al. 2021)." to Section 2.19 as suggested.*

COMMENT 75: Regarding the statement in Section 2.20 (Genotoxicity)—These studies suggest differing molecular mechanisms of carcinogenesis in humans and rodents—the Reviewer commented "Based on the evidence provided, the closing sentence comes across as too strong. The section either needs to be extended to better support that claim or the sentence should be deleted."

RESPONSE: *The sentence was deleted as suggested,*

COMMENT 76: Regarding the statement in Section 3.1.1 (Absorption)—No information is available regarding dermal absorption of vinyl chloride from liquid or solid mediums—the Reviewer commented "The more preferred term is "media" in this case."

RESPONSE: *Revised as suggested.*

COMMENT 77: Regarding Section 3.1.3 (Metabolism), the Reviewer commented "This paragraph should also include a discussion on the following mechanism: Another enzyme involved in VC metabolism is ALDH2. Chen 2019 has shown that activation of ALDH2 with agonist Alda-1 has protected from injury caused by VC. Moreover, VC metabolite directly inhibits ALDH2 enzyme, which can be partially rescued by Alda-1. PMID: 31026768."

RESPONSE: *Revised to include Chen et al. (2019) by adding: "Mitochondrial aldehyde dehydrogenase 2 (ALDH2) may also play a role in detoxifying 2-chloroacetaldehyde (Chen et al. 2019). Activation of ALDH2 with an agonist (Alda-1) was shown to attenuate liver injury and reduce oxidative stress in mice exposed to vinyl chloride (Chen et al. 2019)."*

COMMENT 78: Regarding the statement in Section 3.1.3 (Metabolism)—These results are consistent with conjugation of the metabolites of vinyl chloride with limited reserves of glutathione and/or cysteine (Bolt et al. 1976b; Hefner et al. 1975b; Jedrychowski et al. 1984; Watanabe et al. 1978b)—the Reviewer commented "This statement is confusing. I assume it refers to the fact that the lung inherently has limited glutathione supplies? This should be clarified more."

RESPONSE: *Revised for clarity as suggested. Sentence was replaced with "A reduction in these functional groups is expected since there are limited amounts of liver glutathione and/or cysteine to conjugate the metabolites of vinyl chloride."*

COMMENT 79: Regarding the statement in Section 3.1.3 (Metabolism)—Single oral doses of ^{14}C-vinyl chloride (0.05, 0.25, 1.0, 20, 100, and 450 mg/kg) were administered to rats, and the excretion of radioactivity was monitored over a 72-hour period (Green and Hathway 1975; Watanabe and Gehring 1976; Watanabe et al. 1976a)—the Reviewer changed *Green and Hathway 1975* to *Green and Hathaway 1975*).

RESPONSE: *Hathway is the correct spelling. No revision was made.*

COMMENT 80: Regarding the statement in Section 3.1.3 (Metabolism)—Following an intraperitoneal dose of 0.25 mg/kg, exhalation of unchanged vinyl chloride, exhalation of carbon dioxide, and urinary and fecal excretion of radioactivity accounted for 43.2, 11.0, 43.1, and 1.8% of the administered dose, respectively (Green and Hathway 1975)—the Reviewer changed *Green and Hathway 1975* to *Green and Hathaway 1975*).

RESPONSE: *Hathway is the correct spelling. No revision was made.*

COMMENT 81: Regarding the statement in Section 3.1.3 (Metabolism)—Doses administered intravenously were eliminated very rapidly and almost entirely by exhalation of unchanged vinyl chloride. Green and Hathway (1975) administered a 0.25-mg/kg intravenous dose of 14C-vinyl chloride to rats and recovered 80% of the dose within 2 minutes and 99% within 1 hour as unchanged compound in expired air—the Reviewer changed *Green and Hathway 1975* to *Green and Hathaway 1975*).

RESPONSE: *Hathway is the correct spelling. No revision was made.*

COMMENT 82: Regarding Section 3.2 (Children and Other Populations that are Unusually Susceptible), the Reviewer commented "Include this new study on neonates PMID: 29768398."

RESPONSE: *PMID 29768398 is El-Metwally et al. (2018) and was added by including: "Urinary metabolites of vinyl chloride and other volatile compounds have been measured in preterm infants in a neonatal intensive care unit (El-Metwally et al. 2018)."*

COMMENT 83: Regarding the statement in Section 3.2 (Children and Other Populations that are Unusually Susceptible)—No studies were located that specifically address the toxicokinetics of vinyl chloride in children; however, the toxicokinetic behavior of vinyl chloride in children is expected to be similar to that in adults—the Reviewer commented "Is there a reference for this?"

RESPONSE*: References were added by revising the sentence to: "The toxicokinetic behavior of vinyl chloride in children is expected to be similar to that in adults (Clewell et al. 2004; EPA 2000; Gentry et al. 2003)."*

COMMENT 84: Regarding the statement in Section 3.2 (Children and Other Populations that are Unusually Susceptible)—Young children appear capable of metabolizing vinyl chloride to reactive intermediates that form DNA adducts that lead to cancer—the Reviewer changed *capable* to *to have the capacity*.

RESPONSE: *Revised to change "capable" to "to have the capacity to".*

COMMENT 85: Regarding the statement in Section 3.2 (Children and Other Populations that are Unusually Susceptible)—People with liver disease and genetic polymorphisms of HLA-DR5, HLA-DR3, and B8 alleles are unusually susceptible to the effects of vinyl chloride—the Reviewer changed *People*

with liver disease to *Individuals with comorbidities (e.g. obesity and liver disease)* commented "This section would also benefit from a discussion on this point. However, this is also referred to in Section 3.4. So a simple referral to that section in this sentence would also be helpful."

RESPONSE: *Revised as suggested. The paragraph: "The results of recent studies…subsequent oxidative stress (Lang et al. 2019)." from Section 3.4 was adapted to "Mice fed a high-fat diet… subsequent oxidative stress (Lang et al. 2019)… high-fat diet mice exposed to vinyl chloride (Chen et al. 2019)." and moved to the section on susceptibility (Section 3.2)."*

COMMENT 86: Regarding the statement in Section 3.2 (Children and Other Populations that are Unusually Susceptible)—Lifestyle factors such as exposure to organochlorine pesticides, consuming high-caloric diets, ethanol or barbiturates, or taking Antabuse for alcoholism may make people have increased susceptibility to vinyl chloride effects—the Reviewer added high-caloric diets and commented "Added this to reflect the research efforts of many researchers over the last few years."

RESPONSE: *Revised as suggested. The paragraph: "The results of recent studies…subsequent oxidative stress (Lang et al. 2019)." from Section 3.4 was adapted to "Mice fed a high-fat diet… subsequent oxidative stress (Lang et al. 2019)… high-fat diet mice exposed to vinyl chloride (Chen et al. 2019)." and moved to the section on susceptibility (Section 3.2)."*

COMMENT 87: Regarding the statement in Section 3.2 (Children and Other Populations that are Unusually Susceptible)—Vinyl chloride workers with genetic polymorphisms of genes related to metabolism, DNA repair, and cell cycle control may be more susceptible to liver toxicity and liver cancer—the Reviewer commented "An important point here would be the inclusion of the ALDH2 polymorphism. Aldehyde dehydrogenase 2 (ALDH2) have been shown to influence the degree of genetic damage in Taiwanese and certain French VC workers. PMID: 12705718, PMID: 17384900 Chen 2019 has also shown that activation of ALDH2 with agonist Alda-1 has protected from injury caused by VC. Moreover, VC metabolite directly inhibits ALDH2 enzyme, which can be partially rescued by Alda-1. PMID: 31026768."

RESPONSE: *Li et al. (2003) (PMID: 12705718) was named Li et al. (2003b) and added to the paragraph: "Vinyl chloride is metabolized in the liver in a multistep process.", showing an association between ALDH2 polymorphism and mutation biomarkers in serum of exposed workers. Schindler et al. (2007) (PMID: 17384900) was not added to this section because none of the exposed workers were found to have the variant ALDH2-2 allele. Information from Chen et al. (2019) was added to the paragraph "Mice fed a high-fat diet… fed a normal or low-fat diet (Chen et al. 2019; ….)."*.

COMMENT 88: Regarding the statement in Section 3.2 (Children and Other Populations that are Unusually Susceptible)—It is because the intermediary metabolites of vinyl chloride, 2-chloroethylene oxide and 2-chloroacetaldehyde, have been suggested to be responsible for some of the adverse effects produced by vinyl chloride—the Reviewer removed *It is because*.

RESPONSE: *Revised as suggested.*

COMMENT 89: Regarding *persons* in the statement in Section 3.2 (Children and Other Populations that are Unusually Susceptible)—Thus, persons taking barbiturates or who might be exposed to organochlorine pesticides that are known to induce microsomal enzymes (such as Aroclor 1254) would be

expected to be at increased risk for developing vinyl chloride-induced hepatotoxicity—The Reviewer commented "Preferred would be 'individuals'."

RESPONSE: *Revised as suggested.*

COMMENT 90: Regarding paragraphs in Section 3.3.1 (Biomarkers of Exposure): "Thiodiglycolic acid is a major urinary…"; "The amount of thiodiglycolic acid"; "Similar to the measurement"; "Excretion of thiodiglycolic acid"; and "Boyle et al. (2016) suggest…", the Reviewer commented "These seem like microparagraphs compared to the others. Can some of them be combined?"

RESPONSE: *Paragraphs were combined as requested.*

COMMENT 91: Regarding the statement in Section 3.3.1 (Biomarkers of Exposure)—The origin of this thiodiglycolic acid in neonates is unknown, but is not believed to be associated with vinyl chloride exposure (Pettit 1986)—the Reviewer changed *not believed to be* to *likely not*.

RESPONSE: *Revised as suggested.*

COMMENT 92: Regarding the statement in Section 3.3.2 (Biomarkers of Effect)—This may be because of the extent of hepatic damage produced by vinyl chloride and the late development of necrotic areas in the disease process (Popper et al. 1981)—the Reviewer changed *may be because of* to *is likely due to*.

RESPONSE: *Revised as suggested.*

COMMENT 93: Regarding the statement in Section 3.3.2 (Biomarkers of Effect)—2-Chloroethylene oxide is believed to bind primarily to DNA and RNA, whereas 2-chloroacetaldehyde binds primarily to proteins (Bolt 1986; Guengerich and Watanabe 1979; Guengerich et al. 1979, 1981; Kappus et al. 1976; Watanabe et al. 1978a, 1978b)—the Reviewer changed *believed* to *hypothesized*.

RESPONSE: *Revised as suggested.*

COMMENT 94: Regarding the statement in Section 3.3.2 (Biomarkers of Effect)—This is because of the characteristic pattern of hepatic histopathology associated with vinyl chloride-induced damage (Popper et al. 1981)—the Reviewer commented "This is largely inaccurate. VC-induce liver damage cannot be distinguished purely by histology. Histology of VC- or alcohol- or obesity- induced liver disease is very similar and can only be distinguished with known background information, such as lifestyle choices, biomarkers, BMI, exposure etc. Please expand! Important information on this can be found here: PMID: 31540728."

RESPONSE: *The paragraph referenced in this comment was deleted from the profile based on a comment from another Reviewer indicating that disease processes are not biomarkers. No changes was made in response to this comment.*

COMMENT 95: Regarding Section 3.4 (Interactions with Other Chemicals), the Reviewer changed the section title to *Interactions with Other Chemicals and/or Comorbidities.*

RESPONSE: *Change was not incorporated as numbered Section and Chapter names follow the standard outline in the ATSDR Guidance for the Preparation of Toxicological Profiles: https://www.atsdr.cdc.gov/toxprofiles/guidance/profile_development_guidance.pdf. Additionally, comorbidities were moved to Section 3.2.*

COMMENT 96: Regarding the statement in Section 3.4 (Interactions with Other Chemicals)—High-fat diet mice exposed to 0.85 ppm vinyl chloride for 12 weeks showed enhanced liver damage, neutrophil infiltration, apoptosis, and oxidative and endoplasmic reticulum stress compared to mice fed a normal or low-fat diet (Chen et al. 2019; Fujiwara 2018; Lang et al. 2018, 2020; Liang et al. 2018; Wahlang et al. 2020)—the Reviewer added *non-parenchymal cell* and *mitochondrial dysfunction*.

RESPONSE: *Revised as suggested.*

COMMENT 97: Regarding the statement in Section 3.4 (Interactions with Other Chemicals)—Mice fed diets high in fat or lipopolysaccharide and exposed orally to 2-chloroethanol also experienced enhanced liver injury when compared to mice fed a normal or low-fat diet (Anders et al. 2016a, 2016b; Lang et al. 2019; Warner et al. 2013)—the Reviewer commented "They were not fed lipopolysaccharide, but injected. I would reword to: Mice injected with lipopolysaccharide or fed diets high in fat and exposed orally to 2-chloroethanol…" and "This is a poster abstract. The full study was peer reviewed and published here: Anders et al 2016b (PMID: 27693805)."

RESPONSE: *The text was revised as suggested. Warner et al. (2013) was deleted as a reference.*

COMMENT 98: Regarding the statement in Section 3.4 (Interactions with Other Chemicals)—Studies have been performed that examine the effect of agents intended to alter the metabolism of vinyl chloride on its toxicity—the Reviewer changed *that* to *to*.

RESPONSE: *Revised as suggested.*

COMMENT 99: Regarding Section 3.4 (Interactions with Other Chemicals), the Reviewer commented "Chen 2019 has also shown that activation of ALDH2 with agonist Alda-1 has protected from injury caused by VC. Moreover, VC metabolite directly inhibits ALDH2 enzyme, which can be partially rescued by Alda-1. PMID: 31026768."

RESPONSE: *Added to Section 3.4:* "*Activation of ALDH2 with an agonist (Alda-1) was shown to attenuate liver injury and reduce oxidative stress in high-fat diet mice exposed to vinyl chloride (Chen et al. 2019).*"

COMMENT 100: Regarding the statement in Section 3.4 (Interactions with Other Chemicals)—The study authors hypothesized that the enhancement of vinyl chloride toxicity was a result of the ability of TCPO to inhibit epoxide hydrase rather than its ability to deplete glutathione levels—the Reviewer changed The study authors to In this study the authors and changed hydrase to hydrolase with the comment "It was misspelled. I corrected it."

RESPONSE: *Revised as suggested.*

COMMENT 101: Regarding the statement in Section 3.4 (Interactions with Other Chemicals)—The lack of the effect of glutathione depletion indicates that the glutathione pathway is not very important at normal levels of exposure—the Reviewer changed *of the effect* to *of effect* and commented "This is a confusing statement. But it is a toxicologically important point. Please Clarify. At concentrations that do not saturate the detoxification pathways, glutathione depletion will not have detrimental effects."

RESPONSE: *The sentence was deleted to improve clarity.*

COMMENT 102: Regarding the statements in Section 5.1 (Overview)—Aerobically, vinyl chloride is expected to degrade rapidly. While anaerobic degradation can occur, this process is much slower—the Reviewer commented "This is very vague. Please identify a range such as relative t half-life."

RESPONSE: *The following change was made in response to this comment: "Aerobically, vinyl chloride is expected to degrade by 25% in a week and by >99% in 15.4 week. The quickness of anaerobic degradation is dependent on the components of the media (e.g., increased iron)."*

COMMENT 103: Regarding Section 5.3 (Releases to the Environment), the Reviewer commented "Should more information on fracking fluids, military installations and private wells be included? E.g.: PMID: 25115749 PMID: 24304547 PMID: 26943595."

RESPONSE: *The following was added to address PMIDs 25115749 and* 24304547*: "Vinyl chloride may be found in groundwater near military installations as a breakdown product of chlorinated solvents (Bove et al. 2014; Ruckart et al. 2013)." The article on fracking did not include information on vinyl chloride and was not added (Carpenter 2016; PMID 26943595).*

COMMENT 104: Regarding the statement in the Acute-Duration MRLs paragraph in Section 6.2 (Identification of Data Needs)—The inhalation database is adequate to derive an acute-duration inhalation MRL. The oral database is inadequate to derive an acute-duration oral MRL (no acute oral studies are available)—the Reviewer commented "A reminder or a referral to the section where the definition on acute, intermediate and chronic exposures are identified, would be helpful."

RESPONSE: *The Reviewer's request is not consistent with standard formatting as outlined in the ATSDR Guidance for the Preparation of Toxicological Profiles: https://www.atsdr.cdc.gov/toxprofiles/guidance/profile_development_guidance.pdf. ATSDR will consider this Reviewer's suggestion in future revisions of the profile guidance.*

COMMENT 105: Regarding the statement in the Exposure Levels in Environmental Media paragraph in Section 6.2 (Identification of Data Needs)—Current data on the extent of release (if any) of vinyl chloride from PVC pipes and from car interiors are also needed to estimate the risk of exposure of the general population—the Reviewer commented "And from homes within a certain radius of exposure points. Also important to know would be how plants decrease the exposure risk. There are several studies around the country, working on that. However none of the looks at VC specifically. Here is an example: https://greenheartlouisville.com/. More valuable data would come from monitoring private wells and humans exposure levels associated with that."

RESPONSE: *The Reviewer's request regarding a description of the use of plants in reducing vinyl chloride exposure is not consistent with standard methodology as outlined in the ATSDR Guidance for the Preparation of Toxicological Profiles: https://www.atsdr.cdc.gov/toxprofiles/guidance/profile_development_guidance.pdf. ATSDR will consider this Reviewer's suggestions in future revisions of the profile guidance.*

COMMENT 106: Regarding the ongoing study in Table 6-1 by Juliane I. Beier, the Reviewer changed *Pittsburg* to *Pittsburgh* and commented "It was misspelled. I fixed it."

RESPONSE: *Revised as suggested.*