Disposition of Peer Review Comments for Toxicological Profile for 2-Butanone

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

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

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Comments provided by Peer Reviewer #1

ATSDR Charge Questions and Responses

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

COMMENT: My literature search did not turn up other relevant references.

RESPONSE: *No response needed.*

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

COMMENT: Standard toxicological practice is to regard effects in animals as reasonable evidence for likely effects in humans.

RESPONSE: *No response needed.*

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

COMMENT: The descriptions of exposures seem standard and reasonable.

RESPONSE: *No response needed.*

QUESTION: Do you believe the derived acute duration, inhalation route MRL value is justifiable? If you disagree, please explain. (see also Appendix A)

COMMENT: Yes

RESPONSE: *No response needed.*

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

COMMENT: Yes

RESPONSE: *No response needed.*

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

COMMENT: Yes

RESPONSE: *No response needed.*

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

COMMENT: Yes

RESPONSE: *No response needed.*

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

COMMENT: Yes

RESPONSE: *No response needed*

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

COMMENT: The animal studies do not seem to have yielded any remarkable indicators of toxicity. The most prominent indicate some neurotoxicity.

RESPONSE: *No response needed.*

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

COMMENT: The studies seem appropriate.

RESPONSE: *No response needed.*

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

COMMENT: No

RESPONSE: *No response needed.*

QUESTION: Are you aware of any studies that are not included in the profile that may be relevant to deriving MRLs for any of the 2-butanone isomers?

COMMENT: I am not clear which isomers are being referred to here. But in any case I am not aware of significant studies not included in the profile.

RESPONSE: *There are no isomers of 2-butanone. No response needed.*

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

COMMENT: Yes

RESPONSE: *No response needed.*

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

COMMENT: Yes

RESPONSE: *No response needed.*

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

COMMENT: I did not see significant discussion of mechanisms of action.

p.19 - The repeated observation that the incidence of cancers in some industrial cohorts were less than expected should be accompanied by a brief discussion of the known artifact--the "healthy worker effect".

RESPONSE: *A sentence was added to describe the "healthy worker effect" as follows: "The decrease in cancer-related mortality from these studies (Alderson and Rattan 1980; Wen et al. 1985) may be due to the "healthy worker effect" because the mortality of workers (a population considered to have a lower overall death rate than the general population) was compared to that of the general population."*

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

COMMENT: No

RESPONSE: *No response needed.*

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

COMMENT: No

RESPONSE: *No response needed.*

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

COMMENT: Agree

RESPONSE: *No response needed.*

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

COMMENT: Agree

RESPONSE: *No response needed.*

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

COMMENT: Yes

RESPONSE: *No response needed.*

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

COMMENT: Yes

RESPONSE: *No response needed.*

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

COMMENT: Yes

RESPONSE: *No response needed.*

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

COMMENT: Yes

RESPONSE: *No response needed.*

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

COMMENT: Have not used toxicological profiles before except for reviews

RESPONSE: *No response needed.*

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

COMMENT: Yes

RESPONSE: *No response needed.*

Specific Comments

COMMENT (page 56): "Using physiologically based pharmacokinetic (PBPK) model simulations for 8-hour exposures, the investigators estimated that metabolic saturation would occur at 100 ppm at rest and at 50 ppm during exercise (Liira et al. 1990b)." It is not correct to say that metabolic saturation occurs at a defined concentration. Saturation is approached but never is fully reached. Better to say that the concentration producing half of the maximal metabolism is X, ¾ of maximal metabolism is y, etc. Perhaps the author of the cited study says it is "reached" at a particular concentration, but ATSDR should not propagate this misleading way of describing the dose response relationship for metabolism.

RESPONSE: *The text was revised as follows: "The increase in blood concentration was steeper during exposure for 200 and 400 ppm compared to 25 ppm. Slower elimination from the blood after cessation of exposure was also seen at 400 ppm. These concentration-dependent changes in blood kinetics suggest that metabolic saturation may occur at higher exposure concentrations. Using physiologically based pharmacokinetic (PBPK) model simulations for 8-hour exposures, the investigators estimated that metabolic saturation may be approached at concentrations near 100 ppm at rest and 50 ppm during exercise (Liira et al. 1990b)."*

Comments provided by Peer Reviewer #2

ATSDR Charge Questions and Responses

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

COMMENT: Pertinent information is added.

RESPONSE: *No response needed.*

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

COMMENT: Yes. Such possibility exists under certain conditions.

RESPONSE: *No response needed.*

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

COMMENT: Yes. Described with proper details.

RESPONSE: *No response needed.*

QUESTION: Do you believe the derived acute duration, inhalation route MRL value is justifiable? If you disagree, please explain. (see also Appendix A)

COMMENT: Yes and properly justified.

RESPONSE: *No response needed.*

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

COMMENT: Yes. Followed the current guidelines for derivation of MRLs.

RESPONSE: *No response needed*

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

COMMENT: Yes

RESPONSE: *No response needed.*

QUESTION: Were adequately designed human studies identified in the text (i.e., good exposure data, sufficiently long period of exposure to account for observed health effects, adequate control for confounding factors)? Were the major study limitations sufficiently described in the text without going into lengthy discussions?

COMMENT: Yes. No changes are suggested.

RESPONSE: *No response needed.*

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

COMMENT: Yes. Identified animal studies are described with proper details needed for the derivation of MRLs.

RESPONSE: *No response needed.*

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

COMMENT: Yes. No other suggestion.

RESPONSE: *No response needed.*

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

COMMENT: No

RESPONSE: *No response needed.*

QUESTION: Are you aware of any studies that are not included in the profile that may be relevant to deriving MRLs for any of the 2-butanone isomers?

COMMENT: What 'isomers' means is not clear. 2-butanone cannot have isomeric forms.

RESPONSE: *Agreed. No further response is needed.*

QUESTION: Were all appropriate NOAELs and/or LOAELs identified for each study (both in the text and the Levels of Significant Exposure (LSE) tables and figures)? If not, did the text provide adequate

justification for excluding NOAELs/LOAELs including, but not limited to, citing study limitations? Please suggest appropriate changes.

COMMENT: Yes. No changes are needed.

RESPONSE: *No response needed.*

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

COMMENT: Yes

RESPONSE: *No response needed.*

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

COMMENT: Yes. Mechanisms of action are properly discussed.

RESPONSE: *No response needed.*

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

COMMENT: No

RESPONSE: *No response needed.*

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

COMMENT: No

RESPONSE: *No response needed.*

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

COMMENT: Agree

RESPONSE: *No response needed.*

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

COMMENT: Fully agree

RESPONSE: *No response needed.*

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

COMMENT: None. Current guidelines are followed.

RESPONSE: *No response needed.*

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

COMMENT: Yes

RESPONSE: *No response needed.*

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

COMMENT: Yes

RESPONSE: *No response needed.*

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

COMMENT: Yes

RESPONSE: *No response needed.*

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

COMMENT: All relevant information is included.

RESPONSE: *No response needed.*

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

COMMENT: Chapter 2 for details about doses, toxicity and target organs

RESPONSE: *No response needed.*

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

COMMENT: Yes

RESPONSE: *No response needed.*

Specific Comments

COMMENT (page 1, line 19-20): Degreasing and dewaxing are similar terms. For degreasing application a short description is added while for dewaxing it is vague (dewaxing applications). Therefore it is suggested that the wording 'dewaxing of lubricating oils' be used as per attached information (Appendix) instead of 'dewaxing applications'.

RESPONSE: *'Dewaxing applications' was changed to 'dewaxing of lubricating oils' as suggested.*

COMMENT (page 46, line 20): Period should be added at the end of the sentence.

RESPONSE: *The suggested editorial change was made.*

COMMENT (page 46, line 28): Should read as -----(3-hydroxy-2-butanone and 2,3-butanediol) with or without conjugation are also excreted in urine.

RESPONSE: *The suggested editorial change was made.*

COMMENT (page 49, line 10): describing phase 2 metabolite O-glucuronides and O-sulfates needs to be supported by an appropriate reference.

RESPONSE: *The reference, DiVincenzo et al. 1976, was added to 3.1.3.*

COMMENT (page 49, Figure 3-1): Structure of 2,3-butanediol depicts one of the carbon as pentavalent. It should be CH-OH rather than CH=OH as shown.

RESPONSE: *The error in the structure of 2,3-butanediol was corrected.*

COMMENT (page 54, line 17): 'PND' need to be described.

RESPONSE: *PND was defined in text as postnatal day.*

COMMENT (page 58, line 25): Should read as ‘histological signs of ethyl-n-butyl ketone neurotoxicity’

RESPONSE: *The suggested editorial change was made.*

Comments provided by Peer Reviewer #3

ATSDR Charge Questions and Responses

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

COMMENT: I agree on the human effects.

RESPONSE: *No response needed.*

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

COMMENT: The effects only observed in animals are not expected to be of concern in humans. The exposures to animals were much higher than for humans and unlikely to be encountered.

RESPONSE: *Text was added to Section 1.2 as follows: "Environmental exposure levels are lower than the concentrations used in animal studies."*

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

COMMENT: Yes, exposure conditions have been adequately defined.

RESPONSE: *No response needed.*

QUESTION: Do you believe the derived acute duration, inhalation route MRL value is justifiable? If you disagree, please explain. (see also Appendix A)

COMMENT: Yes. However, I found the reliance on Tomicic et al. 2011 suspect. The authors of that paper did not present any individual findings, only some statistical conclusions. Given the statistical analysis in other parts of the paper, I question the statistical analysis on the sensory issues. However, one can infer directly from Tomicic et al. 2011 that some individuals did experience discomfort at the exposure used (100 ppm).

In Table 2-1, the work cited to Dick et al., Haumann et al., Seeber et al., van Thriel et al., Wismuller et al., Muttray et al, and Nelson et al. indicates NOAELs of 100-200 ppm, so on this basis I am willing to accept the Tomicic et al. value of 100 ppm. Also, 100 ppm was as LOAEL with monkeys (Table 2-1, Geller et al. 1979).

RESPONSE: *Agree that presentation of the statistical analysis of irritation and neurological symptom data from Tomicic et al. (2011) could be improved. No further response is needed.*

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

COMMENT: See item 4. The "10" factors are typically used (whether really valid or not) so I see no reason to eliminate an MRL of 1-2 ppm.

RESPONSE: *No response needed*

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

COMMENT: Yes

RESPONSE: *No response needed.*

QUESTION: Were adequately designed human studies identified in the text (i.e., good exposure data, sufficiently long period of exposure to account for observed health effects, adequate control for confounding factors)? Were the major study limitations sufficiently described in the text without going into lengthy discussions?

COMMENT: Yes, all was appropriately described.

RESPONSE: *No response needed.*

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

COMMENT: Yes, the animal studies are adequately described.

RESPONSE: *No response needed.*

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

COMMENT: Yes. I have no reason to suggest others as being more appropriate.

RESPONSE: *No response needed.*

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

COMMENT: No

RESPONSE: *No response needed.*

QUESTION: Are you aware of any studies that are not included in the profile that may be relevant to deriving MRLs for any of the 2-butanone isomers?

COMMENT: No. (There are no isomers of 2-butanone.)

RESPONSE: *Agreed. No further response is needed.*

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

COMMENT: I believe all were identified. I am not aware of any of the newer Benchmark Dose Modeling values (now favored by EPA) being proposed for 2-butanone instead of NOAELs. A search did not find any applications. However, this many change.

RESPONSE: *No response needed.*

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

COMMENT: Yes, I agree.

RESPONSE: *No response needed.*

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

COMMENT: I am satisfied. The potentiation of toxicity by acetone and related compounds (2-butanone, isopropanol) was a popular subject in the 1980s, as I recall, and Gabriel Plaa and others worked in this area. After all was done (this has not surfaced recently) the most plausible explanation is probably induction of cytochrome P450 2E1, e.g. see Brady et al., 1989.

RESPONSE: *No response needed.*

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

COMMENT: No

RESPONSE: *No response needed.*

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

COMMENT: No

RESPONSE: *No response needed.*

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

COMMENT: Agree

RESPONSE: *No response needed.*

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

COMMENT: Agree

RESPONSE: *No response needed.*

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

COMMENT: Yes

RESPONSE: *No response needed.*

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

COMMENT: Yes

RESPONSE: *No response needed.*

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

COMMENT: Yes

RESPONSE: *No response needed.*

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

COMMENT: Yes

RESPONSE: *No response needed.*

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

COMMENT: Have not used toxicological profiles before except for reviews

RESPONSE: *No response needed.*

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

COMMENT: Yes

RESPONSE: *No response needed.*

Specific Comments

COMMENT (Chapter 3): Note: The structure of 2,3-Butanediol is incorrect (remove one double bond :C-O).

RESPONSE: *The error in the structure of 2,3-butanediol was corrected.*

COMMENT (Chapter 3, p. 52): "Menten" is misspelled.

RESPONSE: *The spelling error was corrected.*

COMMENT (Chapter 3, p. 54, l. 25): Also, the case for a change in CYP2E1*6 is overstated in parts of Tomicic et al. 2011. The number of individuals is far too small for analysis (as admitted sometimes (p. 222) by the authors but not always). The statistics of the effect of oral contraceptives (Fig. 1) also seems suspect.

RESPONSE: *Text was added to indicate that "interpretation of study findings is limited by the small number of study participants (n=25)."*