Peer Review Charge:
Toxicological Profile for Dinitrophenols - Draft for Public Comment

Summary

ATSDR has updated the previous version of Dinitrophenols (DNPs), released in 1995. The update focuses on Chapter 2, Health Effects, as well as Chapter 7 and any chapters related to changes made in Chapter 2. The updated health effects evaluation resulted in the removal of the original acute oral MRL and the addition of an intermediate oral MRL that we also believe to be protective for chronic exposures.

Thus, we would like for you to focus 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 intermediate oral 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 acute, intermediate, and chronic inhalation 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 1995-present), particularly data affecting the removal of the original acute oral MRL, derivation of the proposed intermediate oral MRL, and conclusion that the proposed intermediate oral MRL would be protective for chronic conditions.

Questions:

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

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 DNPs? 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 DNP 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.

10) The updated DNPs profile includes an unpublished study by Eli Lilly and Co. unavailable to ATSDR when preparing the original profile. Please comment on the quality of the study, namely:
    - Did the study use an adequate number of animals and practice good animal care?
    - Did the study account for competing causes of death?
    - Did the study include a sufficient number of dose groups, and sufficient magnitude of dose levels?
    - If you think the study was not adequately designed or reported, does that negate the utility of the study? Please explain.
    - Do you agree with the conclusions of the author? If not, please explain.

Chapter 7:

Purpose: Chapter 7 summarizes pertinent international and national regulations, advisories, and guidelines regarding DNPs 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 - MRLs:

Purpose: Documents and explains how ATSDR derived its MRLs for DNPs (data only adequate for derivation of intermediate oral MRL for 2,4-DNP).

Questions:

Acute-duration oral MRL: The updated data evaluation includes a number of fatal human case studies involving lower exposure levels than were documented in the original profile (within an order of magnitude of the point of departure used for the original MRL).

1) Do you agree that these human fatality data adequately support ATSDR's decision to remove the original acute oral MRL? In not, please explain.

2) Please comment on any aspect of our MRL database assessment that you would like us to address.

Intermediate-duration oral MRL: ATSDR derived a new intermediate-duration oral MRL of 0.00007 mg/kg/day was derived for 2,4-DNP based on decreased body weight in mice exposed to 0.07 mg/kg/day 2,4-DNP in drinking water for 50 weeks (Caldeira da Silva et al. 2008). The MRL is based on a LOAEL of 0.07 mg/kg/day and a total uncertainty factor of 1,000 (10 for interspecies extrapolation, 10 for human variability, and 10 for use of a LOAEL). An intermediate-duration oral MRL was not derived in the 1995 toxicological

profile due to the lack of intermediate duration studies involving doses lower than those known to cause death in humans.

1) Do you agree or disagree with the proposed intermediate-duration oral 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.

Chronic-duration oral MRL: ATSDR believes the chronic-duration oral exposure database does not provide sufficient data for derivation of a chronic oral MRL. Specifically, the lowest LOAELs for effects of chronic exposure are higher than doses known to cause fatalities in humans. However, we believe the intermediate-duration oral MRL is protective for chronic exposures.

1) Do you agree with ATSDR that the intermediate oral MRL of 0.00007 mg/kg/day would be sufficiently protective for chronic exposures? If not, please explain.

Appendix B:

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 documention 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 easy 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) Having read this Toxicological Profile (and others, if applicable), which chapter(s) or content do you find most valuable and why? If you have previously used any Toxicological Profile(s) for your work, which chapter(s) or content have you used the most and for what purpose(s)?
4) Are the new tables and figures clear and useful? Do they make the Toxicological Profile easier to read?