DISPOSITION OF PEER REVIEW COMMENTS FOR TOXICOLOGICAL PROFILE FOR ACETONE

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Agency for Toxic Substances and Disease Registry

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Peer reviewer comments are shown without alteration. Peer reviewers for the third pre-public draft of the Toxicological Profile for Acetone were:

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Comments provided by Peer Reviewer #1

ATSDR Charge Questions and Responses

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: Yes, the effects described adequately represent the known human effects and exposure levels. I think the references located are comprehensive and convincingly demonstrate that acetone exposure can have an effect on human health. However, evidence for some expsoures (e.g., oral) is inadequate to establish clear MRLs for humans.

RESPONSE: *No revisions were 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: Many of the effects in animals are from very high dose exposures and via routes that are not typical for humans. For example, most human exposures are via inhalation whereas it appears based on the studies presented in this and subsequent chapters that rodent and other animal models are exposed via the oral route. Therefore, based on the data and studies presented, it may be preliminary to extrapolate these high dose exposure studies in rodents or other animals to humans. Additionally, studies at human relevant doses and via typical human exposures would provide more convincing evidence that animal effects can be translated to humans.

I recommend editing of Figures 1-1 and 1-2 as it is not clear in all cases if the studies described are from human or animals. I have indicated these changes in the text.

RESPONSE: *Figure 1-1 (Health Effects Found in Animals and Humans Following Inhalation Exposure to Acetone) has been divided into two figures, one dedicated to animal data and one dedicated to human data. Figure 2-2 (Health Effects Found in Animals and Humans Following Oral Exposure to Acetone) has not been split into two figures because there was not sufficient human data to fill a dedicated figure. It has therefore been renamed to indicate that it contains only animal data. All figures in Chapter 1 have been re-numbered accordingly.*

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

COMMENT: In most cases the conditions are adequately described. I indicated in the text where some confusion around descriptions exists. For example, there are references to “high” and “low” dose but these descriptions are subjective. In this chapter and in subsequent chapters, important descriptions of the various studies are missing. For example, in some cases details about sex and age are provided but not for every study. Given potential sex- and/or age-dependent differences, age and sex of the human subjects and the rodent or animal studies should be provided. I have indicated throughout the text where this should be fixed or clarified.

RESPONSE: *Where flagged, references to "high" and "low" exposure levels have been removed or, if appropriate and available, replaced with specific dose information.*

Regarding age and sex information for cited studies, for studies included in the Levels of Significant Exposure (LSE) Tables (Tables 2-2 and 2-3), sex is specified in the table if provided by the source study and age is provided if the study subjects are not adults. Age and sex information has been added to the text for studies that are not in the LSE tables where requested by the reviewer.

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: Yes, I think the conclusions are appropriate given the rigorous and comprehensive nature of the literature search.

RESPONSE: *No revisions were 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: Many of the studies are based on workplace or anecodotal exposures. The exposure period and environmental conditions are inconsistent across many of the studies thus making it challenging to control for confounding factors. These limitations in most cases are adequately described in the text.

RESPONSE: *No revisions were 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: Yes, the animal studies, mostly in mice and rats, are well designed, well powered, and represent a variety of exposure conditions. While these details may be present in the original publication, some details in the text such as the age and sex of the rodents used are not provided. Adding this information is important as there are age and sex differences with acetone exposure. Most instances where this information is lacking is provided as a comment in the text.

RESPONSE: *For studies included in the Levels of Significant Exposure (LSE) Tables (Tables 2-2 and 2-3), sex is specified in the table if provided by the source study and age is provided if the study subjects are not adults. Age and sex information has been added to the text for studies that are not in the LSE tables where requested by the reviewer.*

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

COMMENT: Yes, mice and rats are standard models.

RESPONSE: *No revisions were suggested.*

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

COMMENT: Dose-response relationships are clear for the rodent studies since these experiments are conducted under controlled conditions. However, clear dose-response relationships for humans is not clear given the nature of the data from work place studies or accidental/intentional exposures. Self-reporting can be unreliable and thus reduces the overall reliability of some of the studies reported in Table 2-1.

RESPONSE: *While some studies in Table 2-1 include self-reported data, all studies included in Table 2-1 also include measured (non-self-report) data. Additionally, the subjectivity of self-report data has been commented on several times in the text of Chapter 2.*

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: I think the topic was adequately researched. I am not aware of any other studies.

RESPONSE: *No revisions were suggested.*

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: I think the topic was adequately researched. I am not aware of any other studies.

RESPONSE: *No revisions were suggested.*

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

COMMENT: I think the figures in some cases represent the NOAELs and LOAELs in misleading ways. I have suggested ways to improve the figures throughout the text.

RESPONSE: *Figures have been developed in compliance with ATSDR guidance; formatting therefore was not changed.*

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: Yes, I think this categorization strategy is appropriate.

RESPONSE: *No revisions were suggested.*

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: Yes, the mechanism of action has been addressed as well as possible given the available literature on acetone exposure.

RESPONSE: *No revisions were suggested.*

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: Yes, the conclusions are appropriate. I agree that there is convincing evidence from animal models yet some routes of exposure for humans (e.g., oral) are not well studied thus limiting the ability of this group to derive estimates for MRLs in humans.

RESPONSE: *No revisions were suggested.*

QUESTION: Would you consider neuro effects to be one of acetone's sensitive endpoints for oral exposure, when not using gavage dosing? (A common oral exposure pathway for humans is contaminated groundwater.)

COMMENT: I am not a neurotoxicology expert but based on the data presented in this report, the neurological effects of acetone exposure are most likely observed under high dose or "serious" levels of exposure. Most of the oral data is from anecdotal incidents but there does appear to be neurological effects at high dose. Evidence with contaminated ground water is not convinving as levels (Table 5-6) were below the limit of detection.

RESPONSE: *No revisions were suggested.*

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

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

COMMENT: Yes, ADME has been addressed thoroughly. I have made comments throughout the text to improve clarity as well as to fix nomenclature issues with gene and protein nomenclature. I would suggest

to carefully review the nomenclature for cytochrome p450s as standard naming conventions are not consistently used throughout the text. Again, I have indicated these changes in the text.

RESPONSE: *The reviewer left a number of comments regarding proper nomenclature for cytochrome p-450 (CYP) genes and enzymes throughout the profile. Specifically, the reviewer requested that long-form names for CYP genes and proteins be consistently shortened (e.g., cytochrome P-450IIE1 be shortened to CYP2E1). Throughout the document, we have made these changes accordingly in compliance with most recent PharmVar nomenclature guidance.*[1] *Specifically, all letters have been capitalized and names for gene alleles have been italicized. In the first instance of use for each specific CYP gene, the long-form name has been provided followed by the shortened name in parentheses. This was done to avoid confusion for readers, especially because many cited studies use the long-form names.*

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

COMMENT: Yes, PKPD is adequately addressed. I have made comments in the text to improve clarity.

RESPONSE: *No revisions were suggested. Editorial comments in the text have been accepted where appropriate. See Annotated Comments on the Profile section for responses to individual comments.*

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: Yes, these points are addressed.

RESPONSE: *No revisions were suggested.*

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: For the most part this has been adequately discussed and addressed. I agree with the discussion that quantitative data is lacking for children.

RESPONSE: *No revisions were suggested.*

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: Yes, the discussion is appropriate for at risk populations as well as provides reasonable discussion on differences between males and females. Please comments above and in the main text as it is

[1] Gaedigk A, Ingelman-Sundberg M, Miller NA, et al. 2017. The Pharmacogene Variation (PharmVar) Consortium: Incorporation of the Human Cytochrome P450 (CYP) Allele Nomenclature Database. Clinical Pharmacology and Therapeutics 103(3): 399-401. https://doi.org/10.1002/cpt.910

important to describe which sex is being studied. I noted that sex (and age) is inconsistently provided in the text.

RESPONSE: *The reviewer left a number of comments requesting that sex and age be included when discussing animal and human studies of acetone exposure. For studies included in the Levels of Significant Exposure (LSE) Tables (Tables 2-2 and 2-3), sex is specified in the table if provided by the source study and age is provided if the study subjects are not adults. Age and sex information has been added to the text for studies that are not in the LSE tables where requested by the reviewer.*

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

COMMENT: No, it does not appear that specific acetone exposure biomarkers exist. Invasive markers such as examination of CYP2E1 activity might be possible but would not represent a specific response to acetone (e.g., CYP2E1 can be induced by alcohol exposure). These markers are likely to be typical of higher doses as acetone is a natural byproduct of human metabolism and it is unclear if these normal levels can induced p450s or potentiate the toxicity of other toxicants.

RESPONSE: *No revisions were suggested.*

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

COMMENT: No, there are no effect biomarkers either other than that described in the previous answer.

RESPONSE: *No revisions were suggested.*

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: Interaction data with acetone and carbon tetrachloride has been well studied. However, this is not a common exposure scenario. Interaction of acetone and carbon tetrachloride is most likely p450-mediated. Data is predominantly from rodents thus limited information about human exposures and chemical interactions makes it challenging to ascertain how chemical interactions may impact human disease.

RESPONSE: *No revisions were suggested.*

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: Yes, interactions with carbon tetrachloride, chloroform, certain alkenes, ethanol, etc are well described in the text. I have added comments throughout the text to improve clarity, edit p450 nomenclature, and provide important details about the study design.

RESPONSE: *The reviewer left a number of comments regarding proper nomenclature for cytochrome p-450 (CYP) genes and enzymes. Specifically, the reviewer requested that long-form names for CYP genes*

and proteins be consistently shortened (e.g., cytochrome P-450IIE1 be shortened to CYP2E1). Throughout the document, we have made these changes accordingly in compliance with most recent PharmVar nomenclature guidance. Specifically, all letters have been capitalized and names for gene alleles have been italicized. In the first instance of use for each specific CYP gene, the long-form name has been provided followed by the shortened name in parentheses. This was done to avoid confusion for readers, especially because many cited studies use the long-form names.

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: No, the information appears to be correct.

RESPONSE: *No revisions were suggested.*

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

COMMENT: Table 4-2 descibes the chemical properties of acetone correctly.

RESPONSE: *No revisions were suggested.*

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: Yes, I think the level of detail is appropriate.

RESPONSE: *No revisions were suggested.*

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

COMMENT: Yes, there is sufficient detail to describe its origination from natural and human made source and its interaction with the environment. Details about acetone as a natural byproduct of human metabolism are also provided.

RESPONSE: *No revisions were suggested.*

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: Yes, there is plenty of detail and thoroughly described.

RESPONSE: *No revisions were suggested.*

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

COMMENT: Yes, the detail is appropriate and adequately described. Units such as parts per million/billion (ppm, ppb) are described and explained in the text.

RESPONSE: *No revisions were suggested.*

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

COMMENT: Yes, the text describes the main sources and locations of exposure in the United States. Figure 5-1 resonbably presents this information from EPA although the shading may not be appropriate for the visually impaired.

RESPONSE: *No revisions were suggested.*

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: No, I do not know of any other studies. The literature search and key words was extremely thorough.

RESPONSE: *No revisions were suggested.*

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

COMMENT: Yes, I agree that there are some limitations that prevent the establishment of MRLs. For example, limited information about oral exposure in humans suggests more studies are needed.

RESPONSE: *No revisions were suggested.*

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

COMMENT: Yes, the data is presented in an unbiased and neutral manner. I did suggest in the text some improvements to the figures (e.g., color choice, altering the scale to better reflect difference).

RESPONSE: *Figures have been developed in compliance with the ATSDR Guidance for the Development of Toxicological Profiles document. Therefore, no changes were made in response to this comment.*

Chapter 7. Regulations and Guidelines

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

COMMENT: No, I am not involved in the discussion or implementation of regulations or guidelines.

RESPONSE: *No revisions were suggested.*

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

COMMENT: No they are appropriate for this text.

RESPONSE: *No revisions were suggested.*

Minimalal 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: n/a

RESPONSE: *No revisions were suggested.*

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: Yes, I agree with the MRL values. The studies presented are adequate for some of these determinations where evidence is available. I also agree as in the case of chronic oral acetone exposure, that no MRL can be derived based on limited data.

I do not think the Figure 1-3 and 1-4 adequately represent the MRL data for target. In fact, it is misleading as the scale is not linear.

The use of uncertainty factors for human variability, interspecies extrapolation, and other factors (e.g., LOAEL) are standard and appropriate.

RESPONSE: *Figures 1-3 and 1-4 have been developed in compliance with ATSDR guidelines (Guide for the Development of Toxicological Profiles, Exhibit 9), and a full discussion of the decisions behind each derived MRL are provided in Appendix A of the Toxicological Profile (ATSDR Minimal Risk Levels and Worksheets). For clarity, a note has been added beneath each figure in Chapter 1 stating that the data presented is further discussed in Chapter 2.*

We would also like to note that the hepatic effect of 7 mg/kg/day originally shown in Figure 4 was a typo. The lowest hepatic LOAEL observed for acetone is 90 mg/kg/day (Ross et al. 1995). Figure 1-4 has been corrected. The reference for this hepatic LOAEL (Ross et al. 1995) is mentioned throughout the text and in the MRL worksheet.

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

COMMENT: Figure 1-1, 1-2, 1-3, and 1-4 need to be edited to improve clarity. For instance, the scales of Figure 1-3 and 1-4 are not linear and therefore misrepresent the large-scale differences between say hepatic and neurological LOAELs via the oral route. I have commented throughout the text where changes need to be made.

RESPONSE: *Figure 1-1 (Health Effects Found in Animals and Humans Following Inhalation Exposure to Acetone) has been divided into two figures, one dedicated to animal data and one dedicated to human data. Figure 2-2 (Health Effects Found in Animals and Humans Following Oral Exposure to Acetone) has not been split into two figures because there was not sufficient human data to fill a dedicated figure. It has therefore been renamed to indicate that it contains only animal data. All figures in Chapter 1 have been re-numbered accordingly.*

See Annotated Comments on the Profile section for responses to individual comments.

Appendices

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

COMMENT: There are NO unpublished studies. This does not apply.

RESPONSE: *No revisions were suggested.*

Annotated Comments on the Profile

NOTE: *The reviewer left a number of editorial revisions throughout the document. All revisions consisting of only minor wording or grammatical changes that were not in boiler plate text areas were accepted. Editorial changes in boiler plate text areas were not made to maintain consistency with the ATSDR Guidance for the Development of Toxicological Profiles.*

NOTE: *The reviewer left a number of comments regarding proper nomenclature for cytochrome p-450 (CYP) genes and enzymes. Specifically, the reviewer requested that long-form names for CYP genes and proteins be consistently shortened (e.g., cytochrome P-450IIE1 be shortened to CYP2E1). Throughout the document, we have made these changes accordingly in compliance with most recent PharmVar*

nomenclature guidance.[2] Specifically, all letters have been capitalized and names for gene alleles have been italicized. In the first instance of use for each specific CYP gene, the long-form name has been provided followed by the shortened name in parentheses. This was done to avoid confusion for readers, especially because many cited studies use the long-form names.

NOTE: *The reviewer left a number of comments requesting that sex and age be included when discussing animal and human studies of acetone exposure. In compliance with ATSDR guidance, age has not been specified for studies in adult animals or population studies in adult humans. For animal studies included in the Levels of Significant Exposure (LSE) Tables (Tables 2-2 and 2-3), sex is specified in the table if provided by the source study. For studies not included in the LSE tables, age and sex have been specified in text if appropriate and available.*

COMMENT (page 2, line 3): I could not find in the biomarker section where this information was obtained.

RESPONSE: *Literature summarizing the use of breastmilk as a biomarker for acetone exposure is summarized in Chapter 3.3 Biomarkers of Exposure and Effect as follows:*

> *"Acetone has been identified in breast milk of lactating women (Pellizzari et al. 1982). According to the authors, mother's milk is an attractive medium for biomonitoring purposes because sample collection is reasonably straight-forward, milk contains a high amount of fat, so that fat-soluble pollutants may be found at higher concentrations in milk than in blood or urine, large volumes are easily collected, and the population of nursing mothers is relatively large. A disadvantage is the fact that only young to middle-age females are nursing, making extrapolation to the general population difficult."*

There were no revisions made to the Profile.

COMMENT (page 2, line 15): It may be style but I am not sure what high dose means here? It would be better to includee the dose or give some indication to how much higher this dose is relative to baseline exposures.

RESPONSE: *Text has been revised to not include "high dose of" where suggested by the reviewer. Specific dose information is provided later in Chapter 2.*

COMMENT (page 2, line 16): At what dose?

RESPONSE: *Specific dose information outlining the effects which are summarized in chapter 1 is provided in Chapter 2. The intent of the summary information in chapter one is to provide a broad overview of potential health effects. Therefore no revisions were made in response to this comment.*

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[2] Gaedigk A, Ingelman-Sundberg M, Miller NA, et al. 2017. The Pharmacogene Variation (PharmVar) Consortium: Incorporation of the Human Cytochrome P450 (CYP) Allele Nomenclature Database. Clinical Pharmacology and Therapeutics 103(3): 399-401. https://doi.org/10.1002/cpt.910

COMMENT (page 2, line 18): Same as above. It is not clear what these doses mean with respect to typical exposures?

RESPONSE: *Specific dose information outlining the effects which are summarized in chapter 1 is provided in Chapter 2. The intent of the summary information in chapter one is to provide a broad overview of potential health effects. Therefore no revisions were made in response to this comment.*

COMMENT (page 4, line 1): It is unclear in the table if the descriptions/effects apply to humans or animals. The effects should be clearly indicated if they were seen in humans or animals or both.

RESPONSE: *Figure 1-1 (Health Effects Found in Animals and Humans Following Inhalation Exposure to Acetone) has been divided into two figures, one dedicated to animal data and one dedicated to human data. Figure 2-2 (Health Effects Found in Animals and Humans Following Oral Exposure to Acetone) has not been split into two figures because there was not sufficient human data to fill a dedicated figure. It has therefore been renamed to indicate that it contains only animal data. All figures in Chapter 1 have been re-numbered accordingly.*

COMMENT (page 5, line 1): Table lacks information about whether it is in human or animal models? For example, is the temporary loss in body weight in humans AND animals?

RESPONSE: *Figure 1-1 (Health Effects Found in Animals and Humans Following Inhalation Exposure to Acetone) has been divided into two figures, one dedicated to animal data and one dedicated to human data. Figure 2-2 (Health Effects Found in Animals and Humans Following Oral Exposure to Acetone) has not been split into two figures because there was not sufficient human data to fill a dedicated figure. It has therefore been renamed to indicate that it contains only animal data. All figures in Chapter 1 have been re-numbered accordingly.*

COMMENT (page 7, line 1): Is this graph necessary? I think it might be better represented by a table. The scale of the graph is misleading and does not capture the stark differences between LOAEL across target organs.

RESPONSE: *Figure 1-4 was developed in compliance with the following ATSDR guidance:*

> *"Organize the figure by duration then in ascending order for each duration. This means to graph the lowest LOAEL first, followed by the second lowest and so on. When possible, make portrait and have two per page. The lowest LOAELs shall be the first entries for these figures. Use a maximum of four health endpoints per duration. If necessary, mention in text/table footer that there are more. Do not adjust exposures to be continuous or daily." (Guide for the Development of Toxicological Profiles, page 186).*

COMMENT (page 12, line 1): Does this color choice accommodate those with color blindness or vision impairment?

RESPONSE: *Yes, Figure 2-1 was reviewed using a colorblindness simulator and the colors used appeared distinct for all potential variations of color blindness. Further, the colors used for Figure 2-1 match those suggested per ATSDR guidance (Guide for the Development of Toxicological Profiles, page 188).*

COMMENT (page 12, line 4): XX needs to be replaced with a number

RESPONSE: *Text has been updated to specify that 131 studies were discussed in Chapter 2.*

COMMENT (page 13, Table 2-1): Sometimes TWA is abbreviated and others it is spelled out. I would choose one for consistency.

RESPONSE: *Text has been updated such that TWA is defined as time-weighted average upon first use in both a table and in narrative text. All other instances of "time-weighted average" throughout the document have been abbreviated to TWA. In addition, TWA is further defined in the legend of Table 7-1 and in Appendix E Glossary.*

COMMENT (page 31, Table 2-1): What is the breakdown of sex? SOmetimes this is explicitly stated but others (as in this example) it is not.

RESPONSE: *In some cases, sex of subjects may not be identified by the researchers. In this case, the study at hand identified all subjects as male. This has been clarified in the text of the table.*

COMMENT (page 17, Table 2-2): Why is this green?

RESPONSE: *References used to derive an MRL are highlighted light green in LSE tables per the following ATSDR guidance:*

> *"Each data point used to derive an MRL is marked with a footnote in the LSE table. Shade the study entry in the LSE table light green (Red 226, Green 239, Blue 217). The footnote should use language similar to the following examples." (Guide for the Development of Toxicological Profiles, page 150).*

For clarity the following footnote was added to the Table: "Highlighted rows indicate an MRL principal study."

COMMENT (page 27, Figure 2-2): There is no "other" as indicated in the legend.

RESPONSE: *"Other" label has been removed from legend.*

COMMENT (page 30, Table 2-3): How so? Increased? Decreased? Adding the direction of change would be consistent with the rest of the table.

RESPONSE: *Suggested revision was implemented. "Changes in dopamine" was updated to "Reduced dopamine" for better specificity.*

COMMENT (page 32, Table 2-3): Why green?

RESPONSE: *References used to derive an MRL are highlighted light green in LSE tables per the following ATSDR guidance:*

> *"Each data point used to derive an MRL is marked with a footnote in the LSE table. Shade the study entry in the LSE table light green (Red 226, Green 239, Blue 217). The footnote should use language similar to the following examples." (Guide for the Development of Toxicological Profiles, page 150).*

For clarity the following footnote was added to the Table "Highlighted rows indicate an MRL principal study."

COMMENT (page 43, line 14): How does this relate to category?

RESPONSE: *Text has been revised to clarify the job category as well as examples for each TWA acetone concentration. The sentence now reads:*

> *"The workers had been employed at the plant for at least 3 months to 23 years. Industrial hygiene surveys found that median TWA acetone concentrations were 380 (low exposure jobs including tow production and some jobs in preparation), 770 (moderate exposure jobs including inspectors and service jobs in filament), and 1,070 (high exposure jobs including operator jobs in filament extrusion) ppm."*

COMMENT (page 45, line 25): irritating to what?

RESPONSE: *Sentence was revised to clarify that the exposure at hand caused irritation to the nose, throat, and eyes of study subjects. The sentence now reads:*

> *"In a controlled exposure study, volunteers were asked to give their subjective complaints, and some reported irritation of the nose, eyes, and throat following exposure to 100 ppm for 6 hours, with more subjects reporting nose, eye, and throat irritation at increasing exposure levels (Matsushita et al. 1969b)."*

COMMENT (page 47, line 15): Which product?

RESPONSE: *Text has been revised to clarify the product in which acetone emissions were monitored. The sentence now reads:*

> *"At ambient temperature, acetone was measured in oak veneer at a concentration of 82 µg/m^3."*

COMMENT (page 47, line 16): Which product?

RESPONSE: *Text has been revised to clarify the three products in which acetone emissions were measured. The text now reads:*

> *"Acetone was one of the most commonly emitted VOCs at 70ºC, being measured in concentrations of 50 µg/m3 in ceiling tile, 70 µg/m3 in Spanished wallcovering, and 2,591 µg/m3 in oak veneer."*

COMMENT (page 47, line 26): Does ingestion imply oral or inhalation?

RESPONSE: *Ingestion implies oral exposure.*

COMMENT (page 48, line 23): What makes the study complex? it is not clear in the proceeding discussion?

RESPONSE: *Text stating that the study used complex protocol has been removed because it was not essential to the discussion of the study.*

COMMENT (page 51, line 6): Why is this repeated?

RESPONSE: *The case study in question (Herman et a. 1997) is discussed under multiple sections of Chapter 2 because multiple bodily systems were affected by the exposure.*

COMMENT (page 56, line 8): Subjective. Intermediate according to which definition?

RESPONSE: *ATSDR defines an intermediate-duration study as one lasting 15-364 days (See Section 2.1 of the Profile, also stated in the Guidance for the Development of Toxicological Profiles, page 201).*

COMMENT (page 63, line 9): Why is repeated exactly as above?

RESPONSE: *This sentence is similar in structure to text introducing case reports in other sections of Chapter 2 for the sake of consistency and organization throughout the document. However, it is not identical and does not repeat information. No revisions were made.*

COMMENT (page 66, line 19): Rodents?

RESPONSE: *In this case, the word "animals" is used to indicate that the proceeding paragraph summarizes all known literature regarding neurological effects of acetone exposure in animals. No revisions were made.*

COMMENT (page 67, line 16): Whichh was?

RESPONSE: *Added text to clarify that the patient was treated with a mixture of saline, glucose, and sodium lactate, delivered intravenously.*

COMMENT (page 70, line 8): What parameters? Motility?

RESPONSE: *Text has been revised to specify sperm parameters of increased sperm mortality and immotility as follows:*

> *"One epidemiological study of 25 male workers at a reinforced plastic production plant found evidence of increased sperm mortality and immotility as compared to 46 age-matched controls recruited from a fertility clinic."*

An in-text citation for Jelnes et al. (1988) has been added to the text as well.

COMMENT (page 73, line 11): Why are some in parentheses and others not?

RESPONSE: *Removed parentheses from sentence for consistency.*

COMMENT (page 75, line 29): If the result was a false positive, then either the sentence should be reformatted to state this first or removed from the report.

RESPONSE: *Text was revised to indicate that the result was a false positive at the beginning of the sentence. The text now reads:*

> *"In one study, acetone produced a false positive result in a biotransformation assay of BALB/c-`3T3 cells; the authors concluded that the result was a false positive because significant transforming activity only occurred at treatment doses above the upper dose limit of the assay (Matthews et al. 1993)."*

COMMENT (page 75, line 32): Which chemicals?

RESPONSE: *Text has been revised to clarify that the nine chemicals observed were MMNG, BP, Trp-P-1, Trp-P-2, BHA, BHT, sodium nitrite, sodium saccharin, and MCA.*

COMMENT (page 80, line 28): Beta or β

RESPONSE: *Text has been revised to correct "P" to "β."*

COMMENT (page 84, line 5): Is this symbol used consistently throughout? It is not defined at the end of the report.

RESPONSE: *"≈" has been defined in glossary as "approximately equal to."*

COMMENT (page 89, Figure 3-1): Use proper nomenclature for CYPs.

RESPONSE: *Nomenclature for Figure 3-1 cannot be changed as it is an original image from Dietz et al. (1991). The nomenclature in this figure is defined in relation to the recommended nomenclature earlier in the document, so we believe the figure will be understandable to readers.*

COMMENT (page 88, line 30): Age? sex?

RESPONSE: *Age and sex information have not been specified in this case because the sentence is summarizing results from several studies.*

COMMENT (92, line 23): Please use proper nomenclature.

RESPONSE: *We were unable to attest how the nomenclature used in the source study (Koop and Casazza 1985) would translate to current nomenclature. The terms have been left as-is.*

COMMENT (page 102, line 7): How is this determined?

RESPONSE: *Sentence has been deleted for lack of citation.*

COMMENT (page 112, line 16): Age? sex?

RESPONSE: *Age and sex information have not been specified in this case because the sentence is summarizing results from several studies.*

COMMENT (page 118, line 2): What is less than 9 fold increase? Perhaps it should be >?

RESPONSE: *Revised text from "<9-fold" to "8-fold" for improved accuracy.*

COMMENT (page 124, line 19): In this case the N and p should be italicized. it can then be abbreviated as NAPQI

RESPONSE: *Capitalization was adjusted and subsequent uses were abbreviated as suggested.*

COMMENT (page 127, Table 4-1): Why is the carbonyl in red?

RESPONSE: *Carbonyl group has been colored black.*

COMMENT (page 153, line 1): This table is very hard to read especially if a number "1" is placed in the blue bar. Further the graph does not appear to be linear. I am not sure the colors are well suit to accommodate those with visual impairment.

RESPONSE: *Figure 6-1 was developed in compliance with ATSDR guidelines (Guidance for the Development of Toxicological Profiles, page 229). Therefore, formatting was not changed in response to this comment.*

COMMENT (page F-1, line 1): I found acronyms etc are used inconsistently throughout

RESPONSE: *Annotated comments regarding acronyms in the profile have been addressed individually. Acronyms, abbreviations, and symbols have been used in compliance with ATSDR guidance (Guidance for the Development of Toxicological Profiles, page G-1).*

COMMENT (page F-4, line 5): some symbols such as ≈ are not defined here

RESPONSE: *"≈" has been defined as "approximately equal to."*

Comments provided by Peer Reviewer #2

ATSDR Charge Questions and Responses

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: Yes, I agree.

RESPONSE: *No revisions were 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: The effects observed both in humans and animals are very similar and dose-dependent. I don't know of any reports of effects only observed in animals and not in humans.

RESPONSE: *No revisions were suggested.*

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

COMMENT: Yes, the exposure conditions been adequately described. However, the text is missing information on Disulfiram (Antabuse), which is used for alcohol aversion therapy and produces aceton in the body (Stowell et al 1983).

Also, animal studies in rats show diethyldithiocarbamidate (metabolite of disulfiram) to induce increased exretion of acetone (Filser and Bolt, 1980).

Addition of these two points and the references would provide a complete picture of the acetone exposure/health effects.

RESPONSE: *Text has been added to address disulfiram as a potential source of acetone exposure as follows:*

> *"Disulfiram, a medicine commonly used in alcohol aversion therapy, has been found to induce endogenous acetone production in humans and animals (Stowell et al. 1980; DeMaster and Stevens 1988)."*

Note that the cited studies are not those suggested by the reviewer because the reviewer did not provide full study names or attachments. However, we believe the cited studies support the reviewer's conclusion that disulfiram is a reasonable source of acetone exposure for humans.

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: Yes.

RESPONSE: *No revisions were 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: Yes.

RESPONSE: *No revisions were 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: Yes.

RESPONSE: *No revisions were suggested.*

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

COMMENT: Yes.

RESPONSE: *No revisions were suggested.*

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

COMMENT: Yes. Ranges of exposures were adequate.

RESPONSE: *No revisions were suggested.*

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: No.

RESPONSE: *No revisions were suggested.*

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: No.

RESPONSE: *No revisions were suggested.*

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

COMMENT: Yes.

RESPONSE: *No revisions were suggested.*

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: I agree, these are adequate categorizatios.

RESPONSE: *No revisions were suggested.*

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: Yes.

RESPONSE: *No revisions were suggested.*

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: Yes.

RESPONSE: *No revisions were suggested.*

QUESTION: Would you consider neuro effects to be one of acetone's sensitive endpoints for oral exposure, when not using gavage dosing? (A common oral exposure pathway for humans is contaminated groundwater.)

COMMENT: Yes.

RESPONSE: *No revisions were suggested.*

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

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

COMMENT: Yes, to my knowledge.

RESPONSE: *No revisions were suggested.*

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

COMMENT: Yes, to my knowledge.

RESPONSE: *No revisions were suggested.*

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: Yes. However, data is missing on interindividual variance, which is due to the lack of published scientific literature.

RESPONSE: *Text has been added to Chapter 6.2, "Identification of Data Needs" as follows:*

> *"Because studies of acetone exposure in humans are limited, there is also little understanding of interindividual variance in human responses to acetone exposure."*

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: Not to my knowledge.

RESPONSE: *No revisions were suggested.*

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: Yes, the discussion is adequate but limited.

RESPONSE: *No revisions were suggested.*

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

COMMENT: Yes, acetone, the parent compound, is the appropriate biomarker of acetone exposure.

RESPONSE: *No revisions were suggested.*

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

COMMENT: Yes, they are adequate, primarily based on the biochemical endpoints involved in metabolism and tissue pathology. It is correctly stated that there are no specific biomarkers of effect for acetone.

RESPONSE: *No revisions were suggested.*

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: Yes, the discussion is adequate.

RESPONSE: *No revisions were suggested.*

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: Yes, the discussion is adequate.

RESPONSE: *No revisions were suggested.*

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: Instead of using 2-propanone, IUPAC name "Propan-2-one" should be used [Nomenclature of Organic Chemistry: IUPAC Recommendations and Preferred Names 2013 (Blue Book). Cambridge: *The Royal Society of Chemistry. 2014. p. 723. doi:10.1039/9781849733069-FP001. ISBN 978-0-85404-182-4.]*

Synonyms are sufficient.

RESPONSE: *Propan-2-one has been added to the list of synonyms for acetone listed in Table 4-1. The PubChem Compound Summary for Acetone includes propan-2-one as a synonym for acetone, so an additional citation was not needed.*

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

COMMENT: Sufficient data on aceton physical and chemical properties are presented.

Other: Update Reference "HSDB. 2019. Hazardous Substances Data Bank. National Library of Medicine, National Toxicology Information Program. https://toxnet.nlm.nih.gov/cgi-bin/sis/search/a?dbs+hsdb:@term+@DOCNO+41 " is not a valid web page. The web page states "TOXNET HAS MOVED As part of a broader NLM reorganization, most of NLM's toxicology information services have been integrated into other NLM products and services."

RESPONSE: *As of 2020, the Hazardous Substances Data Bank has been integrated into PubChem, a database under the National Council for Biotechnology Information. All outdated references to HSDB (internal and external) and accompanying links have been replaced with references to the current PubChem database.*

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: The information is complete as this reviewer could ascertain.

RESPONSE: *No revisions were suggested.*

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: The information is complete as this reviewer could ascertain.

RESPONSE: *No revisions were suggested.*

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: The information is complete as this reviewer could ascertain.

RESPONSE: *No revisions were suggested.*

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: Section 5.1, page 131, 3rd paragraph, last sentence "Acetone concentration in indoor air in the United States is generally slightly higher than outdoor air (8.0 ppb versus 6.9 ppb) (Shah and Singh 1988), due to the use of household consumer products containing acetone." needs to be corrected to reflect the information on Table 5 4. Indoor Air Monitoring Data for Acetone. This table indicates very different indoor air concentrations than the sited 8.0 ppb. [Acetone concentration in indoor air in the United States: More resent publication by Weisel et al (2008). Indoor Air VOC Concentrations in Suburban and Rural New Jersey. Environ Sci Technol. 2008 Nov 15; 42(22): 8231–8238. Acetone Mean 87.1 µg/m3 (36 ppb), SD 301, Max 2,900 µg/m3].

Section 5.6, 1st paragraph, last sentence, should read "…the daily intake for acetone (assuming a person consumes 2 L of drinking water/day) from this source would be <0.012 mg/day." based on the assumption that drinking water level is <6 ppb.

RESPONSE: *The reviewer is correct that this sentence previously contradicted the data presented in Table 5.4. To correct this, the most recent study of indoor air in US homes (Weisel et al. 2008) was used. We have also added a sentence to explain that indoor air acetone concentrations tend to be higher in smoking homes than in nonsmoking homes. The passage now reads:*

> *"Indoor air tends to have a higher concentration of acetone than outdoor air in the United States due to the use of household consumer products. A study of 100 homes in New Jersey reported a mean indoor air acetone concentration of 36.1 ppb (Weisel et al. 2008). In comparison, a study of 17 outdoor air samples across the United States reported a mean outdoor air acetone concentration of 6.9 ppb (Shah and Singh 1988). Smoking homes also tend to have higher indoor air acetone concentrations than nonsmoking homes (20.8 ppb versus 29.5 ppb) (Heavner et al. 1996)."*

Section 5.6, 1st paragraph, last sentence has been revised as suggested:

> *"However, the daily intake for acetone (assuming a person consumes 2 L of drinking water/day) from this source would be <0.012 mg/day based on the assumption that the level of acetone in drinking water is <6 ppb (Section 5.5.2)."*

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: The information is complete as this reviewer could ascertain.

RESPONSE: *No revisions were suggested.*

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: No. The information is complete as this reviewer could ascertain.

RESPONSE: *No revisions were suggested.*

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

COMMENT: Yes, the information is complete as this reviewer could ascertain.

RESPONSE: *No revisions were suggested.*

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

COMMENT: Yes, non noted.

RESPONSE: *No revisions were suggested.*

Chapter 7. Regulations and Guidelines

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

COMMENT: For occupational guidelines in Table 7-1, ACGIH TLVs and BEI should be provided in the table as these are commonly used by practicing occupational health and environmental professionals to protect the human health (American Conferecne of Governmental Industrial Hygiensts: TLVs® and BEIs® 2020.)

RESPONSE: *Table 7-1 has been developed in compliance with the following ATSDR guidelines:*

> *"Include relevant CDC, NIOSH, FDA, OSHA, or other governmental recommendations about [Substance x] in Table 7-1. Report ACGIH Threshold Limit Values (TLVs) only when there is no information for OSHA or NIOSH. Some of this type of information may not be able to be as presentable in tabular form and should therefore be included in the introductory text of Chapter 7." (Guidance for the Development of Toxicological Profiles, page 115).*

Because occupational information was available for both OSHA and NIOSH, ACGIH Threshold Limit Values (TLVs) were not included. ACGIH BEIs were also not included as they were not specified to be included by ATSDR guidance.

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

COMMENT: No.

RESPONSE: *No revisions were suggested.*

Minimalal 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: MRLs have been derived appropriately.

RESPONSE: *No revisions were suggested.*

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: MRLs have been derived appropriately. However, Figure 1-3 and 1-4 data are critical and should provide the reference like in the tables that follow or an explanation for their basis. This table may the first to be consulted in emergencies. I understand that this section is a summary, so it could be stated specifically where in the body of the document the reader can find the data and references that support the data in these tables (i.e., footnote).

However, in Table 1-1, it could be a bit confusing for non-exposure scientist to have different units (LOAEL), although this is conventional, for inhalation rather than BMCL like for the oral exposure. The dose response data from Dick et al. 1989 could be used to calculate BMCL for neurobehavioral or biochemical endpoint.

These uncertainty factors are commonly used.

RESPONSE: *Figures 1-3, and 1-4 have been developed in compliance with ATSDR guidelines (Guide for the Development of Toxicological Profiles, Exhibit 9), which does not include citations within figures. A note has been added beneath each figure stating that the data presented is further discussed in Chapter 2.*

Benchmark Dose Modeling was not selected for the derivation of inhalation MRLs as the principal study (Dick et al. 1989) examined only one dose of acetone. Multiple doses would be necessary for Benchmark Dose Modeling to be effective, so a LOAEL was used instead.

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

COMMENT: No additional comments.

RESPONSE: *No revisions were suggested.*

Appendices

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

COMMENT: Appropriate, nothing to note.

Note, one unpublished study has been included in the document (Striegel JA CC. 1961. Progress report for the month ending August 31, 1961. Mellon Institute of Industrial Research. Unpublished study submitted by Union Carbide Corporation, Danbury, CT, to EPA. OTS0536615.)

RESPONSE: *All unpublished studies have been peer reviewed and are flagged as unpublished in the Reference section of this Profile.*

Annotated Comments on the Profile

COMMENT (page 1, line 20): Note: Disulfiram (Antabuse) used for alcohol aversion therapy produces aceton in the body (Stowell et al 1983).

Note: Animal studies in rats show diethyldithiocarbamidate (metabolite of disulfiram) to induce increased exretion of acetone (Filser and Bolt, 1980).

RESPONSE: *Text has been added to address disulfiram as a potential source of acetone exposure as follows:*

> *"Disulfiram, a medicine commonly used in alcohol aversion therapy, has been found to induce endogenous eacetone production in humans and animals (Stowell et al. 1980; DeMaster and Stevens 1988)."*

Note that the cited studies are not those suggested by the reviewer because the reviewer did not provide full study names or attachments. However, we believe the cited studies support the reviewer's conclusion that disulfiram is a reasonable source of acetone exposure for humans.

COMMENT (page 1, line 30): Is it clear to the the general public what "recent" means in this context? Consider clarifying.

RESPONSE: *The full sentence reads: "However, because acetone is eliminated within 1 to 3 days, these methods should only be used to monitor recent acetone exposure." Because the sentence specifies an elimination time of 1 to 3 days for acetone in the body, we feel the time period is clear.*

COMMENT (page 2, line 3): Why is this separated from breath, urine, and blood monitoring? The reason should be given or this can be incorporated into the first sentence in this paragraphl

RESPONSE: *Sentence has been removed, and breastmilk has been listed alongside other forms of biomonitoring in the first sentence as follows:*

> *"Acetone exposure can be detected in exhaled breath, urine, blood, and breastmilk."*

COMMENT (page 4, Figures 1-1, 1-2, 1-3, and 1-4): Figure 1-1: These data are critical and require reference like in the tables that follow or an explanation for their basis. This table may the first to be consulted in emergencies.

Note: it could be stated specifically where in the body of the document the reader can find the data and references that support the data in these tables (i.e., footnote).

RESPONSE: *Figures 1-1, 1-2, 1-3, and 1-4 have been developed in compliance with ATSDR guidelines (Guide for the Development of Toxicological Profiles, Exhibit 9), which does not include citations within figures. A note has been added beneath each figure stating that the data presented is further discussed in Chapter 2.*

COMMENT (page 8, Table 1-1): It is confusing to have different units (LOAEL) for inhalation rather than BMCL like for the oral exposure. The dose response data from Dick et al. 1989 should be used to calculate BMCL for neurobehavioral or biochemical endpoint.

RESPONSE: *Benchmark Dose Modeling was not selected for the derivation of inhalation MRLs as the principal study (Dick et al. 1989) examined only one dose of acetone. Multiple doses would be necessary for Benchmark Dose Modeling to be effective, so a LOAEL was used instead.*

COMMENT (page 8, line 3): Why are these words capitalized while the others are not (i.e., for NOAEL the words are not capitalized)? This should be consistent throughout the document.

RESPONSE: *Revisions have been accepted to de-capitalize "benchmark dose lower confidence limit, 1 standard deviation" to be consistent with other capitalization in this footnote.*

COMMENT (page 12, line 4): Incomplete.

RESPONSE: *Text has been updated to specify that 131 studies were discussed in Chapter 2.*

COMMENT (page 15, Table 2-1 and throughout document): SI unit abbreviation for hour and hours is "h". this should be consistent throughout the document.

RESPONSE: *Abbreviations for "hours" have been adjusted in all relevant tables to "h."*

COMMENT (page 17, Table 2-1): Why is thie colored? This study and the use of the data produed mys be reviewed and verified for the biochemical outcomes.

RESPONSE: *References used to derive an MRL are highlighted light green in LSE tables per the following ATSDR guidance:*

> *"Each data point used to derive an MRL is marked with a footnote in the LSE table. Shade the study entry in the LSE table light green (Red 226, Green 239, Blue 217). The footnote should use language similar to the following examples." (Guide for the Development of Toxicological Profiles, page 150).*

For clarity the following footnote was added to the Table "Highlighted rows indicate an MRL principal study."

*C***OMMENT (page 24, line 1):** All figures, like table, require reference and/or indicate they are a composite composed of data in the reference list. Simply listing animals and not indicating which surrogate species is unsatisfactory.

The figure should have a note that the number associated with the point in the figure corresponds to the "Figure Key" in Table 2-2.

RESPONSE: *Figures 2-2 and 2-3 have been developed in compliance with ATSDR guidance for Levels of Significant Exposure (LSE) Figures and therefore were not changed (Guidance for the Development of Toxicological Profiles, page 201). However, we believe Figures 2-2 and 2-3 are clear and accurate. For Figures 2-2 and 2-3, point labels correspond to study ID and species, while point shapes correspond to data type (Human NOAEL; Human LOAEL, Less Serious; Human LOAEL, More Serious; Animal NOAEL; Animal LOAEL, Less Serious; Animal LOAEL, More Serious). Point labels and shapes are defined in the legend directly below each figure, while study IDs correspond directly with the "Figure Key" column in the preceding LSE table, which contains the full reference.*

COMMENT (page 25, line 1): All figures, like table, require reference and/or indicate they are a composite composed of data in the reference list. Simply listing animals and not indicating which surrogate species is unsatisfactory.

The figure should have a note that the number associated with the point in the figure corresponds to the "Figure Key" in Table 2-2.

RESPONSE: *Figures 2-2 and 2-3 have been developed in compliance with ATSDR guidance for Levels of Significant Exposure (LSE) Figures and therefore were not notchanged (Guidance for the Development of Toxicological Profiles, page 201). However, we believe Figures 2-2 and 2-3 are clear and accurate. For Figures 2-2 and 2-3, point labels correspond to study ID and species, while point shapes correspond to data type (Human NOAEL; Human LOAEL, Less Serious; Human LOAEL, More Serious; Animal NOAEL; Animal LOAEL, Less Serious; Animal LOAEL, More Serious). Point labels and shapes are defined in the legend directly below each figure, while study IDs correspond directly with the "Figure Key" column in the preceding LSE table, which contains the full reference.*

COMMENT (page 27, line 1): No reference citation for the user to check.

RESPONSE: *Figures 2-2 and 2-3 have been developed in compliance with ATSDR guidance for Levels of Significant Exposure (LSE) Figures and therefore were not changed (Guidance for the Development of Toxicological Profiles, page 201). However, we believe Figures 2-2 and 2-3 are clear and accurate. For Figures 2-2 and 2-3, point labels correspond to study ID and species, while point shapes correspond to data type (Human NOAEL; Human LOAEL, Less Serious; Human LOAEL, More Serious; Animal NOAEL; Animal LOAEL, Less Serious; Animal LOAEL, More Serious). Point labels and shapes are defined in the legend directly below each figure, while study IDs correspond directly with the "Figure Key" column in the preceding LSE table, which contains the full reference.*

COMMENT (page 31, Table 2-3): Note: unpublished study.

RESPONSE: *All unpublished studies have been peer reviewed and are flagged as unpublished in the Reference section of this Profile.*

COMMENT (page 32, Table 2-3): Should be consistent in abbreviation of week and weeks (wk or wks) in the document.

RESPONSE: *Abbreviations for "weeks" have been adjusted in all relevant tables to "wk."*

COMMENT (page 32, Table 2-3): Why is this section colored?

RESPONSE: *References used to derive an MRL are highlighted light green in LSE tables per the following ATSDR guidance:*

> *"Each data point used to derive an MRL is marked with a footnote in the LSE table. Shade the study entry in the LSE table light green (Red 226, Green 239, Blue 217). The footnote should use language similar to the following examples." (Guide for the Development of Toxicological Profiles, page 150).*

For clarity the following footnote was added to the Table "Highlighted rows indicate an MRL principal study."

COMMENT (page 35, Table 2-3 legend): Why use to different abbreviations for the same thing?

RESPONSE: *"BW" is the abbreviation used for Body Weight when referring to Parameters Monitored. "Bd wt" is the abbreviation used for Body Weight when referring to Health Endpoints. This is dictated by the Guide for the Development of Toxicological Profiles.*

COMMENT (page 36, Figure 2-3): All figures, like table, require reference and/or indicate they are a composite composed of data in the reference list. Simply listing animals and not indicating which surrogate species is unsatisfactory.

The figure should have a note that the number associated with the point in the figure corresponds to the "Figure Key" in Table 2-3.

RESPONSE: *Figures 2-2 and 2-3 have been developed in compliance with ATSDR guidance for Levels of Significant Exposure (LSE) Figures and therefore were not notchanged (Guidance for the Development of Toxicological Profiles, page 201). However, we believe Figures 2-2 and 2-3 are clear and accurate. For Figures 2-2 and 2-3, point labels correspond to study ID and species, while point shapes correspond to data type (Human NOAEL; Human LOAEL, Less Serious; Human LOAEL, More Serious; Animal NOAEL; Animal LOAEL, Less Serious; Animal LOAEL, More Serious). Point labels and shapes are defined in the legend directly below each figure, while study IDs correspond directly with the "Figure Key" column in the preceding LSE table, which contains the full reference.*

COMMENT (page 39, Table 2-4): There is no Figure presented on dermal exposure levels but the Figure keys have been provided in this table.

RESPONSE: *Figure Key column has been removed from Table 2-4 (Levels of Significant Exposure table for Dermal exposures) because there is no accompanying figure.*

COMMENT (page 43, line 27): Note: Unpublished study.

RESPONSE: *All unpublished studies have been peer reviewed. We have removed the language flagging studies as unpublished in the References section of this Profile to reduce confusion.*

COMMENT (page 56, line 29): This study used ob/ob B6 mice predisposed to obesity on normal dietsand B6 wildtype mice that are not predisposed but can be induce through HFD

RESPONSE: *We believe our interpretation of the cited study is correct. From Dey and Cedebaum (2007), emphasis added:*

> *"Male 8-week-old homozygous obese C57BL/6J ob/ob mice and heterozygous lean littermate C57BL6/J+/? mice were purchased from the Jackson Laboratory (Bar Harbor, ME). The animals were housed in a facility approved by the American Association for Accreditation of Laboratory Animal Care and divided into 10 groups, each of which consisted of 4-6 animals.* ***Group 1 and 2 consisted of lean and obese mice****, respectively, fed a commercially available high-fat control dextrose diet (Bio-Serv, Frenchtown, NJ) with 42% of calories derived from fat, 16% from protein, and 42% from carbohydrates (dextrin-maltose) ad libitum for 2 weeks. These animals, which served as controls, had access to regular drinking water.* ***Groups 3 and 4 consisted of lean and obese mice****, respectively, fed the liquid diet plus 2% acetone in drinking water for the same time period."*

The above excerpt from Day and Cedebaum (2007) indicates that animals in the "obese" category were obese at the start of the experiment and that all rats in both "obese" and control groups received the same high-fat diet (HFD). Therefore no revisions were made to the profile.

COMMENT (page 67, line 22): Provide volume in SI units in parenthesis.

RESPONSE: *SI units (178 mL) have been provided in parentheses.*

COMMENT (page 127, Table 4-1): Update the reference web link.

RESPONSE: *As of 2020, the Hazardous Substances Data Bank has been integrated into PubChem, a database under the National Council for Biotechnology Information. All outdated references to HSDB (internal and external) and accompanying links have been replaced with references to the current PubChem database.*

COMMENT (page 127, Table 4-1): IUPAC name: Propan-2-one

RESPONSE: *Propan-2-one has been added to the list of synonyms for acetone listed in Table 4-1. The PubChem Compound Summary for Acetone includes propan-2-one as a synonym for acetone, so an additional citation was not needed.*

COMMENT (page 131, lines 15-17): Table 5 4. Indoor Air Monitoring Data for Acetone indicates very different indoor air concentrations than the sited 8.0 ppb. This sentence needs to be corrected.

More resent publication by Weisel et al (2008). Indoor Air VOC Concentrations in Suburban and Rural New Jersey. Environ Sci Technol. 2008 Nov 15; 42(22): 8231–8238.

Acetone Mean 87.1 µg/m3, SD 301, max 2,900 µg/m3

RESPONSE: *The reviewer is correct that this sentence previously contradicted the data presented in Table 5.4. To correct this, the most recent study of indoor air in US homes (Weisel et al. 2008) was used. We have also added a sentence to explain that indoor air acetone concentrations tend to be higher in smoking homes than in nonsmoking homes. The passage now reads:*

> *"Indoor air tends to have a higher concentration of acetone than outdoor air in the United States due to the use of household consumer products. A study of 100 homes in New Jersey reported a mean indoor air acetone concentration of 36.1 ppb (Weisel et al. 2008). In comparison, a study of 17 outdoor air samples across the United States reported a mean outdoor air acetone concentration of 6.9 ppb (Shah and Singh 1988). Smoking homes also tend to have higher indoor air acetone concentrations than nonsmoking homes (20.8 ppb versus 29.5 ppb) (Heavner et al. 1996)."*

COMMENT (page 149, line 14): This sould read "less than 0.012 mg/day based on the assumption that drinking water level is <6 ppb.

RESPONSE: *Sentence has been revised to make this assumption clear as follows:*

> *"However, the daily intake for acetone (assuming a person consumes 2 L of drinking water/day) from this source would be <0.012 mg/day based on the assumption that the level of acetone in drinking water is <6 ppb (Section 5.5.2)."*

COMMENT (page 157, line 3): Should make it clear that the biomarker for acetone is acetone itself (i.e., the parent compound).

RESPONSE: *Sentence has been revised to clarify that acetone can be directly monitored in the body, thus not requiring the use of additional biomarkers as follows:*

> *"Because acetone can be directly measured in breath and urine samples, no additional biomarkers of exposure to acetone are required."*

COMMENT (page 161, Table 7-1): ACGIH TLVs and BEI should be provided in the table as these are commonly used by practicing occupational health and environmental professionals to protect the human health (American Conferecne of Governmental Industrial Hygiensts: TLVs® and BEIs® 2020.)

RESPONSE: *Table 7-1 has been developed in compliance with the following ATSDR guidelines:*

> *"Include relevant CDC, NIOSH, FDA, OSHA, or other governmental recommendations about [Substance x] in Table 7-1. Report ACGIH Threshold Limit Values (TLVs) only when there is no information for OSHA or NIOSH. Some of this type of information may not be able to be as presentable in tabular form and should therefore be included in the introductory text of Chapter 7." (Guidance for the Development of Toxicological Profiles, page 115).*

Because occupational information was available for both OSHA and NIOSH, ACGIH Threshold Limit Values (TLVs) were not included. ACGIH BEIs were also not included as they were not specified by ATSDR guidance.

COMMENT (page 192, line 38): Note: This is an unpublished study.

RESPONSE: *All unpublished studies have been peer reviewed. We have removed the language flagging studies as unpublished in the References section of this Profile to reduce confusion.*

Comments provided by Peer Reviewer #3

ATSDR Charge Questions and Responses

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: Yes, except that the respiratory effect level of 100 ppm should be commented on, e.g. "Very slight mucous membrane irritation and unpleasant odor were reported at 100 ppm after 10, 30, and 90 min of exposure." (top of Figure 1-3).

RESPONSE: *The respiratory effect level of 100 ppm observed by Matsushita et al. (1969a) is discussed in the Minimal Risk Level Worksheet included in Appendix A of the profile:*

> *"Although irritation of the nose, throat, and trachea was reported in one subject exposed to 100 ppm for two 3 hour exposures (with 45 minute interval break) (Matsushita et al. 1969a), other studies in humans report respiratory irritation only at higher levels (>250 ppm) for longer durations (Matsushita et al. 1969b; Nelson et al. 1943; Raleigh and McGee 1972; Ross 1983). Furthermore, the reporting of these irritating effects was subjective, and only five volunteers were exposed to 100 ppm (Matsushita et al. 1969a). Therefore, neurological effects were preferentially selected as the critical effect." (Appendix A, page A-4).*

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: Questionable relevance of reduced reticulocyte count in male rats, see comment on MRL below.

RESPONSE: *A full discussion of derived MRLs is provided in the Minimal Risk Levels (MRLs) section of this document. We have chosen not to revise the text in this case because no revisions were made to derived MRLs. The choice of using a hematopoietic effect over a nephrotoxic effect as the basis for the oral intermediate MRL is explained in detail in the MRL worksheet located in Appendix A.*

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

COMMENT: No comment provided.

RESPONSE: *No revisions were suggested.*

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: No comment provided

RESPONSE: *No revisions were 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: Yes.

RESPONSE: *No revisions were 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: Yes.

RESPONSE: *No revisions were suggested.*

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

COMMENT: Yes.

RESPONSE: *No revisions were suggested.*

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

COMMENT: Yes.

RESPONSE: *No revisions were suggested.*

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: See page by page comments. Copies are supplied as pdf.

RESPONSE: *No revisions were suggested. See Annotated Comments on the Profile section for responses to individual comments.*

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: There are no stereoisomers or tautomers of acetone. There are nine structural isomers, but these have very different functional groups (aldehyde, alcohol, ether, eoxide) and should be treated in separate TPs.

RESPONSE: *No revisions were suggested.*

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

COMMENT: Yes.

RESPONSE: *No revisions were suggested.*

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: Page 16, bottom, Matsushita 1969a: I would consider Resp 100 ppm to be a NOAEC.

RESPONSE: *100 ppm is considered a LOAEL for Matsushita 1969a because irritation of the nose, throat, and trachea was reported in one subject exposed to 100 ppm for two 3 hour exposures (with 45 minute interval break) (Matsushita et al. 1969a). While the effect is mild and only occurred in one subject, it is not considered a NOAEL/NOAEC because an effect was seen.*

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: Yes.

RESPONSE: *No revisions were suggested.*

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: I would go for irritation as critical effect, with the human volunteer study by Matsushita (1969b) as the critical study. The EU-LCI factsheet on acetone from 2018 (attached) reflects my thinking.

RESPONSE: *A full discussion of derived MRLs is provided in the Minimal Risk Levels (MRLs) section of this document. The choice of health endpoint for deriving the acute inhalation MRL is described in detail in Appendix A of the profile. Because the Dick et al. (1989) study reported neurological effects at a slightly lower concentration of acetone than the Matsushita et al. (1969b) study (237 ppm in Dick et al.*

(1989) versus 250 ppm in Matsushita et al. (1969b)), while also exhibiting effects after a shorter duration of exposure (4 hours versus 6 hours/day for 6 days, respectively) we have chosen to derive this minimal risk level using altered auditory tone discrimination and neurobehavioral effects at 237 ppm from the Dick et al. (1989) study as the basis. This rationale is described in the acute-duration inhalation MRL worksheet in Appendix A. The EU-LCI factsheet that was included with peer reviewer's comment represents a slightly different concept than the acute-duration inhalation MRL that is being derived here, as the lowest concentrations of interest (LCI) are derived to represent a chronic-duration guideline for the assessment of health risks of VOC emissions from building materials. The European Union website describing the EU-LCI concept specifies that EU-LCI values should not be considered indoor air quality guidelines, but rather should only be used within the context of building material emission testing. We believe that this EU-LCI document did not consider the Dick et al. (1989) study because of its shorter duration of exposure compared with the Matsushita et al. (1969b) study. Because ATSDR only considers studies for MRL derivation for the exposure duration contained within the study, the Matsushita et al. (1969b) study can only be considered for this acute-duration MRL, and is not eligible to be considered for the intermediate- or chronic-duration inhalation MRLs.

QUESTION: Would you consider neuro effects to be one of acetone's sensitive endpoints for oral exposure, when not using gavage dosing? (A common oral exposure pathway for humans is contaminated groundwater.)

COMMENT: Yes.

RESPONSE: *No revisions were suggested.*

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

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

COMMENT: See page by page comments.

RESPONSE: *No response written for this comment because responses were provided to page-by-page comments.*

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

COMMENT: See page by page comments.

RESPONSE: *No revisions were suggested. See Annotated Comments on the Profile section for responses to individual comments.*

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

COMMENT: No comment provided

RESPONSE: *No revisions were suggested.*

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: Not that I am aware

RESPONSE: *No revisions were suggested.*

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: Yes, there is a discussion and I agree with the description. However, it should be pointed out that the experiments comparing effects of acetone in healthy and diabetic/obese/high-fat-diet animals were conducted with high acetone doses, and the results are not necessarily applicable at realistic human exposure levels.

RESPONSE: *The following sentence has been added to Chapter 3.2, "Children and Other Populations that are Unusually Susceptible."*

> *"While research suggests that the metabolic pathway for acetone is similar in rats and humans, studies of acetone exposure in diabetic and obese animals have been conducted at higher doses than usual human environmental exposures."*

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

COMMENT: Yes (see page by page comments for additional references).

RESPONSE: *No revisions were suggested. See Annotated Comments on the Profile section for responses to individual comments.*

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

COMMENT: Yes.

RESPONSE: *No revisions were suggested.*

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: Yes (see page by page comments for additional references).

RESPONSE: *No revisions were suggested.*

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: Yes.

RESPONSE: *No revisions were suggested.*

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:

RESPONSE: *No revisions were suggested.*

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

COMMENT: Table 4:2

Odor thresholds: consider using mg/L rather than ppm, w/v

Misleading with a single value, as , there is a huge variability, eg Johanson (Patty's) states that a critical review of published studies by Arts et al. (attached) suggested that the odor detection threshold of acetone ranges from about 20 to about 400 ppm and that acetone exposure may lead to increased thresholds.

Units: consider using SI units, e.g. kPa rather than mm Hg, °C rather than °F, etc.

Flashpoint: To many decimals, considering the low accuracy of the method. Check value, Johanson (Patty's) and various other sources state -20 °C.

Conversion factors: Add temperature, the conversion factors are temperature-dependent.

RESPONSE: *All metrics in Table 4-2 are presented in the units used by the source authors. Therefore, no revisions to units in Table 4-2 have been made.*

The study suggested by the reviewer (Arts et al. 2002) to provide an odor threshold range of 20 – 400 ppm does not distinguish between air and water odor thresholds. We therefore chose not to replace the existing odor threshold values.

Information to support a flashpoint of -20 °C was not found in the source provided by the reviewer (Johanson). The existing flashpoint of 16.99 °F has been rounded to 17 °F per the reviewer's guidance regarding low accuracy of the method used.

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: No comment provided

RESPONSE: *No revisions were suggested.*

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: No comment provided

RESPONSE: *No revisions were suggested.*

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: No comment provided

RESPONSE: *No revisions were suggested.*

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: Q 1-3: The text seems adequate, although lengthy for an overview. However, I am not enough familiar with the environmental data competent to judge the correctness of the numerical values.

Q3: There is a mixed use of units in the text and particularly in tables 5-1 and 5-2. I would prefer consistent use, e.g.:

ppm (or ppb) or mg/m3 (or µg/m3) for air

mg/L (or µg/L) for water

mg/kg (or µg/kg) for soil

RESPONSE: *Units for Detection Limits presented in Tables 5-1 and 5-2 have been updated for consistency as follows:*

Air: ppm or ppb

Water: mg/L or µg/L

Soil: µg/kg

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: The text is adequate.

RESPONSE: *No revisions were suggested.*

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: No.

RESPONSE: *No revisions were suggested.*

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

COMMENT: Acute and intermediate MRLs, "Additional high-quality studies would strengthen this MRL.": I don't agree with the statement. Additional high-quality studies might lead to a different MRL, e.g. a lower MRL due to findings of adverse effects at lower exposure levels, or a higher MRL due to reduced uncertainty and therefore lower UFs.

RESPONSE: *This sentence has been deleted.*

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

COMMENT: Yes.

RESPONSE: *No revisions were suggested.*

Chapter 7. Regulations and Guidelines

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

COMMENT: Table 7-1 Air: Consider adding the EU-LCI value of 120 mg/m3, https://ec.europa.eu/docsroom/documents/39985.

Table 7-1 Occupational: Consider adding additional countries, see https://limitvalue.ifa.dguv.de/WebForm_ueliste2.aspx for data.

RESPONSE: *Table 7-1 has been developed in compliance with ATSDR guidance to only include regulations that are specific to the United States or international:*

"Include only international guidance from WHO and IARC. Do not include other international organization regulations." (Guidance for the Development of Toxicological Profiles, page 114).

The suggested regulations are not applicable to the US and therefore were not included in Table 7-1.

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

COMMENT: No.

RESPONSE: *No revisions were suggested.*

Minimalal 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: Yes.

RESPONSE: *No revisions were suggested.*

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: I do not agree with the acute inhalation MRL.

Although statistically significant, the human neurobehavioral effects (summarized on page A-5, 2nd para) were minimal, as also stated by the authors. Moreover, only two out of six endpoints showed significant effects (disregarding POMS).

Response time: The significance may have been a random effect, considering that the RT during exposure (694 ms) is within the range of RTs in non-exposed (617-691 ms).

False alarms: the effect of acetone is questionable. Exposure to acetone caused essentially no change in false alarm rate (pre-during-post). The significance stems from improved performance in the control group, attributed to a learning effect. In contrast to acetone, learning effects were seen in the ethanol, acetone/MEK and MEK exposed groups but not the ethanol placebo group.

In addition, no effects on reaction time or vigilance were seen in the Muttray 2005 study.

In conclusion, 237 ppm might be considered a NOAEC as well as a LOAEC. Thus, an UF of 1 for NOAEC might be used. Alternatively, UF=3 could be used for human variability as. Dick 1989 is a relatively large study with 22 acetone and 21 controls that addresses much of the variability.

Overall, I would propose:

MRL = LOAEC:UF = 237:10 = 24 ppm , where UF = either 1x10 or 3x3

Additional studies that lend support: Consider adding Geller 1979a, with neurobehavioral effects in baboons at 500 ppm.

I also do not agree with the oral intermediate MRL.

The relevance of the effect (lowered reticulocyte count) for humans at low dose is questionable as it was seen in male rats only and not in female rats neither in mice. The effect was apparently not seen in rats in the American Biogenic study, although details are lacking. There seems to be no reports on macrocytic anemia from acetone, apart from the Dietz study.

Furthermore, the MRL needs to be put in relation to endogenous production rate (Page A-10). The proposed MRL value is 2-3 orders lower than the endogenous production rate in humans in fasting and diabetes of 8-31 mg/min corresponding to 165-638 mg/kg/d. It is even lower than the production rate in healthy subjects, 0.1-0.25 mg/min or 2-5 mg/kg/d (assuming 70 kg bw) (Johanson, Patty's, attached). The proposed MRL thus likely falls within the variability in endogenous formation in healthy humans.

Finally, it seems overly conservative to use UF=10x10 when departing from the BMDL, as BMDL is already a conservative approach (page A-13).

RESPONSE: *Acute Inhalation MRL: The neurological effects observed by Dick et al. (1989) at 237 ppm were minimal but statistically significant. In addition, clear dose-response relationships were observed for neurological effects including reaction time and false alarm percentage. Similar neurological effects were observed at 250 ppm by Matsushita et al. (1969a) and Matsushita et al. (1969b), including decreased reaction time, weakness, tension, and lack of energy, further supporting the conclusion that the statistically significant effects observed by Dick et al. (1989) were not random. Subsequently, we have not revised the MRL in response to this comment.*

In Muttray et al. (2005), subjects were exposed to a mixture of acetone and toluene. Because of potential interaction such as additive, potentiation or synergism between chemicals in mixtures, they cannot be considered for derivation of an ATSDR MRL for a single component of that mixture. MRLs are intended to protect against the most sensitive effects, which are demonstrated in Dick et al. (1989).

It is ATSDR policy to use an uncertainty factor of 10 for human variability unless the study population for the principal study represents sensitive sub-populations (i.e., children or adults with preexisting health conditions such as diabetes mellitus where significant increases in ketone bodies (beta-hydroxybutyrate, acetoacetate and acetone) levels in blood may occur. In this case, the primary study (Dick et al. 1989) sampled 22 working adults without preexisting conditions, so does not meet this criterion. In addition, Dick et al. (1989) observed the effects of inhaled acetone on adults at rest, therefore not accounting for potentially increased respiratory rates for those exposed occupationally. Finally, there is no evidence or analysis of variance to support the assumption that a sample size of 22 individuals is large enough to account for all human variability. Therefore, the suggested uncertainty factor of 3 for human variability is not appropriate. Further, the suggested uncertainty factor of 1 for a LOAEL (LOAEC) is not appropriate. It is ATSDR policy to use an uncertainty factor of 3 for use of a minimal LOAEL or 10 for use of a LOAEL. 237 ppm is considered to be a minimal LOAEL because the neurological effects observed at that dose are statistically significant, however, the health effects were considered minimal. Regardless, effects are seen, so this is not considered a NOAEL.

Geller et al. (1979a) is discussed in Chapter 2 (page 65, line 27). It was not selected as the principal study for derivation of the MRL because the dose at which neurological effects were observed (500 ppm)

is significantly higher than 237 ppm that caused minimal neurologic health effects in otherwise healthy humans (Dick et al. 1989).

Intermediate Oral MRL: ATSDR finds lowered reticulocyte count to be a relevant critical effect in humans. It is ATSDR policy to select the most sensitive endpoint in species/organ for which data is available to protect human health when deriving an MRL. Lowered reticulocyte count is a hematological effect, and hematological effects have been observed in humans exposed to acetone via inhalation, suggesting that the critical effect is relevant to human physiology (Matsushita et al. 1969a, 1969b). Furthermore, an appropriate uncertainty factor of 10 was employed to account for interspecies extrapolation based on the assumption that humans are more sensitive to the effects of hazardous substance than animals.

It is not appropriate to compare a pathological level of endogenous acetone production to that of a healthy adult. The endogenous rates of acetone production were accounted for when comparing healthy exposed groups with healthy controls. Comparing external exposure to internal pathologic levels is not relevant to an MRL derived for the general population. The level of endogenous acetone production in healthy individuals is also not relevant to the derivation of an MRL, as the MRL is derived with regard to exposure from external sources. The MRL therefore concerns exposure to acetone which, upon entering the body, is added to acetone that is produced endogenously. Therefore, endogenous acetone production rates mentioned by the reviewer are not relevant to determination of an MRL.

It is ATSDR policy to use an uncertainty factor of 10 for interspecies extrapolation when the principal study is not in humans unless a dosimetric adjustment is possible, which it is not in this case. It is also ATSDR policy to use an uncertainty factor of 10 for human variability unless the study population for the principal study represents sensitive sub-populations (i.e., children or adults with preexisting health conditions). In this case, the primary study was in animals, so this does not meet this criterion.

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

COMMENT: No additional comments.

RESPONSE: *No revisions were suggested.*

Appendices

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

COMMENT: No comment provided

RESPONSE: *No revisions were suggested.*

Annotated Comments on the Profile

NOTE: The reviewer left a number of comments requesting changes to Glossary (Appendix E) text. The content of Appendix E is dictated by ATSDR guidance (Guidance for the Development of Toxicological Profiles, page F-1) and was therefore not changed.

COMMENT (page 1, line 11): Would be good to mention diabetes here and how it influences acetone levels.

RESPONSE: *Text has been added explaining the relationship between acetone and diabetes:*

> *"Background levels of acetone vary from person to person. Children and adolescents tend to produce more endogenous acetone than adults due to their relatively high metabolic rates (Johanson 2012). People with diabetes may produce high levels of endogenous acetone in the process of metabolizing fatty acids in blood (Johanson 2012)."*

COMMENT (page 2, line 12): Mention also the studies used to derive the MRL

RESPONSE: *The following sentence referencing the study used to derive the acute inhalation MRL has been added:*

> *"Neurobehavioral effects, including altered auditory tone discrimination; increases in anger and hostility, have been observed in rats (Dick et al. 1989)."*

COMMENT (page 4, Figure 1-1): Suggested change Doses to Exposure concentration

RESPONSE: *The left-hand vertical axes in Figures 1-1 and 1-2 have been updated to "Exposure Concentration (ppm)" per the reviewer's suggestion.*

COMMENT (page 5, Figure 1-2): Consider adding endogenous production rates in fasting/diabetics and in healthy subjects (se earlier comment)

RESPONSE: *Figure 1-2 is intended to summarize dose-effect data for external exposures to acetone only. Endogenous acetone production rates were therefore not considered relevant to this figure. No revisions were made to the profile.*

COMMENT (page 6, line 8): The respiratory effect level of 100 ppm the respiratory effect level of 100 ppm should be commented on, e.g. "Very slight mucous membrane irritation and unpleasant odor were reported at 100 ppm after 10, 30, and 90 min of exposure."

As now standing, it contradicts (in the reader´s eye) the choice of neurological effects at 237 ppm as POD for the MRL

RESPONSE: *The decision to use neurological effects seen at 237 ppm rather than respiratory effects seen at 100 ppm to derive the acute inhalation MRL is explained in the Minimal Risk Level Worksheet included in Appendix A of the profile:*

> *"Although irritation of the nose, throat, and trachea was reported in one subject exposed to 100 ppm for two 3 hour exposures (with 45 minute interval break) (Matsushita et al. 1969a), other studies in humans report respiratory irritation only at higher levels (>250 ppm) for longer*

durations (Matsushita et al. 1969b; Nelson et al. 1943; Raleigh and McGee 1972; Ross 1983). Furthermore, the reporting of these irritating effects was subjective, and only five volunteers were exposed to 100 ppm (Matsushita et al. 1969a). Therefore, neurological effects were preferentially selected as the critical effect." (Appendix A, page A-4).

For clarity the following footnote was added to the Table: "Highlighted rows indicate an MRL principal study."

COMMENT (page 7, Figure 1-4): The hepatic effect at 7 mg/kg/day is not described in the document. It raises the question if this is the critical effect and should be used as POD for the MRL.

RESPONSE: *The hepatic effect of 7 mg/kg/day was a typo. The lowest hepatic LOAEL observed for acetone is 90 mg/kg/day (Ross et al. 1995). Figure 1-4 has been corrected. The reference for this hepatic LOAEL (Ross et al. 1995) is mentioned throughout the text and in the MRL worksheet.*

COMMENT (page 13, Table 2-1): Strange wording, all hexane isomers are C6.

RESPONSE: *Removed "C6" specification.*

COMMENT (page 39, Table 2-4): Where is the comment?

RESPONSE: *"See comment" refers to comments in the supplemental document which are internal documents ATSDR uses to summarize and evaluate studies included in the profile. The "see comment" text was deleted. Table was revised to clarify that for this study, dose was not specified (NS).*

COMMENT (page 40, Table 2-4): Where is the comment?

RESPONSE: *"See comment" refers to comments in the supplemental document which are internal documents ATSDR uses to summarize and evaluate studies included in the profile. The "see comment" text was deleted and the Table was revised to clarify that for this study, subjects were administered 3.9 +/- 0.2 M solution in eyelid, total volume not specified (NS).*

COMMENT (page 43, line 2): There are a few fatalities reported. Johanson (Patty's) states:

> "The relatively low toxic potency of acetone is illustrated by the annual reports of the American Association of Poison Control Centers. From 1996 to 2004, there were nearly 11,000 registered incidents of exposure to acetone (yearly average 1330, no data retrieved for 2001), whereof 31% were treated in health-care facilities. The health outcome was reported as "minor" in 26%, as "moderate" in 7%, and as "major" in 0.4% of the registered incidents. Three intoxications had a fatal outcome. Incidents with acetone-containing nail polish removers were more frequent (yearly average 3328) but resulted in less severe health effects with 18% "minor," 1% "moderate," and 0.03% "major" effects. One fatal outcome was reported."

References:

Johanson G. Acetone. In: Patty's Toxicology. Bingham E, Cohrssen B, Powell CH (eds). Wileys , 6th ed, vol 3 (2012) pp. 735-752.

1.T. L. Litovitz, W. Klein-Schwartz, K. S. Dyer, M. Shannon, S. Lee, and M. Powers, 1997 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am. J. Emerg. Med., 16, 443–497 (1998).

2.T. L. Litovitz, W. Klein-Schwartz, G. C. Rodgers, Jr., D. J. Cobaugh, J. Youniss, J. C. Omslaer, M. E. May, A. D. Woolf, and B. E. Benson, 2001 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am. J. Emerg. Med., 20, 391–452 (2002).

3.T. L. Litovitz, W. Klein-Schwartz, S. White, D. J. Cobaugh, J. Youniss, A. Drab, and B. E. Benson, 1999 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am. J. Emerg. Med., 18, 517–574 (2000).

4.T. L. Litovitz, W. Klein-Schwartz, S. White, D. J. Cobaugh, J. Youniss, J. C. Omslaer, and B. E. Benson, 2000 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am. J. Emerg. Med., 19, 337–395 (2001).

5.T. L. Litovitz, M. Smilkstein, L. Felberg, W. Klein-Schwartz, R. Berlin, and J. L. Morgan, 1996 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am. J. Emerg. Med., 15, 447–500 (1997).

6.W. A. Watson, T. L. Litovitz, W. Klein-Schwartz, G. C. Rodgers, Jr., J. Youniss, N. Reid, W. G. Rouse, R. S. Rembert, and D. Borys, 2003 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am. J. Emerg. Med., 22, 335–404 (2004).

7.W. A. Watson, T. L. Litovitz, G. C. Rodgers, Jr., W. Klein-Schwartz, N. Reid, J. Youniss, A. Flanagan, and K. M. Wruk, 2004 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am. J. Emerg. Med., 23, 589–666 (2005).

8.W. A. Watson, T. L. Litovitz, G. C. Rodgers, Jr., W. Klein-Schwartz, J. Youniss, S. R. Rose, D. Borys, and M. E. May, 2002 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am. J. Emerg. Med., 21, 353–421 (2003).

RESPONSE: *Text has been revised to cite Johanson (2012) as follows:*

> *"There are very few reports of deaths in humans attributable to acetone. Between 1994 and 1996, there were over 10,000 incidents of acetone exposure reported to the American Association of Poison Control Centers (AAPCC), of which only 3 resulted in death (Johanson 2012)."*

COMMENT (page 46, line 29): Consider separating human and animal data under separate subheadings for clarity (applies to several sections, see General comments).

RESPONSE: *Section headers for Chapter 2 are in compliance with ATSDR guidelines (Guidance for the Development of Toxicological Profiles, page 6). Discussions of human and animal data are separated into distinct paragraphs, but individual headers for each are not specified by ATSDR guidance, so were not added.*

COMMENT (page 47, line 4): RC50 is usually abbreviated as RD50 (several occurrences). Missing in Glossary and list of acronyms.

RESPONSE: *"RC50" replaced with "RD50" for consistency.*

COMMENT (page 48, line 1): Cytochrome PIIEI often written as CYP2E1 in this document

RESPONSE: *"Cytochrome PIIEI" replaced with "CYP2E1" for consistency.*

COMMENT (page 80, line 20): Regarding sex differences, consider mentioning at some point the study by Ernstgard L, Sjogren B, Warholm M, Johanson G. Sex differences in the toxicokinetics of inhaled solvent vapors in humans 2. 2-propanol. Toxicol Appl Pharmacol. 2003;193(2):158-67:

> "The aim of this study was to evaluate possible sex differences in the inhalation toxicokinetics of 2-propanol vapor. Nine women and eight men were exposed on different occasions for 2 h during light physical exercise (50 W) to 2-propanol (350 mg/m3) and to clean air (control exposure). …The following sex differences were significant at the p = 0.05 level (Student's t test). …Acetone in blood was markedly higher in females than in males in the control experiment and slightly higher following exposure to 2-propanol. … The most marked sex difference was that of salivary acetone, for which an approximately 100-fold increase was seen in women, but no increase in men, after exposure to 2-propanol compared to clean air."

RESPONSE: *The following sentence has been added to Chapter 3, Section 1 to cite Ernstgard et al. (2003) with regard to sex differences following acetone exposure:*

"In a study of humans exposed to acetone in air during light exercise for 2 hours, women had higher levels of acetone in blood, saliva, and exhaled air than men (Ernstgard et al. 2003)."

A full citation for Ernstgard et al. (2003) has been added to the References section of the Toxicological Profile.

COMMENT (page 81, line 1): Should 1986 be 1986a, b or c?

RESPONSE: *Text has been revised to cite Charbonneau et al. 1986c specifically.*

COMMENT (page 81, line 28): Consider citing the study by Johanson G. Modelling of respiratory exchange of polar solvents. Ann Occup Hyg. 1991;35(3):323-39.:

> " … Experimental data suggest, however, that the 'inert tube' model may be erroneous for polar solvents which have a high water solubility. To explore this possibility further a tentative pbpk model was developed. Model structure and parameters were obtained from the literature on lung anatomy and physiology and by visual fitting to experimental acetone, carbon dioxide, diethyl ether and ethanol data. The model was written and solved by spreadsheet programming on a personal computer. Simulations were carried out to illustrate the difference between end-exhaled and alveolar air and how water solubility and workload influence the uptake and excretion kinetics of polar solvents. It is concluded that the model is valuable for predicting the lung kinetics of polar vapours under various circumstances. It may therefore be useful in the

development of biological monitoring methods based on breath sampling and help us to understand and to explain experimental data."

RESPONSE: *Johanson (1991) provides confirming evidence for the wash-in/wash-out effect discussed in the text. A citation has therefore been added in addition to Wignaeus et al. 1981, however it was deemed unnecessary to revise the text. A full citation for Johanson (1991) has been added to the References section.*

COMMENT (page 83, line 3): Additional studies:

Johanson G, Rauma M. Basis for skin notation. Part 1. Dermal penetration data for substances on the Swedish OEL list. Arbete och Hälsa. 2008;42(2).

Appendix A

Substance: Acetone
CAS: 67-64-1
Scientific basis: AoH 1988:32

Skin notation: No
Skin permeability: Low

Molecular weight: 58.1
Density: 0.786 g/cm³
Melting point: -94.3°C
Boiling point: 56.2°C
Vapour pressure: 24 kPa (at 25°C)
Evaporation rate: 10
Log Kow: -0.24

Reported data

Sp	Loc	Cell	L (μm)	A (cm²)	V	Vehicle	C (mg/ml)	n	T_{Exp} (h)	T_{Obs} (h)	T_{Lag} (h)	Abs (%)	K_p (10^{-4} cm/h)	Flux (μg/cm²/h)	Reference
In vitro															
Hum	Br	Fl	280	0.64	0.2		Neat	5	24	24	0.31	0.05	0.13	10	Wilkinson et al. (2001)
Hum	Br	Fl	280	0.64	0.2	H2O	3	5	24	24	0.38	0.41	14	4.2	Wilkinson et al. (2001)
In vivo															
Hum	Fi				Inf	H2O	1%	12	15s	0.3			*0.28*	0.22	Naitoh et al. (2002)
Hum	Fi				Inf	H2O	1%	12	15s	0.3			*12*	9.5	Naitoh et al. (2002)

Asessment

The only available in vivo study is that of Naitoh et al. (2002). An unconventional technique was used in that one thumb was dipped once or several times (15 sec/occasion) in an aqueous solution. The flux was calculated from the evaporation from the thumb. The evaporation profile was biphasic, thus two different fluxes were reported. The reported fluxes reflects absorption into (and out of) rather than through skin. Thus the calculated Kp may represent an serious overestimate of the "true" value.

The permeability for neat acetone ($1 \cdot 10^{-5}$) may be considered as "low", whereas the permeability in water ($1 \cdot 10^{-3}$) is about 100-fold higher and may be considered as "high". Thus, there is a strong vehicle effect of water.

Based on neat solvent, the permeability is considered "low".

Wilkinson SC & Williams FM (2001) Volatility, LogP, and vehicle effects on dermal absorption of a range of solvents. Poster 621. Society of Toxicology, 40th Annual meeting. https://www.toxicology.org/pubs/docs/Tox/2001Tox.pdf

621 VOLATILITY, LOGP AND VEHICLE EFFECTS ON DERMAL ABSORPTION OF A RANGE OF SOLVENTS.

S. C. Wilkinson and F. M. Williams. *University of Newcastle, Environmental and Occupational Medicine, Newcastle upon Tyne, United Kingdom.* Sponsor: T. Gray.

The dermal absorption of methyl ethyl ketone (MEK), tetrahydrofuran (THF), acetone, toluene, *m*-xylene and *o*-xylene in neat (10.5 µl) and aqueous (200 µl) vehicles was studied *in vitro*. Dermatomed human breast skin was mounted in Scott-Dick flow through diffusion cells at 32°C for 24 h. Receptor fluid (Eagle Minimal Essential Medium, pH 7.4, supplemented with 2% (w/v) PEG 20 oleyl ether for aromatic compounds) was pumped below the skin at 1.5 ml h^{-1}. Receptor fluid samples were analysed for parent compounds by GC following extraction with CS_2. Absorption of MEK, THF and acetone into receptor fluid ceased after 1 to 1.5 h in both vehicles due to the high vapour pressure (12.1 to 30.8 KPa) of these solvents. Absorption after 24 h was 0.05 to 1.68% of the applied dose. The apparent k_p values measured with neat MEK (4.1 ± 0.7 x 10-5 cm h^{-1}), THF (4.6 ± 0.9 x 10-5 cm h^{-1}) and acetone (1.3 ± 0.3 x 10-5 cm h^{-1}) were related to logP. Apparent k_p values measured with aqueous MEK, THF (41.6 mM) and acetone (51.6 mM)were much higher (0.0014 to 0.0028 cm h^{-1}) than with neat doses. Apparent k_p values for neat toluene (1.4 ± 0.3 x 10-5 cm h^{-1}), *m*-xylene (3.0 ± 0.5 x 10-5 cm h^{-1}) and *o*-xylene (2.2 ± 0.3 x 10-5 cm h^{-1}) were lower than for neat MEK or THF, probably due to the low solubility of the aromatics in aqueous matrices. The lower vapour pressure of aromatic compounds the (0.88 to 1.11 KPa) was reflected in their longer absorption phase (3 to 5 h). The apparent k_p (0.035 to 0.083 cm h^{-1}) with aqueous toluene (211.8 µM), *m*-xylene (244.1 µM) and *o*-xylene (295.8 µM) were again much greater than neat doses in each case. Absorption of the aromatic compounds after 24 h from aqueous doses was also greater (25 to 79% of the applied dose) than from neat doses (0.2 to 0.6% of the applied dose). Volatility, logP and the vehicle had marked effects on absorption. Vehicle effects should be taken into account in risk assessment models. Supported by the UK Health and Safety Executive.

Naitoh K, Inai Y, Hirabayashi T, Tsuda T. Exhalation behavior of four organic substrates and water absorbed by human skin. Biol Pharm Bull. 2002;25(7):867-71.

RESPONSE: *he Johanson et al. (2008) reference is a supporting document for a Swedish Occupational Exposure Limit (OEL) for acetone. Given that the studies included in the Johanson et al. (2008) document related to acetone permeability are not considered appropriate to include in the profile (Wilkinson and Williams (2001) is an abstract from the Society of Toxicology meeting, and Naitoh (2002) used an aqueous solution containing ethanol, acetone, diethyl ether, and toluene to assess acetone permeability), we are not including the summary information of these two studies contained in Johanson et al. (2008).*

Wilkinson and Williams (2001) is an abstract for the Society of Toxicology 40th Annual Meeting and is not a complete study, therefore it was not added to the profile.

In the Naitoh (2002) study, subjects were not exposed to acetone independently. Subjects were exposed to "an aqueous solution containing ethanol, acetone, diethyl ether, and toluene" (Naitoh 2002, page 867). Because of potential interaction such as antagonism, potentiation, or synergism between chemicals in mixtures, this reference was not added to the Profile.

COMMENT (page 85, line 26): Schenk L, Rauma M, Fransson MN, Johanson G. Percutaneous absorption of thirty-eight organic solvents in vitro using pig skin. PLoS One. 2018;13(10):e0205458.

> "Percutaneous absorption is highly variable between chemicals but also within chemicals depending on exposure conditions and experimental set up. We tested a larger number of organic solvents with the same experimental set up, using skin from new-born piglets and static diffusion cells. Thirty-six common organic solvents were studied neat (and 31 of them also in water dilution): acetone, …"

RESPONSE: *Text has been revised to cite the permeability coefficient for acetone in piglet skin reported by Schenk et al. (2018). A full citation for Shenk et al. (2018) has been added to the References section.*

> *"There is little data regarding the absorption of acetone in animals after dermal exposure. One study reported a permeability coefficient (Kp) for acetone of 0.00249 cm h-1 when administered to the skin of newly deceased piglets (Shenk et al. 2018)."*

COMMENT (page 86, line 23): Mixed use of half-life and half-time (only half-life in Glossary). I would prefer half-time.

RESPONSE: *Text has been revised to read "half-lives" for consistency.*

COMMENT (page 94, line 34 and page 96, line 2): Repeat sentence.

RESPONSE: *Repeat sentence has been removed.*

COMMENT (page 100, line 8): Consider adding Johanson G, Naslund PH. Spreadsheet programming--a new approach in physiologically based modeling of solvent toxicokinetics. Toxicol Lett. 1988;41(2):115-27.

The study describes well the effect of physical workload on blood levels of acetone (and other solvents).

RESPONSE: *Text has been added citing the PBPK model developed by Johanson et al. (2008) as follows:*

> *"The PBPK model developed by Johanson et al. (2008) accounts for variation in workload by separating working and resting muscle groups."*

A full reference for Johanson et al. (2008) has been added to the References section of the Toxicological Profile.

COMMENT (page 104, line 12): Consider describing early in the chapter (before complicating factors) studies that derive quantitative relations between exposure and biomarker levels, eg:

Ghittori S, Imbriani M, Pezzagno G, Capodaglio E. The urinary concentration of solvents as a biological indicator of exposure: proposal for the biological equivalent exposure limit for nine solvents. Am Ind Hyg Assoc J. 1987;48(9):786-90.

Leung HW. Development and utilization of physiologically based pharmacokinetic models for toxicological applications. J Toxicol Environ Health. 1991;32(3):247-67.

Leung HW, Paustenbach DJ. Application of pharmacokinetics to derive biological exposure indexes from threshold limit values. Am Ind Hyg Assoc J. 1988;49(9):445-50.

RESPONSE: *Text has been added citing Ghittori et al. (1987) and Leung et al. (1988) to describe the relationships between acetone exposure and its biomarkers as follows:*

"Studies show that acetone levels in the body are an accurate indicator of acetone exposure (Leung et al. 1988). A study of 659 factory workers exposed to acetone occupationally reported a strong positive correlation between acetone levels in workplace air and acetone levels in workers' urine after their shift (Ghittori et al. 1987)."

We chose not to cite Leung et al. (1991) because the methods described were not specific to acetone exposure or its biomarkers.

Leung et al. (1988) is already cited in the References section of the Toxicological Profile. A full citation for Ghittori et al. (1987) has been added to the References section of the Toxicological Profile.

COMMENT (page 109, line 15): pharmacological should be pharmacokinetic?

Did the paper really use PBPK (cannot tell from abstract, but later paper by Leung used PBPK)? If yes, add abbreviation (PBPK).

Leung HW. Development and utilization of physiologically based pharmacokinetic models for toxicological applications. J Toxicol Environ Health. 1991;32(3):247-67.

RESPONSE: *Text has been updated to replace "pharmacological" with "pharmacokinetic." The reference (Leung et al. 1991) does not specifically use the term PBPK, so the full abbreviation was not used.*

COMMENT (page 111, line 22): Consider including at some point in this chapter: Ernstgard L, Gullstrand E, Johanson G, Lof A. Toxicokinetic interactions between orally ingested chlorzoxazone and inhaled acetone or toluene in male volunteers. Toxicol Sci. 1999;48(2):189-96.

RESPONSE: *Text has been added under the Miscellaneous Chemicals sub-heading in section 3.4 of Chapter 3 as follows:*

"In a study of 10 male volunteers, ingestion of 500 mg chlorzoxazone prior to inhalation of 250 ppm acetone for 2 hours resulted in slight but significant increases in steady state blood level and area under the blood concentration-time curve (AUC) for acetone (Ernstgard et al. 1999)."

A full citation for Ernstgard et al. (1999) has been added to the References section of the Profile.

COMMENT (page 121, line 19): Consider adding these studies:

Ikeda, M. and Hirayama, T., Possible metabolic interaction of styrene with organic solvents, Scand. J. Work Environ. Health, 4 Suppl. 2, 41, 1978.

Marhuenda, D., Prieto, M. J., Periago, J. F., Marti, J., Perbellini, L., and Cardona, A., Biological monitoring of styrene exposure and possible interference of acetone co-exposure, Int. Arch. Occup. Environ. Health, 69, 455, 1997.

RESPONSE: *The Styrene section has been revised to include information from both Ikeda and Hirayama (1978) and Marhuenda et al. (1997) as follows:*

*"**Styrene**. Data regarding interactions between acetone and styrene in the expression of toxic effects in animals is limited. In rats exposed to 2.2 mmol/kg styrene by intraperitoneal injection, a*

co-injection of 2.2 mmol/kg acetone was ineffective at attenuating symptoms of toxicity (Ikeda and Hirayama 1978). Several studies in humans have reported that coexposure to acetone and styrene produce different changes in the content or activity of biotransformation enzymes in the liver and lungs, compared with the changes seen with styrene alone (Elovaara et al. 1990, 1991; Vainio and Zitting 1978). A study of 19 male workers exposed to styrene and acetone in air at work for 4 hour intervals reported an inverse correlation between acetone concentration in air and styrene metabolite levels in subjects' urine post-shift, suggesting that acetone may slow metabolism of styrene (Marhuenda et al. 1997). However, in human subjects exposed for 2 hours to 293 mg/m3 styrene alone or to a mixture of 301 mg/m3 styrene and 1,240 mg/m3 (517 ppm) acetone, there was no indication that acetone alters the uptake, distribution, metabolism, or elimination of styrene (Wigaeus et al. 1984)."

Full citations for both Ikeda and Hirayama (1978) and Marhuenda et al. (1997) have been added to the References section of the Toxicological Profile.

COMMENT (page 163, lines 4 and 6 and page 164, line 1): Abe, Abrams, Anders: Incomplete references

RESPONSE: *References have been updated as follows:*

"Abe S, Sasaki M. 1982. SCE as an index of mutagenesis and/or carcinogenesis. In: Sister Chromatid Exchange, v.2. New York, NY: Alan R. Liss, Inc., 461-514.

Abrams EF, Derkics D, Fong CV, et al. 1975. Identification of organic compounds in effluents from industrial sources. Report to U.S. Environmental Protection Agency, Office of Toxic Substances, Washington, DC, by Versar, Inc., General Technologies Division, Washington, DC. EPA-560/3-75-002. NTIS no. PB-241641.

Anders MW. 1969. Stimulatory effect of acetone on the activity of microsomal aniline para-hydroxylase. In: Microsomes and Drug Oxidations, 1st Ed. Ithaca, NY: Elsevier, 533-540."

COMMENT (page 169 and page A-4): Dick 1989: Journal name missing, should be Br J Ind Med.

RESPONSE: *The full citation is provided as indicated at this website: https://oem.bmj.com/content/46/2/111.info. No revisions have been made.*