

Peer Review Charge:

Toxicological Profile Update for 2-Butanone - Draft for Public Comment

Summary

ATSDR has updated the previous version of 2-Butanone, released in 1992. The update focuses on Chapter 1 – Relevance to Public Health, Chapter 2 – Health Effects, and Chapter 7 – Regulations and Guidelines, as well as any chapters related to changes made in Chapter 2. The updated health effects evaluation resulted in the derivation of a new MRL for the acute duration, inhalation route of exposure.

Thus, we would like for you to focus your review on Chapters 1 (Relevance to Public Health), 2 (Health Effects), and 7 (Regulations & Guidelines), as well as Appendix A (MRL Worksheets), and Appendix B (Literature Search Framework). Finally, we are soliciting feedback on the overall usability of the profile, as per the last set of charge questions. The questions that follow (see “Charge to Reviewer” section) are intended to provide structure for your review and to enable ATSDR to address your comments in a direct manner.

Background on Toxicological Profiles

Target audiences: Public health professionals, clinicians, and informed citizens who need a succinct interpretation of the toxicological data but may not have the resources to gather and consider all of the toxicological data themselves.

Content: The toxicological profiles provide ATSDR's evaluations concerning whether adverse health effects occur and/or at what levels of exposure. Profiles are written with an emphasis on human health effects. They also contain information about health effects in animals, potential for human exposure, and environmental fate that may help the reader to determine the significance of levels found in the environment.

Scope: In these profiles, the emphasis is on providing succinct interpretations of the key literature. This distinguishes "profiles" from comprehensive criteria documents. Specifically, the profiles incorporate ATSDR's evaluations concerning the validity of particular studies and the inferences that can be made from them. The profile is not meant to contain all of the details necessary to support these interpretations. It is beyond the intended scope of the profile to present extensive details for users to weigh all the evidence themselves; such data are incompatible with the concept of a "profile."

The authors have been instructed to avoid lengthy descriptions of studies. If there is uncertainty or controversy about a conclusion, however, a more detailed description of the studies that are the basis for the uncertainty may be included in the text. The description should be limited to those factors that are necessary to summarize the issue. Also, the "Supplemental Document" contains detailed descriptions of studies that provide no-observed-adverse-effect levels (NOAELs) and lowest-observed-adverse-effect levels (LOAELs).

Format: The Profiles have a standard format, including introductory standard language in some sections (in bold), and certain tables, figures, headings, etc. Comments that relate to general format are welcome, and they will be considered in future revisions of the "Guidance for the Preparation of a Toxicological Profile." (See also charge questions relating to profile usability.)

Charge to Reviewer:

As you review the profile, if you wish to comment or suggest specific changes, please annotate directly in the text where the change or additional work is needed. After reviewing the document, prepare a summary report that addresses your major issues. Please present your comments in a constructive manner, be specific about the issues/changes suggested, and cite the section numbers whenever possible. If an issue has been missed or addressed improperly, please give specific information as to how it should be addressed. If you are citing a new reference, please provide a copy and indicate where in the text it should be included. Do not cite secondary sources except when the facts are widely accepted and non-controversial (as in the case of chemical identity information and physical property values).

Chapter 1:

Purpose: Chapter 1 essentially serves as an executive summary of the entire profile, with emphasis on the health effects chapter. Specifically, the text should address: effects known to occur in humans; effects observed in animals but not in humans; and exposure conditions (route, duration, or level) that are likely to be of concern to humans, especially around hazardous waste sites.

Questions:

- 1) 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.
- 2) 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.
- 3) Have exposure conditions been adequately described? If you disagree, please explain.
- 4) Do you believe the derived acute duration, inhalation route MRL value is justifiable? If you disagree, please explain. (see also Appendix A)
- 5) Do you agree that the data do not support derivation of any other MRLs?

Chapter 2:

Purpose: Chapter 2 provides a summary evaluation of the weight of evidence. ATSDR does not include detailed descriptions of every relevant study in this chapter.

Note: We are asking reviewers to focus primarily on health data published since the release of the original profile (data available 1992 to date), particularly data affecting the derivation of the acute duration, inhalation route MRL.

Questions:

- 1) Do the health effect conclusions made in Chapter 2 adequately reflect the findings in the published literature for 2-butanone?
- 2) 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.

- 3) 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.
- 4) 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?
- 5) 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.
- 6) 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?
- 7) 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.
- 8) Do you agree with the categorization of "less serious" or "serious" for the effects cited in the LSE tables?
- 9) Have all possible mechanisms of action been discussed within their relevant health effect section? If not, please explain.

Chapter 7:

Purpose: Chapter 7 summarizes pertinent international and national regulations, advisories, and guidelines regarding 2-butanone in air, water, and other exposure media.

Questions:

- 1) Are you aware of any additional regulations or guidelines that we should add? Please provide citations.
- 2) Are there any that should be removed? Please explain.

Appendix A – Minimal Risk Levels (MRLs):

Purpose: Documents and explains how ATSDR derived its MRLs for 2-butanone. New data has become available for the derivation of an acute duration, inhalation route MRL

Questions:

A new acute duration, inhalation route MRL:

An acute duration, inhalation route MRL was not previously derived in the 1992 toxicological profile due to insufficient data. However, new data has become available.

A provisional acute duration MRL of 1 ppm was derived for 2-butanone based on reported neurological symptoms (headache, fatigue, and feeling of intoxication) in human volunteers. The MRL is based on the lowest-observed-adverse-effect level (LOAEL) (not adjusted for continuous exposure) of 99.15 ppm and a total uncertainty factor of 100 (10 for use of a LOAEL and 10 for human variability).

Clinical signs of neurotoxicity were reported by humans exposed to 100 ppm 2-butanone (i.e., headache, fatigue, and feeling of intoxication) (Tomicic et al. 2011). In addition, neurobehavioral effects were reported in primates exposed to the same concentration (i.e., slower response times in a match-to-sample task) (Geller et al. 1979). Tomicic et al. (2011) was selected as the principal study because neurological effects were reported in volunteers exposed to 100 ppm.

The LOAEL of 100 ppm (measured concentration of 99.15 ppm) for neurological effects (headache, dizziness, and feeling of intoxication) was selected as the point of departure (POD) for the provisional acute-duration inhalation MRL. The POD was derived from human exposure studies; therefore, the POD is equivalent to a LOAEL. The LOAEL is divided by a total uncertainty factor (UF) of 100:

- 10 for human variability
- 10 for use of a LOAEL (neurological endpoints)

$$\text{MRL} = \text{LOAEL} \div \text{UFs}$$

$$\text{MRL} = 99.15 \text{ ppm} \div (10 \times 10) = 0.99 \text{ ppm} = 1 \text{ ppm}$$

- 1) 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.
- 2) 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.
- 3) Please comment on any aspect of our MRL database assessment that you feel should be addressed.

Appendix B – Literature Search Framework:

Purpose: Appendix B presents the protocol ATSDR used to complete the literature search and screen for the health effects chapter of the profile.

Questions:

- 1) Does Appendix B provide a sufficiently clear documentation of ATSDR's health effects literature search strategy and inclusion/exclusion criteria?
- 2) 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)?

Overall Usability of the Profile:

In an effort to improve the usability of the profiles, ATSDR recently made content and organizational changes based on user feedback, as well as data identifying the most used profile content. We would like your opinions on the content and general usability of the profile, specifically:

- 1) 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?
- 2) Does the profile contain all of the information you need? Is there information you would like to see that is not currently included?
- 3) If you have used the Toxicological Profiles before, which chapter(s) have you used the most and for what purpose?
- 4) Are the new tables and figures clear and useful? Do they make the toxicological profile easier to read?

