

**DISPOSITION OF PEER REVIEW COMMENTS FOR
TOXICOLOGICAL PROFILE FOR
VINYL ACETATE**

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

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

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Comments provided by Reviewer #1

GENERAL COMMENTS

COMMENT 1: The graphical presentation of information is very helpful.

RESPONSE: *ATSDR thanks the Reviewer for their comments on the graphical presentations.*

ATSDR Charge Questions and Responses and Reviewer Comments

Chapter 1. Relevance to Public Health

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

COMMENT 2: I have no additional references relevant to vinyl acetate health effects in humans.

RESPONSE: *No response needed.*

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

COMMENT 3: The effects observed in the study of rats used to develop the MRL are consistent with effects observed in humans based on the limited human data provided in the toxicological profile. Also, the mechanism for the adverse effect is understood and can occur in both rats and humans.

RESPONSE: *No response needed.*

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

COMMENT 4: The inclusion of very specific athletic equipment (ski boots and bicycle seats) seems too specific for these products compared to the other categories listed. A broader reference such as consumer products or consumer products made of polymers (such as ski boots and bicycle seats).

RESPONSE: *The list of uses was updated to be more general in Sections 1.1 and 5.2.3.*

Section 1.1:

It is used in adhesives, paints and powder coatings, plastics and resins, rubber foam, packaging, sporting equipment (e.g., ski boots, bicycle seats), auto-related films, and intermediates in construction and building materials.

Section 5.2.3:

Consumer and commercial uses included use as an adhesive, intermediate, or monomer for packaging; an adhesive or intermediate in single- and two-component glues and adhesives; an intermediate in powder coatings, water-based paints, rubber foam, sporting equipment (e.g., ski

boots, bicycle seats), and auto-related films; and an intermediate in construction and building materials (EPA 2022).

Minimal Risk Levels (MRLs)

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

COMMENT 5: No comment.

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.

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

COMMENT 6: The MRL values have been developed using study data, PBPK modeling, and adjustment factors. The three MRLs are very close because the acute, intermediate, and chronic MRLs are based on the same NOAEL in separate studies by the same authors. Since all three evaluations in Bogdanffy, 1994 had intermittent exposures (6 hours per day for 5 days per week) it would seem that chronic effects from continuous 24-hour exposure could occur at a lower concentration. I understand that the PBPK model was intended to address the intermittent exposure, but I think that should be discussed in the main text and not just in the appendix.

RESPONSE: *Footnote b in Table 1-1 was revised to address the Reviewer's request for details regarding duration adjustment in Chapter 1.*

^bHEC values were calculated using a PBPK model (Bogdanffy et al. 1999; Hinderliter et al. 2005) with model parameters from Bogdanffy et al. (1999) and Plowchalk et al. (1997) with the exception of body weights, which were based on TWA body weights calculated for the principal study. Parameters in this model account for adjustments to a continuous (24 hours/day) exposure scenario. See Appendix A for additional details and calculations.

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

COMMENT 7: No comment.

RESPONSE: *No response needed.*

Chapter 2. Health Effects

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

COMMENT 8: The health effect conclusions appear to adequately represent the findings in the literature.

RESPONSE: *No response needed.*

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

COMMENT 9: Human study limitations were adequately discussed.

RESPONSE: *No response needed.*

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

COMMENT 10: Animal studies were adequately designed for this purpose.

RESPONSE: *No response needed.*

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

COMMENT 11: For the specific effects of inhalation exposure to vinyl acetate (irritation of the respiratory system, specifically nasal cavity), use of the rat study seems appropriate.

RESPONSE: *No response needed.*

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

COMMENT 12: No comment.

RESPONSE: *No response needed.*

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

COMMENT 13: I am not aware of any additional studies.

RESPONSE: *No response needed.*

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

COMMENT 14: I am not aware of any additional studies.

RESPONSE: *No response needed.*

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

COMMENT 15: NOAELs and LOAELs seemed appropriate.

RESPONSE: *No response needed.*

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

COMMENT 16: I found the categorization of serious and less serious effects appropriate and very useful.

RESPONSE: *No response needed.*

QUESTION: Have all possible mechanisms of action been discussed within their relevant health effect section? If not, please explain. If citing a new reference, please provide a copy and indicate where (in the text) it should be included.

COMMENT 17: No comment.

RESPONSE: *No response needed.*

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

COMMENT 18: The conclusions seem appropriate.

RESPONSE: *No response needed.*

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

Toxicokinetics

COMMENT 19: Not an area of expertise.

RESPONSE: *No response needed.*

Children and Other Populations that are Unusually Susceptible

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

COMMENT 20: While there is no discussion of human children exposures, there are references to efforts to look at developmental effects in off-spring of exposed animals. This seems adequate.

RESPONSE: *No response needed.*

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

COMMENT 21: No discussion of higher risk populations provided.

RESPONSE: *No changes to Section 3.2 were made in response to this comment. ATSDR notes that Section 3.2 identifies human populations with potentially increased susceptibility, including individuals with preexisting upper respiratory tract conditions, smokers, and individuals with certain genetic polymorphisms.*

Biomarkers of Exposure and Effect

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

COMMENT 22: Biomarkers are not particularly applicable to vinyl acetate since it readily breaks down into acetaldehyde, which is present from general metabolism as well. I agree with the text that unless the vinyl acetate is radio-labeled, there really isn't a biomarker for it.

RESPONSE: *No response needed.*

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

COMMENT 23: Not applicable based on previous answer.

RESPONSE: *No response needed.*

Interactions with Other Chemicals

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

COMMENT 24: There isn't much discussion of interactions with other chemicals.

RESPONSE: Available data did not identify any chemicals that influence the toxicity of vinyl acetate in the body.

Chapter 4. Chemical and Physical Information

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

COMMENT 25: Not aware of any.

RESPONSE: No response needed.

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

COMMENT 26: Not applicable since acetate is a simple molecule.

RESPONSE: No response needed.

Chapter 5. Potential for Human Exposure

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

COMMENT 27: No comment on this information.

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 28: The NPL site information on vinyl acetate dates back to 1981 prior to many efforts to improve handling of hazardous chemicals. So as not to mislead the public (1981 was 40 years ago), it would seem more appropriate to go back 10 years or split the data between historic and more current data.

RESPONSE: Data pertaining to detections at NPL sites are downloaded from ATSDR's science database, and not all datapoints have date information. For vinyl acetate, only about a third of the data have a date reported. More recent data cannot reliably be separated from the rest without this information.

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 29: The discussion of environmental fate and transport seems appropriate.

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 30: The report does present environmental monitoring data. I do not have any recommendations for additional sources. Those I looked at do not monitor for vinyl acetate.

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 31: No comment for this question.

RESPONSE: *No response needed.*

Chapter 6. Adequacy of the Database

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

COMMENT 32: I don't know of any additional studies. The graphical summary of information is very informative.

RESPONSE: *No response needed.*

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

COMMENT 33: It would be useful to have a summary table of data needs at the end of this chapter.

RESPONSE: *ATSDR thanks the Reviewer for the suggestion and will consider it in future updates of ATSDR's [Draft Guidance for the Preparation of Toxicological Profiles \(2018\)](#).*

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

COMMENT 34: The data need are presented in a neutral, non-judgmental fashion.

RESPONSE: *No response needed.*

Chapter 7. Regulations and Guidelines

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

COMMENT 35: I'm not aware of any additional regulations or guidelines.

RESPONSE: *No response needed.*

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

COMMENT 36: I don't recommend removing any of the regulations or guidelines.

RESPONSE: *No response needed.*

Appendices

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

COMMENT 36: The level of detail provided in Appendix B Is very helpful.

RESPONSE: *No response needed.*

Annotated Comments

COMMENT 37: Section 1.1, Page 1, Line 8: It seems unusual to mention such specific consumer items [ski boots, bicycle seats] unless these are the only or predominant consumer items that contain vinyl acetate.

RESPONSE: *See response to Comment 4.*

COMMENT 38: Section 2.1, Page 10, Line 19 "11 human studies and 46 animal studies": Caption for Figure 2-1 identifies 56 studies.

RESPONSE: *Study counts were fully audited and corrected. Text was corrected in Section 2.1 and the caption for Figure 2-1.*

Section 2.1: The health effects of vinyl acetate have been evaluated in 8 human studies and 44 animal studies.

Figure 2-1: A total of 52 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

COMMENT 39: Section 2.1, Page 11, Lines 13–14, "Available data are inadequate to determine if renal effects will occur in humans following exposure to vinyl acetate": This sentence seems out of place with developmental effects without more context.

RESPONSE: *The text in Section 2.1 was corrected. “Renal effects” was replaced with “developmental effects.”*

Available data are inadequate to determine if developmental effects will occur in humans following exposure to vinyl acetate based on no human data and a low level of evidence in laboratory animals following oral exposure.

COMMENT 40: Figure 2-1, Footnote “A total of 56 studies . . .”: Previously, the document identifies 46 animal and 11 human studies.

RESPONSE: *See response to Comment 38.*

Comments provided by Reviewer #2

GENERAL COMMENTS

COMMENT 1: NCEH/ATSDR Office of Science requested a review of the draft ATSDR Toxicological Profile for Vinyl Acetate. As such over the last couple weeks, I reviewed the draft document and associated documents, conducted brief literature searches, and reviewed selected references cited by the draft ATSDR Toxicological Profile for Vinyl Acetate in an effort to evaluate data presented, conclusions made by ATSDR, and charge questions posed for this process.

Within these timelines and context, I found the draft ATSDR Toxicological Profile for Vinyl Acetate provided a comprehensive review to my knowledge of toxicity, pharmacokinetics, environmental levels, and human exposures of vinyl acetate. I generally agreed with ATSDR's assessments and conclusions regarding vinyl acetate. I did have some specific comments and suggestions for improvement, mostly regarding units used within the document and statistical analysis of unpublished data from Morris 1995. I notated a few minor suggestions in a tracked-changes draft of the ATSDR Toxicological Profile for Vinyl Acetate and responses to specific charge questions below in blue. Please let me know if you have questions regarding these comments or suggestions.

***RESPONSE:** ATSDR thanks the Reviewer for their comments on the toxicological profile. Responses to specific comments (text color changed from blue to black by ATSDR) and suggestions for improvement (e.g., units used within the document, statistical analysis of unpublished data from Morris 1995) can be found below in response to the charge question comments that follow. The Reviewer suggested a number of editorial revisions in the profile; these suggested revisions were made to the profile. Responses to Reviewer's comments that were not considered editorial or stylistic are presented below.*

ATSDR Charge Questions and Responses and Reviewer Comments

Chapter 1. Relevance to Public Health

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

COMMENT 2: 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 3: I agree effects are likely to be of concern in humans. In rodents, researchers have postulated a toxicity mechanism consisting of vinyl acetate metabolized intracellularly to acetic acid (causing reducing cellular pH) and acetaldehyde (a genotoxicant) at portal of entry site (e.g. upper airways, esophagus, etc.). Although differing upper airways and breathing patterns of rodents and humans would impact dosimetry translations, I would expect that mechanisms of toxicity are consistent among animal species.

RESPONSE: *No response needed.*

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

COMMENT 4: Yes.

RESPONSE: *No response needed.*

Minimal Risk Levels (MRLs)

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

COMMENT 5: Justifications to not derive oral MRL values appear appropriate.

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.

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

COMMENT 6: MRL appear to be calculated appropriately. Data selected for point of departures are well justified by dose response data in rats and Benchmark Dose Analysis. Benchmark Dose Analysis model were selected based on lowest AIC of model that did not have a p-value ~ 1 (which suggests overfitting). AUCs were selected as the dose metric based on evidence that the severity of lesions in the olfactory epithelium of rats exposed to vinyl acetate is affected by exposure concentration and duration. This does metric is consistent with rapid hydrolysis of vinyl acetate and the most plausible mode of action hypothesis: intracellular acidification. A human intraspecies variability uncertainty factor (UF) of 10 is appropriate, as further data supporting UF reduction is not available. An UF of 3 for interspecies extrapolation is appropriate since a validated PBPK calculated HEC factors based on AUC translation reducing uncertainty.

RESPONSE: *No response needed.*

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

COMMENT 7: No further comment.

RESPONSE: *No response needed.*

Chapter 2. Health Effects

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

COMMENT 8: Conclusions in Chapter 2 are consistent with those published in the literature.

RESPONSE: *No response needed.*

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

COMMENT 9: Yes. Human studies were adequately described including limitations.

RESPONSE: *No response needed.*

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

COMMENT 10: Yes, study parameters are adequately described. Studies used for POD determination were adequately designed.

RESPONSE: *No response needed.*

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

COMMENT 11: Other animal models may have more similar upper airway morphology and breathing physiology to humans. For example, non-human primates have more similar upper airway morphologies but exhibit a more rapid respiratory rate. Conducting studies with non-human primates is expensive. Computational tools, like PBPK modeling, allow for translation of dose metrics from imperfect animal models to humans.

RESPONSE: *No response needed.*

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

COMMENT 12: ATSDR presented excellent figures demonstrating NOEALS and LOEALS across various studies for numerous endpoints. These visual summaries are a nice visual.

RESPONSE: *No response needed.*

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

COMMENT 13: No.

RESPONSE: *No response needed.*

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

COMMENT 14: No.

RESPONSE: *No response needed.*

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

COMMENT 15: 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 16: Yes, I agree with the categorizations in the table based on the Effects description. I did not review every primary source.

RESPONSE: *No response needed.*

QUESTION: Have all possible mechanisms of action been discussed within their relevant health effect section? If not, please explain. If citing a new reference, please provide a copy and indicate where (in the text) it should be included.

COMMENT 17: The report discusses all plausible mechanisms of action that I am familiar for vinyl acetate.

RESPONSE: *No response needed.*

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

COMMENT 18: Yes.

RESPONSE: *No response needed.*

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

Toxicokinetics

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

COMMENT 19: It looks good to me.

RESPONSE: *No response needed.*

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

COMMENT 20: Bogdanffy et al. and Hinderliter et al. offer the most refined vinyl acetate PBPK models that I am aware of and are well described in the report.

RESPONSE: *No response needed.*

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

COMMENT 21: The report describes species differences of carboxylesterase activity. Other aspects not discussed could include species dependent breathing patterns and upper airway morphology and physiology.

RESPONSE: *The following text was added to Section 3.1.6:*

Additional species-specific properties of the respiratory system also impact animal-to-human extrapolations. In addition to differences in physiology (e.g., carboxylesterase distribution and/or activity), there are differences in upper airway morphology between rodents and humans resulting in a higher ratio of the nasal passage surface area to ventilation volume in rodents, compared to humans (EPA 1994). PBPK models evaluating nasal effects of vinyl acetate exposure account for these differences in morphology in dosimetric calculations (Bogdanffy et al. 1997). However, PBPK models do not account for situations in which nasal exposure would be lower when ventilation in the human occurs from a mix of nasal and oral breathing (e.g., during moderate to heavy exercise or in people who habitually breathe through their mouth) (ICRP 1994). This introduces some uncertainty in animal-to-human extrapolations since rodents are obligate nasal breathers (EPA 1994). Additionally, the available PBPK models were developed for adult rodents and humans. In order to extrapolate across life stages, all parameters (e.g., ventilation rate) would have to be reevaluated and assigned values that represent specific pre-adult ages (e.g., infants, children).

Children and Other Populations that are Unusually Susceptible

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

COMMENT 22: Not that I am aware of.

RESPONSE: *No response needed.*

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

COMMENT 23: Some polymorphisms are speculated but data does not exist. I agree with ATSDR's assessment.

RESPONSE: *No response needed.*

Biomarkers of Exposure and Effect

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

COMMENT 24: Only vinyl acetate is specific to vinyl acetate exposure and is very short lived, making it a poor biomarker. Metabolites formed are not specific to vinyl acetate but could be useful in biomonitoring. High quality, specific biomarkers do not appear to exist.

RESPONSE: *No response needed.*

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

COMMENT 25: No. Effects (adducts, intracellular pH) could result from other chemical exposures.

RESPONSE: *No response needed.*

Interactions with Other Chemicals

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

COMMENT 26: No known chemicals.

RESPONSE: *No response needed.*

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

COMMENT 27: No known chemicals.

RESPONSE: *No response needed.*

Chapter 4. Chemical and Physical Information

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

COMMENT 28: Add units to molecular weight? Units to air odor threshold reported by US Coast Guard? CAS? SMILES? Vapor density?

RESPONSE: *The CASRN (108-05-4) was already reported in Table 4-1; the SMILES string was added to Table 4-1. Vapor density and units for molecular weight and odor threshold were added to Table 4-2.*

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

COMMENT 29: Properties are presented on liquid and gas states.

RESPONSE: *No response needed.*

Chapter 5. Potential for Human Exposure

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

COMMENT 30: As far as I can tell, yes.

RESPONSE: *No response needed.*

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

COMMENT 31: Yes, ATSDR identified sources appropriately by state. I do not know of other relevant references.

RESPONSE: *No response needed.*

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

COMMENT 32: No available information.

RESPONSE: *No response needed.*

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

COMMENT 33: Yes. ATSDR reports near detection limit levels in air as background. Except for concentrations in air, I suggest that ATSDR refrain from ratio (ppb/ppm/etc.) units and report in consistent mass per volume, mass per mass, or molar units. Ratio units are ambiguous and can lead to confusion. There are some inconsistencies in units used throughout the document (e.g. ppb and $\mu\text{g}/\text{m}^3$ both used for concentrations in air). I suggest making units consistent each media throughout the document.

RESPONSE: *Air monitoring data in Table 5-4 were updated to include ratio conversions in parenthesis, in accordance with ATSDR guidance of reporting the original units. Table 5-5 was updated to include a footnote for unit conversions. Units for other environmental compartments are reported consistently. For toxicological data, vinyl acetate vapor concentrations are consistently reported in ppm, in accordance with the [ATSDR Draft Guidance for the Preparation of Toxicological Profiles \(2018\)](#).*

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

COMMENT 34: Yes to both questions.

RESPONSE: *No response needed.*

Chapter 6. Adequacy of the Database

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

COMMENT 35: No.

RESPONSE: *No response needed.*

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

COMMENT 36: Yes. Compared to many chemicals, an adequate amount of data exists for risk assessment of vinyl acetate.

RESPONSE: *No response needed.*

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

COMMENT 37: Yes, language is neutral.

RESPONSE: *No response needed.*

Chapter 7. Regulations and Guidelines

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

COMMENT 38: No.

RESPONSE: *No response needed.*

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

COMMENT 39: No, all listed are appropriate.

RESPONSE: *No response needed.*

Annotated Comments

The Reviewer suggested a number of editorial revisions. The suggested revisions were made to the profile. Responses to Reviewer comments that were not considered editorial or stylistic are presented below.

COMMENT 40: Section 2.20, Page 74, Lines 9–10 “Radiolabel provided evidence that the observed N2-ethyl-dG adducts were exogenous in nature, rather than detection of endogenous acetaldehyde adducts”: Please clarify.

RESPONSE: *Section 2.20 was revised for clarity.*

Since acetaldehyde is produced endogenously by living cells during normal metabolism, presence of radiolabel was critical to provide evidence that the observed N2-ethyl-dG adducts were exogenous in nature, rather than detection of endogenous acetaldehyde adducts.

Unpublished Studies

Vinyl acetate has an unpublished study by Morris dated 1995 and 54 pages in length. The title is: Delayed contact hypersensitivity study in guinea pigs (Buehler Technique) of Vinyl acetate.

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

COMMENT 41: Study approved by Hill Top Biolabs IACUC with USDA registration. As such, the live animal experiments were conducted per Hill Top Biolabs IACUC's oversight and interpretation of regulatory standards.

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

COMMENT 42: Death was not observed. Study accounted for competing causes of skin sensitization.

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

COMMENT 43: No dose response data reported in the final test.

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

COMMENT 44: I think the study was conducted appropriately. Additional dose response data would offer additional information potentially valuable for risk assessment.

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

COMMENT 45: I would suggest that statistical evaluation of results would offer additional evidence to support the authors conclusions. Assuming these observations are indeed statistically significant, I agree with the conclusions of Morris that 25% w/v of vinyl acetate in acetone seem to induce grade 1 response.

RESPONSE: *Morris (1995) did not conduct statistical analysis. As per their interpretation protocol, any skin reaction graded <1 (0 or +/-) is considered "normal." Any reaction graded ≥1 in an exposed animal is considered evidence of sensitization, provided that no vehicle control animals show a reaction graded ≥1. Based on the findings of grade 1 (slight) responses in 6/20 exposed animals, compared to 0/10 vehicle controls, vinyl acetate is considered a skin sensitizer based on their protocol. Based on a 2-tailed Fisher's Exact Test conducted for this review (GraphPad), findings were marginal (p=0.07).*

Analyze a 2x2 contingency table

| | Grade 1 | No response | Total |
|---------|---------|-------------|-------|
| Control | 0 | 10 | 10 |
| 25% w/v | 6 | 14 | 20 |
| Total | 6 | 24 | 30 |

Fisher's exact test

The two-tailed P value equals 0.0741

Comments provided by Reviewer #3

GENERAL COMMENTS

COMMENT 1: One human study is listed as both Human Controlled Exposure Study and Human Observational Study. Deese DE, Joyner RE. 1969. Vinyl acetate: A study of chronic human exposure. Am Ind Hyg Assoc J 30:449-457. <http://doi.org/10.1080/00028896909343154>.

The study is listed in both Table C-8 (Human Controlled Exposure Studies) and Table C-9 (Human Observational Studies). The abstract seems to indicate that this was an occupational observational study. Furthermore, the study has been assigned very different points/categories in the risk of bias assessment in Table C-8 and Table C-9, which seems confusing. It would be helpful to add a footnote on why the same study is listed as both observational and experimental study.

RESPONSE: *Deese and Joyner (1969) contains two distinct studies. The main study is an occupational health survey on 21 workers and 21 controls evaluating potential effects of chronic exposure to vinyl acetate (chronic study in Table C-9). However, while sampling was being conducted, three individuals purposely stood in close proximity to the sample collector for intentional (albeit not strictly controlled) exposure. In each of the four sampling areas, this included three "volunteers:" one of the study authors, a laboratory analyst assisting in the sampling, and a chemical operator from each of the four areas. This was the study in Table C-8; however, upon re-examination, it is not strictly a controlled exposure, and it was moved to Table C-9. However, since it examined potential effects of acute exposure in a distinct set of subjects that differed from the main study, it is considered separately from the occupational health survey study in the risk of bias analysis. They are clearly distinct in Table C-9, as one is under the "Inhalation acute exposure" subheading and the other is under the "Inhalation chronic exposure" subheading.*

COMMENT 2: For MRL derivation, UF of 3 is used for extrapolation from animals to humans. Why is it 3 instead of 10? Is it because the HEC derivation has accounted for the toxicokinetic part of the difference and 3 is used to account for the pharmacodynamic difference? It would be helpful to provide a brief explanation.

RESPONSE: *The Reviewer is correct that use of dosimetric adjustments accounts for the toxicokinetic portion of the interspecies uncertainty factor. Using an uncertainty factor of 3 for extrapolation from animals to humans with dosimetric adjustment is in accordance with the [ATSDR Draft Guidance for the Preparation of Toxicological Profiles \(2018\)](#) and is standard practice for other regulatory agencies. Therefore, the explanation of "3 for extrapolation from animals to humans with dosimetric adjustments" is considered adequate.*

COMMENT 3: Chapter 2. It says at the beginning of Chap 2 that the "health effects of vinyl acetate have been evaluated in 11 human studies". However, only two studies are listed in the LSE tables (Table 2-3). Furthermore, I believe that only 5 studies are discussed in the chapter, which are Gruvberger et al. 1998, Tanaka and Lucas 1984, Deese and Joyner 1969, Union Carbide 1973, and Union Carbide 1989. It would be helpful to 1) provide a brief description on the study design before the above studies are discussed, except for Union Carbide 1989 which a brief description on the study design is provided for; and 2) report all 11 studies in a table in Chapter 2.

RESPONSE: Human studies in LSE tables are restricted to reliable studies with known exposure levels, in accordance with the [ATSDR Draft Guidance for the Preparation of Toxicological Profiles \(2018\)](#). For this database, studies that qualify are restricted to two dermal studies reported by Gruvberger et al. (1998) and Tanaka and Lucas (1984). The human results from controlled and occupational exposure studies reported by Deese and Joyner (1969), Hinderliter et al. (2005), and Union Carbide (1958, 1973) were not included in LSE tables due to study limitations (e.g., unknown or varying exposure durations, small subject number) and/or inadequate data reporting. The rationale for not including these studies is explicitly stated in Chapter 2 (e.g., Section 2.4: “While these studies suggest that vinyl acetate is non-irritating at concentrations <3 ppm, potentially irritating between 4 and 34 ppm, and irritating at ≥72 ppm, reliable NOAEL/LOAEL determinations for these studies could not be identified due to the small group numbers, limited reporting, and/or variable or unreported exposure durations.” and “As with the acute studies, several limitations of this study preclude identification of a reliable NOAEL/LOAEL value, including small number of subjects, lack of control for confounding factors, and lack of statistical analyses.”) The following statements were added to Section 2.4 for clarity:

Due to the aforementioned limitations, the Deese and Joyner (1969), Hinderliter et al. (2005), and Union Carbide (1973) human results were not included in LSE tables.

Therefore, the chronic occupational study by Deese and Joyner (1969) is also excluded from the LSE table.

Similar statements were added in other sections of the profile:

Sections 2.5, 2.7, 2.9, 2.10, and 2.15:

Pertaining to Deese and Joyner (1969): As previously discussed, this study was not included in the LSE table due to numerous limitations.

Section 2.11:

While these occupational studies suggest that skin exposure to vinyl acetate vapor or liquid may cause dermal effects, reliable NOAEL/LOAEL determinations for these studies could not be identified due to the small group numbers, limited reporting, and/or variable or unreported exposure durations. Therefore, Deese and Joyner (1969) and Union Carbide (1958) were not included in the LSE tables.

Section 2.12

As previously discussed, these human studies were not included in the LSE table due to numerous limitations precluding identification of a reliable NOAEL/LOAEL value, including small number of subjects, lack of control for confounding factors, and lack of statistical analyses.

Regarding the number of human studies, study counts were fully audited. Human studies with multiple potential exposure routes (e.g., inhalation exposure plus direct dermal contact with vapor) were erroneously double counted. That has been corrected, leaving a total of eight human studies from the seven reports containing human data reported in Chapter 2.

| Reference | Study type | Route |
|------------------------|---|--|
| Deese and Joyner 1969 | Study 1: Acute | Inhalation and ocular (via air) |
| | Study 2: Chronic | Inhalation, ocular, and dermal (via air) |
| Gruvberger et al. 1998 | Occupational exposure + controlled exposure | Dermal (patch test) |
| Hinderliter 2005 | Controlled exposure | Inhalation |

| Reference | Study type | Route |
|------------------------------|--|--|
| <i>Tanaka and Lucas 1984</i> | <i>Occupational exposure (initiation) + controlled exposure (patch test)</i> | <i>Dermal (patch test)</i> |
| <i>Union Carbide 1958</i> | <i>Occupational exposure</i> | <i>Dermal</i> |
| <i>Union Carbide 1973</i> | <i>Controlled exposure</i> | <i>Inhalation and ocular (via air)</i> |
| <i>Union Carbide 1989</i> | <i>Occupational exposure</i> | <i>Inhalation</i> |

ATSDR notes that in addition to the occupational study by Union Carbide (1989) mentioned by the Reviewer, the occupational study by Deese and Joyner (1969) currently includes a brief overview of the study design in Section 2.4: “In an occupational health survey, 21 male chemical operators exposed to vinyl acetate for a mean of 15.2 years were compared to 21 matched unexposed controls by thorough multiphasic screening examinations (Deese and Joyner 1969). Air samples obtained at several locations in the plant over a period of 1 month showed that vinyl acetate concentrations ranged from undetectable to 49.3 ppm, with a mean of 8.6 ppm.” Additional details, when available, were added to the profile for other human studies to provide clarity for the reader.

Section 2.4:

During the course of an occupational survey study, Deese and Joyner (1969) evaluated subjective complaints of odor and respiratory irritation in three individuals (a study author, a laboratory technician, and a factory worker) in three locations of a factory during air sampling for intervals ranging from 20 to 120 minutes. During the sampling periods, exposure levels were 4.2–9.9 ppm in Production Unit A, 2.7–9.5 ppm in Production Unit B, and 0.4–21.6 ppm in Production Unit C. Vinyl acetate odor was detected by at least one of three individuals at all exposure levels (≥ 0.4 ppm), with “marked” odor at 21.6 ppm. Hoarseness and/or cough was observed in three of three individuals at 21.6 ppm. Respiratory irritation was not consistently observed at <10 ppm (Deese and Joyner 1969). In a controlled exposure experiment in volunteers, complaints of odor and respiratory irritation were evaluated in subjects exposed to concentrations ranging from 0.6 to 20 ppm for 2 minutes or from 20 to 72 ppm for up to 4 hours (Union Carbide 1973). No odor detection or respiratory irritation was observed at 0.6 ppm; odor was detected but vinyl acetate was not irritating at 1.3 ppm. Irritation was reported in one or two (of nine) volunteers after exposure to 4–20 ppm for 2 minutes. At longer durations and higher concentrations, volunteers reported irritation after exposure to 20 ppm for 3 hours (one of three) or 72 ppm for 30 minutes (four of four). All volunteers (four of four) reported olfactory irritation after 4 hours at 20 ppm, 2 hours at 34 ppm, or 30 minutes at 72 ppm.

Section 2.11:

In the occupational health survey by Deese and Joyner (1969) described in Section 2.4 (Respiratory), 18/21 male chemical operators did not complain of any dermatitis or skin burns associated with dermal exposure to mean vinyl acetate air concentrations of 8.6 ppm. One operator complained of dermatitis, a second complained of “dryness of the hands,” and a third answered the survey with a question mark. None of the 21 matched unexposed controls complained of skin issues.

Section 2.12

In the acute occupational exposure study described in Section 2.4 (Respiratory), subjective reports of eye irritation were recorded following exposure to vinyl acetate at concentrations ranging from 0.4 to 21.6 ppm for up to 2 hours (Deese and Joyner 1969). All individuals (three of three) exposed to 21.6 ppm complained of eye irritation that “would be intolerable over an extended period.” At lower concentrations, no irritation was observed at ≤ 4.2 ppm or between 7.6 and 9.9 ppm; however, one of three individuals exposed to 5.7 or 6.85 ppm reported slight eye

irritation. In a controlled exposure experiment in volunteers, complaints of eye irritation were evaluated in subjects exposed to concentrations ranging from 0.6 to 20 ppm for 2 minutes or from 20 to 72 ppm for up to 4 hours (Union Carbide 1973). No eye irritation was observed at 0.6 ppm. Irritation was reported in 1 or 2 (of 9) volunteers after exposure to 4–20 ppm for 2 minutes. At longer durations and higher concentrations, no eye irritation was reported in volunteers exposed to 20 ppm for 4 hours or 34 ppm for 2 hours. However, volunteers exposed to 72 ppm for 30 minutes complained of eye irritation that persisted for up to 60 minutes after exposure (Union Carbide 1973). In the chronic occupational study by Deese and Joyner (1969) described in Section 2.4 (Respiratory), 6/21 exposed male workers indicated that vinyl acetate was irritating to their eyes, nose, or throat; three of these workers specifically indicated that it was irritating to their eyes. The mean exposure level was 8.6 ppm and the mean duration of exposure was 15.2 years (Deese and Joyner 1969).

ATSDR Charge Questions and Responses and Reviewer Comments

Chapter 1. Relevance to Public Health

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

COMMENT 4: 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 5: Respiratory effects – yes; Developmental effects – Not sure. This information is not provided in the chapter. Whether developmental effects observed in lab animals are likely to happen to human should be explained in Page 5 Line 12-13. I am not a toxicologist and have little expertise to comment on this question. Same for cancer, it would be helpful if the relevance to human could be comment on in Page 5 Line 25–26.

RESPONSE: *As stated in the [ATSDR Draft Guidance for the Preparation of Toxicological Profiles \(2018\)](#): “Unless otherwise indicated, studies in rats, mice, and other mammalian species are considered relevant to humans.” Therefore, in the absence of human data (as is the case for developmental and carcinogenic effects for vinyl acetate) the default assumption in risk assessment is that effects observed in animals are relevant to humans.*

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

COMMENT 6: Yes. It would be helpful to provide the major exposure pathways for populations living near contaminated sites. Are the groundwater contamination and vapor intrusion pathways the major ones of concern in general?

RESPONSE: *Section 1.1 was revised to address this comment.*

Since vinyl acetate has been detected at hazardous waste sites, populations living near contaminated sites may have increased exposure via ambient air, groundwater contamination, and/or vapor intrusion, compared to the general population.

Minimal Risk Levels (MRLs)

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

COMMENT 7: Yes, I agree that the data on oral exposure were inadequate to develop MRLs as explained in the profile.

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.

- a. 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 8: For MRL derivation, UF of 3 is used for extrapolation from animals to humans. Why is it 3 instead of 10? Is it because the HEC derivation has accounted for the toxicokinetic part of the difference and 3 is used to account for the pharmacodynamic difference? It would be helpful to provide a brief explanation.

RESPONSE: *See response to Comment 2.*

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

COMMENT 9: None, except for the UF of 3.

RESPONSE: *See response to Comment 2.*

Chapter 2. Health Effects

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

COMMENT 10: Yes.

RESPONSE: *No response needed.*

QUESTION: Were adequately designed human studies identified in the text (i.e., good exposure data, sufficiently long period of exposure to account for observed health effects, adequate control for

confounding factors)? Were the major study limitations sufficiently described in the text without going into lengthy discussions? If study limitations were not adequately addressed, please suggest appropriate changes.

COMMENT 11: It says at the beginning of Chap 2 that there are 11 human studies that evaluated health effect of the compound. However, only two studies listed in the LSE tables and/or figures. It seems a bit confusing regarding how studies are selected to be listed in the LSE tables/figures. An explanatory description provided in Page 10 Line 30, before presenting the tables and figures, would be helpful.

Furthermore, I believe that only 5 studies are discussed in the chapter, which are Gruvberger et al. 1998, Tanaka and Lucas 1984, Deese and Joyner 1969, Union Carbide 1973, and Union Carbide 1989. How about the rest 6 studies? Did they provide any meaningful information, or maybe they did not? It would be helpful to report all 11 studies for example in a table. It would be also helpful if a brief description on the study design could be provided before each study is discussed in the chapter. This does not include Union Carbide 1989, for which a brief description on the study design is provided.

The major study limitations are sufficiently and concisely described in the text.

RESPONSE: *See response to Comment 3.*

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 12: I am not a toxicologist and have little expertise to comment on this question. But I think this information would be helpful to be provided in a concise way in Chap 2, such as whether these studies generally provided good animal care, accounted for competing causes of death, and had sufficient number of dose groups. If not, whether there is a significant heterogeneity in these aspects across the studies.

RESPONSE: *Study design details are presented at a high level in the LSE tables in Chapter 2. In accordance with ATSDR guidelines, any study with major deficiencies is identified in the text of Chapter 2, but they are excluded from the LSE tables. For example, Umeda et al. (2004) is discussed in Section 2.6, but it is excluded from the LSE table due to methodological deficiencies precluding accurate exposure assessment. For all studies evaluating sensitive effects, detailed analysis of study quality can be found in the Systematic Review Appendix C. Further quality concerns may be addressed by reviewing the [ATSDR Draft Guidance for the Preparation of Toxicological Profiles \(2018\)](#), Attachments A and B.*

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 13: I am not a toxicologist and have little expertise to comment on this question.

RESPONSE: *No response needed.*

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

COMMENT 14: There is little discussion on dose-response relationships for human data.

RESPONSE: *Most available studies did not have adequate exposure details to inform dose-response relationships. A general concentration-response relationship for respiratory irritation is discussed in Section 2.4, beginning with paragraph: Studies in small groups of humans (3–9/group)... continuing through paragraph starting: Limited human data indicate that long-term....*

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 15: I am not aware of any studies that should be but are not included in the profile.

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 16: I am not aware of any studies that should be but are not included in the profile.

RESPONSE: *No response needed.*

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

COMMENT 17: I believe that appropriate NOAELs and/or LOAELs were identified and listed in the tables and figures.

RESPONSE: *No response needed.*

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

COMMENT 18: 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 and indicate where (in the text) it should be included.

COMMENT 19: I am not a toxicologist and have little expertise to comment on this question.

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 20: Yes, I believe that the conclusions are appropriate.

RESPONSE: *No response needed.*

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

Toxicokinetics

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

COMMENT 21: Yes, there is adequate discussion of ADME.

RESPONSE: *No response needed.*

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

COMMENT 22: I'd rather to skip this question.

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 23: Yes. The discussion is brief but helpful to a non-toxicologist.

RESPONSE: *No response needed.*

Children and Other Populations that are Unusually Susceptible

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

COMMENT 24: No data relevant to child health and developmental effects are discussed, due to lack of such data.

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 25: Yes, and I agree with the choice of potential susceptible populations.

RESPONSE: *No response needed.*

Biomarkers of Exposure and Effect

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

COMMENT 26: No. The compound is rapidly metabolized to CO₂, which is mainly exhaled out. CO₂ is not specific to vinyl acetate. No other biomarkers have been identified.

RESPONSE: *ATSDR agrees with the comment in that there are no specific exposure biomarkers for vinyl acetate, as discussed in Section 3.3.1.*

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

COMMENT 27: No biomarkers of effects specific to vinyl acetate have been identified.

RESPONSE: *ATSDR agrees with the comment in that there are no specific effect biomarkers for vinyl acetate, as discussed in Section 3.3.2.*

Interactions with Other Chemicals

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

COMMENT 28: “There are no chemicals known that influence the toxicity of vinyl acetate in the body.”

RESPONSE: *Thank you. ATSDR acknowledges authorship of that sentence in Section 3.4.*

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 29: “There are no chemicals known that influence the toxicity of vinyl acetate in the body.”

RESPONSE: *See response to comment 28.*

Chapter 4. Chemical and Physical Information

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

COMMENT 30: Not as noticed.

RESPONSE: *No response needed.*

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

COMMENT 31: Not sure what this question asks for.

RESPONSE: *No response needed.*

Chapter 5. Potential for Human Exposure

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

COMMENT 32: Yes. The information is comprehensive.

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 33: Yes. The information is comprehensive.

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 34: Yes. The description is comprehensive.

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 35: Yes. The information is comprehensive.

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 36: Yes. The information is comprehensive.

RESPONSE: *No response needed.*

Chapter 6. Adequacy of the Database

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

COMMENT 37: Not as I am aware of.

RESPONSE: *No response needed.*

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

COMMENT 38: 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 39: Yes, they are.

RESPONSE: *No response needed.*

Chapter 7. Regulations and Guidelines

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

COMMENT 40: Not as I am aware of.

RESPONSE: *No response needed.*

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

COMMENT 41: No.

RESPONSE: *No response needed.*

Annotated Comments

The Reviewer suggested a few editorial revisions. The suggested revisions were made to the profile. Responses to Reviewer comments that were not considered editorial or stylistic are presented below.

COMMENT 42: Section 1.1, Page 1, Lines 30-31: What are the major exposure pathways for people living near contaminated sites? Contaminated water and vapor intrusion?

RESPONSE: *See response to Comment 6.*

COMMENT 43: Section 1.2, Figure 1-1: Maybe this is a little bit too personal preference - I think the color density should be the other way around, with the acute exposure having the darkest color (standing for higher exposure concentrations) and the chronic exposure having the lightest color (standing for lower exposure concentrations).

RESPONSE: *ATSDR thanks the Reviewer for the suggestion and will consider it in future updates of ATSDR's [Draft Guidance for the Preparation of Toxicological Profiles \(2018\)](#).*

COMMENT 44: Section 1.3, Figure 1-3: LOAEL of 998.6 ppm for death is not mentioned anywhere in Chapter 1, but shows up in this figure. Suggest to add descriptions about the value in the main text. Similar comments about the values corresponding to death in Figure 1-1 and 1-2 and Figure 1-4.

RESPONSE: *Sections 1.2 and 1.3 were revised to address death.*

Section 1.2 text was revised to address death: As illustrated in Figures 1-1 and 1-2, sensitive noncarcinogenic effects in laboratory animals following vinyl acetate exposure include respiratory effects (inhalation) and developmental effects (inhalation, oral). Decreased body weight effects were also noted in some drinking water studies; however, assessment of compound-related effects on body weight is difficult due to concomitant decreases in water and/or food intake. No additional nonneoplastic effects were noted at concentrations or doses below high levels associated with increased mortality.

Text in Section 1.3, preceding Figure 1-3, was revised to address death: As presented in Figure 1-3, the available inhalation data for vinyl acetate suggest that the respiratory system is the most sensitive target of toxicity in laboratory animals following inhalation exposure. Additional effects noted at higher exposure levels included neurological, developmental, body weight, and cancer effects. No other effects were noted below high concentrations associated with increased mortality.

Text in Section 1.3, preceding Figure 1-4, already addressed death: No exposure-related effects were observed in acute-duration oral exposure studies in animals below the lowest identified median lethal dose (Figure 1-4).

COMMENT 45: Section 2.1, Page 10, Line 4: Remove "a NOAEL"?

RESPONSE: *The suggested change was not made to the introductory text. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an endpoint should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these endpoints. Sometimes "effects" are classified as a NOAEL if they are not considered biologically relevant (e.g., body weight changes <10%), as per ATSDR's [Draft Guidance for the Preparation of Toxicological Profiles \(2018\)](#).*

COMMENT 46: Section 2.4, Page 54, Lines 2-3: Would be helpful to have some specifics here [regarding respiratory parameters studied].

RESPONSE: *The paragraph was revised for clarity (parameters moved from prior sentence to sentence discussing the lack of adverse findings).*

No major differences were found between the exposed and unexposed workers with respect to any of the respiratory parameters studied, including complete physical examinations, chest x-ray, and spirometry.

COMMENT 47: Section 2.12, Page 61, Line 27: Were these workers in a workplace observational study or volunteers in an experimental study? It would be helpful to specify.

RESPONSE: *Discussion of human studies in Section 2.12 was revised for clarity.*

Eye irritation has been reported in individuals after acute exposures to vinyl acetate vapor. In the acute occupational exposure study described in Section 2.4 (Respiratory), subjective reports of eye irritation were recorded following exposure to vinyl acetate at concentrations ranging from 0.4 to 21.6 ppm for up to 2 hours (Deese and Joyner 1969). All individuals (three of three) exposed to 21.6 ppm complained of eye irritation that "would be intolerable over an extended period." At lower concentrations, no irritation was observed at ≤ 4.2 ppm or between 7.6 and 9.9 ppm; however, one of three individuals exposed to 5.7 or 6.8 ppm reported slight eye irritation. In a controlled exposure experiment in volunteers, complaints of eye irritation were evaluated in subjects exposed to concentrations ranging from 0.6 to 20 ppm for 2 minutes or from 20 to 72 ppm for up to 4 hours (Union Carbide 1973). No eye irritation was observed at 0.6 ppm. Irritation was reported in one or two (of nine) volunteers after exposure to 4–20 ppm for 2 minutes. At longer durations and higher concentrations, no eye irritation was reported in volunteers exposed to 20 ppm for 4 hours or 34 ppm for 2 hours. However, volunteers exposed to 72 ppm for 30 minutes complained of eye irritation that persisted for up to 60 minutes after exposure (Union Carbide 1973). In the chronic occupational study by Deese and Joyner (1969) described in Section 2.4 (Respiratory), 6/21 exposed male workers indicated that vinyl acetate was irritating to their eyes, nose, or throat; three of these workers specifically indicated that it was irritating to their eyes. The mean exposure level was 8.6 ppm and the mean duration of exposure was 15.2 years (Deese and Joyner 1969). As previously discussed, these human studies were not included in the LSE table due to numerous limitations precluding identification of a reliable NOAEL/LOAEL value, including small number of subjects, lack of control for confounding factors, and lack of statistical analyses.

COMMENT 48: Section 3.1.6, Page 88, Line 8: Section 3.1.6 is this section.

RESPONSE: *The section call-out was corrected from “Section 3.1.6” to “Section 3.1.5.” As described in Section 3.1.5, steady-state olfactory tissue concentrations of vinyl acetate, acetaldehyde, and acetic acid were predicted to be higher in humans compared to rats given the same external exposure levels (Bogdanffy et al. 1999).*

COMMENT 49: Section 5.1, Page 94, Line 19: And contaminated indoor air when products containing the compound are used (due to its high vapor pressure).

RESPONSE: *Section 5.1 was revised to include suggested information.*

The general population is most likely exposed to low levels of vinyl acetate through inhalation of contaminated ambient air and cigarette smoke, inhalation of contaminated indoor air from vapor intrusion or vaporization from water (during domestic water use activities) or products containing the compound (e.g., glues and paints), dermal contact with products containing the compound (e.g., glues and paints), and ingestion of residual vinyl acetate monomers in food (that may have migrated from plastic food wraps) or food items containing the compound as a starch modifier.

COMMENT 50: Appendix A, Page A-9, Line 12: Why is it 3 instead of 10? Is it because the HEC derivation has accounted for the toxicokinetic part of the difference and 3 is used to account for the pharmacodynamic difference? I would be helpful to explain.

RESPONSE: *See response to Comment 2.*

COMMENT 51: Appendix C.5.1. Page C-9, Line 6: Why were only 3 human studies evaluated in the section C.5? I would suggest providing a summary description on how the studies evaluated in the section were selected.

RESPONSE: *ATSDR does not perform study evaluation on all studies in Chapter 2. Rather, all data presented in Chapter 2 are reviewed to identify the most sensitive endpoints to be considered in MRL derivation. Only these endpoints are carried through the targeted systematic review process, in accordance with ATSDR’s [Draft Guidance for the Preparation of Toxicological Profiles \(2018\)](#). Section C.4 was revised to more clearly indicate the rationale for which health effects were carried through systematic review (Respiratory effects, Developmental Effects). Of the available human studies, only the three studies evaluated in Section C.5 evaluated respiratory effects; no human studies evaluated developmental effects.*

Overviews of the potential health effect outcomes for vinyl acetate identified in human and animal studies are presented in Tables C 3 and C-4, respectively. Human data include a limited number of human controlled inhalation exposure and occupational studies with potential for exposure via multiple routes. These limited human studies indicate that the respiratory system may be susceptible to vinyl acetate toxicity. Animal studies examined a comprehensive set of endpoints following inhalation or oral exposure, but dermal studies were limited to acute lethality, skin and eye irritation, and skin sensitization. Respiratory effects were considered sensitive outcomes following inhalation exposure and developmental effects were considered sensitive outcomes following inhalation and oral exposure (i.e., effects were observed at low concentrations or doses). Decreased body weight effects were also noted in some drinking water studies; however, assessment of compound-related effects on body weight is difficult due to concomitant decreases in water and/or food intake. No additional nonneoplastic effects were noted at concentrations or doses below high levels associated with increased mortality. Studies examining identified sensitive outcomes (respiratory effects following inhalation exposure;

developmental effects following inhalation or oral exposure) were carried through to Steps 4–8 of the systematic review. There were 21 studies (published in 14 documents) examining these potential outcomes carried through to Steps 4–8 of the systematic review.

COMMENT 52: Appendix C.6.1. Page C-15, Line 5: Why do not include human studies examining other health outcomes, e.g., cardiovascular, hematological, hepatic, renal, dermal, or cancer?

RESPONSE: *See response to Comment 51.*