Peer Review Charge:
ATSDR's Toxicological Profile – Molybdenum Final and Unpublished Studies

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."

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).

Please pay special attention to the revised minimum risk levels (MRLs) and their corresponding Worksheets in Appendix A as discussed in Chapter 1 instructions below.

Also, be sure to review and compile your comments on each and all of the 31 unpublished studies as discussed in the charge further below. The names of the 31 studies are included in the additional 'list of unpublished studies' document.

Chapter 1. Relevance to Public Health

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, please explain why and 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.

Minimal Risk Levels (MRLs): Where scientific literature warrants, ATSDR derives MRLs to serve as screening levels to identify contaminants and potential health effects that may be of concern. An MRL is an estimate of the daily human exposure to a substance that is likely to be without appreciable risk of adverse noncancer health effects.

A detailed presentation of each MRL derivation is presented in Appendix A and summarized in Section 1.3. Please review Appendix A MRL Worksheets in conjunction with Section 1.3 and answer the following questions:

4) If no MRLs have been derived, do you agree that the data do not support such a derivation? Please explain.
5) 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.
6) Please comment on any aspect of our MRL database assessment that you feel should be addressed.

Appendix A – MRL Worksheets

Please provide any additional comments on the content, presentation, and derivation of the revised MRL values presented in the Worksheets. Are they justifiable? Do you agree with the study selection, the point of departure used and the uncertainty factors?

Chapter 2. Health Effects

Purpose: Chapter 2 provides a summary evaluation of the weight of evidence for health effects from human and animal studies. ATSDR does not include detailed descriptions of every relevant study in this chapter.

Questions:

1) Do the health effect conclusions made in Chapter 2 adequately reflect the findings in the published literature? If not, please suggest appropriate changes.
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) Has adequate attention been paid to dose-response relationships for both human and animal data? Please explain.
6) 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.
7) 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.
8) 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.
9) 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.
10) 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.
11) 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.

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

Purpose: Chapter 3 overviews other relevant information for evaluating health effects which includes toxicokinetics, susceptible populations, biomarkers of exposure and effect, and interactions with other chemicals.

Questions:

Toxicokinetics:

1) Is there adequate discussion of absorption, distribution, metabolism, and excretion of the substance? If not, suggest ways to improve the text.
2) Have all available pharmacokinetic/pharmacodynamic models and supporting data been presented? If not, please explain.

3) 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?

Children and Other Populations that are Unusually Susceptible:

1) 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.
2) 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.

Biomarkers of Exposure and Effect:

1) Are the biomarkers of exposure specific for the substance? Please explain.
2) Are the biomarkers of effect specific for the substance? Please explain.

Interactions with Other Chemicals:

1) 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.
2) If interactive effects with other substances are known, does the text discuss the mechanisms of these interactions? Please explain and provide any additional references.

Chapter 4. Chemical and Physical Information

Purpose: Chapter 4 summarizes the chemical and physical information. This chapter should contain very little text. Most of the information should be presented in tabular form.

Questions:

1) 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.
2) Is information provided on the various forms of the substance? Please explain.

Chapter 5. Potential for Human Exposure

Purpose: Chapter 5 discusses the production, import/export, use, and disposal of substances, as well as substance releases and how those are modified by time and environmental fate processes. Moreover, this chapter discusses substance levels in the environment and the potential for human exposure to the substance via different pathways. The level of detail in this chapter should be appropriate to an overview.

Questions:

1) Is the information on production, import/export, use, and disposal of the substance complete? Please explain and provide any additional relevant references.
2) 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.
3) 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.
4) 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.

5) 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?

Chapter 6. Adequacy of the Database

Purpose: Chapter 6 summarizes the adequacy of the database and any "data needs," which are substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment.

Questions:

1) Do you know of other studies that may fill a data gap? Please provide any relevant references.
2) Do you agree with the identified data needs? Please explain.
3) Are the data needs presented in a neutral, non-judgmental fashion? Please note any bias in the text.

Chapter 7. Regulations and Guidelines

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

Questions:

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

Appendices

Please provide any comments on the content, presentation, etc. of the included appendices. See especially the guidelines for Appendix A included under the Chapter 1 instructions.

Unpublished Studies (See Complete List of 31)

For each of the unpublished studies included with the profile, prepare a brief evaluation using the following questions as prompts:

- 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.

Then, please compile comments for all 31 studies into ONE document (Word or PDF) before sending to ATSDR along with your comments on the Profile itself.