DISPOSITION OF PEER REVIEW COMMENTS FOR TOXICOLOGICAL PROFILE FOR MOLYBDENUM

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 Molybdenum were:

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Comments provided by Peer Reviewer #1

General Comments

COMMENT 1: There is a body of literature dealing with molybdenum toxicity in nonmammalian and invertebrate species. Inclusion of this data my provide insights into toxicities observed in higher organisms.

RESPONSE: *The focus of the toxicological profile is on mammalian species.*

ATSDR Charge Questions and Responses and Reviewer Comments

Chapter 1

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 2: I agree with the effects reported for humans

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 3: This is difficult to assess. Among the three species in which molybdenum was tested; rat, mouse and rabbit; there were significant inter-species variations in response, with rabbit being the most sensitive. On the cautionary side, I would be concerned with the animal response in cases where similar responses are seen in two or three species.

RESPONSE: *Potential species differences are discussed in greater detail in Chapters 2 and 3.*

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

COMMENT 4: The authors did an excellent job in the other chapters describing exposure conditions, when the information was available in the original study. Additionally, they noted when information was missing in the cited studies.

RESPONSE: *Chapter 1 is intended to be a high-level discussion of the available data; as noted by the Reviewer, more information regarding exposure conditions is provided in Chapter 2***.**

Minimal 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 5: Molybdenum MLR's were reported for specific exposure conditions: chronic inhalation and intermediate oral exposures. I agree that the data support the MRL's derived from the available literature. I am concerned that studies using tetrathiomolybdate were excluded. Tetrathiomolybdate is an established copper chelator, thus the mechanism of molybdenum toxicity in this chemical form most likely is due to molybdenum-induced copper deficiency. (Note: excluding studies with insufficient copper was appropriate). I am unsure if excluding tetrathiomolybdate because of it known mechanism of toxicity is appropriate. A separate MRL for tetrathiomolybdate could be determined.

RESPONSE: *Tetrathiomolybdate compounds were excluded from consideration as the basis of MRLs because these compounds may not be representative of other molybdenum compounds; exposure to tetrathiomolybdate compounds results in a more dramatic shift in copper levels, as compared to other molybdenum compounds.*

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 6: I agree with the uncertainty factors (UF) used in calculating human MRLs. It would be beneficial to include a reference or short explanation of the UF used for the extrapolations from animals to humans. For oral and inhalation exposers UF of 10 and 3 were used, respectively. This may raise some confusion.

RESPONSE: *ATSDR uses a standard uncertainty factor of 10 to extrapolate from animals to humans. There are two components to this uncertainty factor: toxicokinetic differences and toxicodynamic differences. For the chronic-duration inhalation MRL, dosimetric adjustments were made, which decreased the uncertainty associated with potential toxicokinetic differences; thus, a partial uncertainty factor of 3 was used. The rationale for using the partial uncertainty factor is included in the MRL worksheet in Appendix A.*

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

COMMENT 7: I noted my concern regarding the exclusion of tetrathiomolybdate above

RESPONSE: *See the previous response regarding this issue.*

Appendix A – MRL Worksheets

QUESTION: 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?

COMMENT 8: I agree with the use of POD and the UF in the calculations of MRL's. I have no additional comments.

RESPONSE: *No response needed.*

Chapter 2. Health Effects

COMMENT 9: Page 9, line 13: change *will not be discussed* to *will not be further discussed*

RESPONSE: *The suggested revision was made to Section 2.1:*

Thus, ruminant data will not be further discussed in the toxicological profile.

COMMENT 10: Page 9, line 34: change *from studies in which there was adequate dietary to from studies in which there were adequate dietary*

RESPONSE: *The suggested revision was made to Section 2.1:*

Studies in which the laboratory animals were fed a basal diet with inadequate copper levels are clearly identified in the text, are discussed separately from studies in which there were adequate dietary copper levels, and are not included in the LSE table or figure.

COMMENT 11: Page 10 line 6: *Wilson's disease, a genetic disease that limits copper excretion.* This is the cause of the disease. The pathology is accumulation of toxic levels of copper in the liver and then brain. I suggest putting the pathology in the text.

RESPONSE: *The suggested revision was made to Section 2.1:*

Ammonium tetrathiomolybdate is an experimental chelating agent used to decrease excess copper levels in individuals with Wilson's disease, a genetic disease that limits copper excretion resulting in an accumulation of toxic levels of copper in the liver, brain, and eyes.

COMMENT 12: Page 36, line 5: delete *very low*

RESPONSE: *The suggested revision was made to Section 2.3:*

Administration of ammonium tetrathiomolybdate resulted in a LOAEL of 4.4 mg molybdenum/kg/day for decreases in body weight gain (Lyubimov et al. 2004); the interaction between the ammonium tetrathiomolybdate and copper may have resulted in copper insufficiency and contributed to the body weight effect.

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 13: The health effect conclusions satisfactorily reflect the findings in the published literature and information from contract laboratory studies.

RESPONSE: *No response needed.*

QUESTION 14: 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 15: In general, human toxicity data is not available of adequate to confirm human toxicity of molybdenum. For each toxicity endpoint or target in humans (e.g., hepatic, renal, dermal, etc.) the availability of human data is presented as well as the limitations in the data.

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 16: The majority of the animal studies were designed using the traditional toxicity SOPs for this type of chemical. The report clearly identifies conflicting results, information that limit the utility of the study and presents multi-species information. Nothing presented negates the utility of the information.

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 17: Measurements of molybdenum toxicity used the accepted animal species: rats, mice, rabbit and guinea pig.

RESPONSE: *No response needed.*

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

COMMENT 18: Molybdenum exposure did not lead to a pathological response in the majority of the studies, even at the highest dose/concentration tested. Thus, dose-response relationships may not be relevant for this chemical. Dose-response data was provided for a limited number of studies.

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 the substance? Please provide a copy of each study and indicate where in the text each study should be included.

COMMENT 19: Where appropriate, the information on the *in vitro* molybdenum toxicity endpoints provided in the *Unpublished Studies* should be incorporated.

RESPONSE: *ATSDR assumes that the Reviewer is referring to the unpublished studies that were peer reviewed. The data from these studies have been incorporated into Chapter 2 of the profile.*

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 20: I am not aware of additional studies that can be used to derive MRLs.

RESPONSE: *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 21: Appropriate NOAELs and LOAELs identified.

RESPONSE: *No response needed.*

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 22: I disagree with the classification of "Serious LOAEL" presented in Table 2-1. In general, animals that showed weight loss during first 2–3 post-exposure days returned to normal weigh or rate of gain. In my opinion, the weight gain response should be classified as a "less serious LOAEL," as it is unlikely that exposure to molybdenum at the LOAEL dose would lead to a *failure in a biological system and can lead to morbidity or mortality,* as defined for a "serious effect."

RESPONSE: *Table 2-1 was revised and the serious LOAELs for body weight identified for the Jackson et al. (1991a, 1991b, 1991c) studies were re-categorized as less serious LOAELs. A note was added that the body weight gain was similar to controls after day 3.*

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 23: The majority of the information in section2.21 focuses on mechanism of action for molybdenum toxicity as related to its ability to disrupt copper homeostasis. The last paragraph on page 60 briefly discusses molybdenum –induced oxidative stress. This section should be expanded to include the following references: PMID 30529889, 26208811, 27297413, 30389395 and 30529889.

RESPONSE: *The discussion of oxidative stress in the mechanism of action section (Section 2.21) was revised to include the Domingo-Relloso et al. 2019 (PMID 30529889), Zhuang et al. 2016 (PMID 26208811), Zhang et al. 2017 (PMID 27297413), and Terpilowska and Siwicki 2019 (PMID 30389395) studies:*

A number of studies have reported that molybdenum induces oxidative stress. An *in vitro* study in mouse fibroblasts and liver cancer cells found that trivalent molybdenum induced oxidative stress as indicated by increases in reactive oxygen species generation and increases in malondialdehyde concentration (Terpilowska and Siwicki 2019). This possible mechanism of action is supported by several *in vivo* studies. A general population study found an association between urinary molybdenum levels and ratio of oxidized glutathione to reduced glutathione in the general population

suggestive of a relationship between molybdenum and oxidative stress (Domingo-Relloso et al. 2019). Zhai et al. (2013) showed that the levels of two enzymatic antioxidants (superoxide dismutase and glutathione peroxidase) in the testes of mice paralleled the molybdenum-induced sperm effects. Increases in antioxidant levels and improvements in sperm parameters were observed at lower molybdenum doses. However, at higher molybdenum doses, there were significant decreases in antioxidant levels and significant decreases in sperm motility and concentration and an increase in the rate of sperm abnormalities. Zhang et al. (2013) reported a similar finding for superoxide dismutase and glutathione peroxidase levels in the ovaries of mice and the rate of MII oocyte abnormalities. Molybdenum-induced hepatocyte apoptosis was observed in goats orally exposed to ammonium molybdate for 50 days (Zhuang et al. 2016). Molybdenum exposure resulted in down-regulation of superoxide dismutase and catalase expression in liver cells and an up-regulation of malondialdehyde, nitric oxide, and total nitric oxide synthase expression. The investigators suggested that the observed effect may be due to a disruption of the mitochondrial antioxidant defense system resulting in apoptosis via activation of the mitochondrial signaling pathways.

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 24: I agree with the conclusions of the authors based on the available data for various chemical form of molybdenum.

RESPONSE: *No response needed.*

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

COMMENT 25: I am not sure why the first paragraph on page 66 is in this section. It seems that it should be in a mechanisms/metabolism section.

RESPONSE: *The referenced paragraph in Section 3.1.4 discusses the excretion mechanisms and belongs in the excretion section rather than the metabolism section (Section 3.1.3). The mechanism of action section in Section 2.21 is limited to the discussion of toxicity mechanisms of action.*

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

COMMENT 26: The discussion is adequate; however a figure of the Novotny and Turnlund PBPK model, with the associated parameters, should be included in the document.

RESPONSE: *The Novotny and Turnlund (2007) PBPK model figure was added to Section 3.1.5.*

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

COMMENT 27: Yes, the molybdenum PBPK models that are presented are up to date.

RESPONSE: *No response needed.*

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 28: The authors note limited data availability to make meaningful interspecies extrapolations. They end section 3.1.6 with the statement, *In the absence of data to the contrary, it is assumed that the toxicity of molybdenum will be similar across species (excluding ruminants*). As there are known interspecies differences in susceptibility to molybdenum toxicity, noted by the authors, this statement seem contraindicated.

RESPONSE: *As noted in Section 3.1.6, studies that suggest species differences are not directly comparable due to differences in the copper content of the diet and differences in other dietary constituents. Thus, a determination cannot be made as to whether there are species differences in molybdenum toxicity. ATSDR does not believe that this contradicts the assumption that there are no species differences.*

Children and Other Populations that are Unusually Susceptible

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 29: There is no conclusive data indicating increased fetal or childhood susceptibility to molybdenum toxicity in humans or laboratory animals. Section 3.2 presents the available information on the levels of molybdenum in children and any studies that examined developmental toxicity.

RESPONSE: *No response needed.*

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 30: High risk populations were not discussed. A comment should be included that populations with a copper-deficiency may be susceptible to molybdenum toxicity. This could include infants with GI problems, and third world countries.

RESPONSE: *There is a statement in Section 3.2 regarding increased risk due to copper deficiency:*
Studies in laboratory animals have found that maintenance on a copper-deficient diet enhances the toxicity of molybdenum (Brinkman and Miller 1961; Franke and Moxon 1937; Johnson and Miller 1961; Sasmal et al. 1968; Valli et al. 1969; Van Reen 1959; Widjajakuma et al. 1973). Administration of additional copper results in a reversal of the adverse effect (Arrington and Davis 1953). Thus, individuals with low copper intakes may be unusually susceptible to the toxicity of molybdenum.

Biomarkers of Exposure and Effect

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

COMMENT 31: The biomarker of molybdenum exposure is the direct physical measurement of the metal in environmental and biological material. Thus, it specifically measures molybdenum.

RESPONSE: *No response needed.*

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

COMMENT 32: There are no biomarkers of molybdenum-specific effects. Many of the toxicity endpoints associated with molybdenum exposure are due to its ability to bind copper. Therefore, it is difficult to differentiate between molybdenum toxicity and copper deficiency. This topic was addressed by the authors in the report. An alternative viewpoint is that molybdenum toxicity is its ability to induce copper deficiency.

RESPONSE: *ATSDR did not identify data that suggest that copper deficiency is a biomarker of molybdenum toxicity.*

Interactions with Other Chemicals

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 33: Molybdenum-chemical interactions were limited to copper. This interaction is discussed in terms of a mechanism for molybdenum toxicity in laboratory animals. There is no discussion of this interaction at hazardous waste sites, as it is not relevant.

RESPONSE: *No response needed.*

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 34: The best studied interaction is between molybdenum and copper. The authors adequately discuss this interaction.

RESPONSE: *No response needed.*

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 35: The information in these tables is correct.

RESPONSE: *No response needed.*

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

COMMENT 36: Information on the physical and chemical characteristics of the eight chemical forms of molybdenum that are discussed in this report is provided.

RESPONSE: *No response needed.*

Chapter 5. Potential for Human Exposure

COMMENT 37: Page 85, line 9 change *those exposures are limited* to *those exposures is limited*

RESPONSE: *The suggested revision was made in Section 5.1:*

The extent of those exposures is limited by U.S. Nuclear Regulatory Commission (USNRC) and agreement state regulations (USNRC 2016a, 2016b).

COMMENT: Page 88, line 4 *this has impacted* to *this impacted*

RESPONSE: *The suggested revision to Section 5.2.1 was made:*

The availability of those reactors was reduced by the closure of the Chalk River facility, and this impacted the supply stream.

COMMENT 38: Page 89, line 2 insert a comma between cobalt and manganese

RESPONSE: *The suggested revision was made in Section 5.2.3:*

Molybdenum is commonly used in combination with other alloy metals like chromium, cobalt, manganese, nickel, niobium, and tungsten.

QUESTION: Is the information on production, import/export, use, and disposal of the substance complete? Please explain and provide any additional relevant references.

COMMENT 39: Overall the information on the production, import/export, use and disposal of molybdenum is complete. Page 88, line12: This statement should be updated as there are now facilities in the US to produce 99Mo (https://www.northstarnm.com/northstar-medicalradioisotopes-announces-construction-completion-of-beloit-wisconsinprocessing-facility-for-expanded-domestic-production-of-medically-importantmolybdenum-99-mo-99/ https://www.nap.edu/read/23563/chapter/6)

Also the following reference should be included *National Academies of Sciences, Engineering, and Medicine; Division on Earth and Life Studies; Nuclear and Radiation Studies Board. Opportunities and Approaches for Supplying Molybdenum-99 and Associated Medical Isotopes to Global Markets: Proceedings of a Symposium. Washington (DC): National Academies Press (US); 2018 Feb 7. 6, Prospects for Molybdenum-99 Future Supply. Available from: https://www.ncbi.nlm.nih.gov/books/NBK487237/*

RESPONSE: *The following statement was added to Section 5.2.1:*

At a NAS symposium in 2017, several companies discussed their plans to produce ^{99}Mo in the United States (NAS 2018).

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 40: The text has appropriately identified the range of molybdenum levels in air, water and soil. The report traced molybdenum from source (e.g., mining) to environmental media. It addressed the presence of molybdenum at NTP sites.

RESPONSE: *No response needed.*

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 41: Information on the chemical species of molybdenum for air, water and soil are presented. Degradation of this chemical is not relevant as it is a naturally occurring stable element. Information on the biotic movement of molybdenum was not reported (i.e., from soil-water to invertebrates and plants as noted in Fitzgerald, 2008).

RESPONSE: *No response needed.*

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 42: The text provides levels of molybdenum as background and in potentially contaminated areas for air, water and soil. Overall, proper units of concentration were used; however, it would be beneficial if ppm were converted to the appropriate mg/kg, mg/L or μg/m3 when possible. The chemical form of molybdenum is not specifically discussed. This however, may not be relevant as other sections clearly state that the most likely environmental form of molybdenum is the oxide. Much of the information was obtained from reviews and government reports; there were no specific discussions of the "quality" of the data. However, sufficient information is provided to allow a reader to access the original documentations to make their own assessment of data quality.

RESPONSE: *The text was revised to also include mg/L or mg/kg units when the ppm unit is used. For example:*

> *Section 5.5.3:* Sediments in streams that drain water from natural deposits of molybdenum in the United States have been reported to have molybdenum concentrations ranging from 10 to 200 ppm (10–200 mg/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 43: The text adequately presents information on the sources of molybdenum exposure to general and at risk populations. I agree with the populations selected: adults, children, nursing mothers and molybdenum workers. The information on page 106, line 4 regarding the forms of molybdenum in dietary supplements should be updated with the information at https://ods.od.nih.gov/factsheets/Molybdenum-HealthProfessional/.

RESPONSE: *Section 5.6 was updated to include other forms of molybdenum in dietary supplements:*

Dietary supplements generally contain molybdenum in the form of sodium molybdate or ammonium molybdate (Momcilovic 1999; NAS 2001), although the molybdenum can also be in the form of molybdenum chloride, molybdenum glycinate, and molybdenum amino acid chelate (NIH 2019).

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 44: There are five technical reports on acute inhalation in rats among the 31 *unpublished studies for peer review* that should be included

RESPONSE: *The unpublished inhalation studies were included in the profile (Jackson et al. 1991a, 1991b, 1991c, 1991d; Leuschner 2010); note that the Haferkorn (2010) study is the same study as Leuschner (2010).*

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

COMMENT 45: I agree with the data gaps that were identified. However, additional gaps should be addressed:

1) Among the *range of potential endpoints*, special attention should be given to systemic immunological endpoints (e.g., changes in white blood cell populations, cytokine levels, macrophage infiltration, etc.).

2) Identification of biochemical or genomic biomarker of exposure should be developed for oral and inhalation exposures.

RESPONSE: *The text in Section 6.2 was revised:*

Immunotoxicity: Studies examining immune function and systemic immunological endpoints (e.g., changes in white cell populations, cytokine levels, macrophage infiltration) would be useful in evaluating whether this is a target of molybdenum toxicity; it would be useful if the studies evaluated different molybdenum compounds.

Biomarkers: Studies evaluating biochemical and/or genomic biomarkers of exposure would also be useful for evaluating potential inhalation and/or oral exposure.

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

COMMENT 46: The information presented thought-out this report is presented in a neutral, unbiased fashion.

RESPONSE: *No response needed.*

Chapter 7. Regulations and Guidelines

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

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

COMMENT 47: I could not find any addition national/international regulations or guidelines associated with molybdenum. The ones that have been cited should not be removed.

RESPONSE: *No response needed.*

Comments provided by Peer Reviewer #2

ATSDR Charge Questions and Responses and Reviewer Comments

Chapter 1

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 1: I agree, however, the effects in most categories as presented on pages 3-4 relate to organs or systems. The effects on Uric Acid stand out in this context; perhaps these effects can be reclassified to another category of the authors' choosing.

RESPONSE: *Because alterations in uric acid levels could be indicative of damage to several organ systems, it is discussed with other noncancer endpoints, rather than with data for a specific organ system.*

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 2: Yes. Respiratory and renal effects have been documented in humans, and inadequate data exist to determine the effects on other organs/systems. Excersing caution, I would suggest that the effects observed only in animals should be of concern in humans as well.

RESPONSE: *No response needed.*

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

COMMENT 3: Yes

RESPONSE: *No response needed.*

Minimal 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 4: I agree, if as stated insufficient data are available for the derivation of an MRL.

RESPONSE: *No response needed.*

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 5: The relationship between copper diet and molybdenum toxicity is not well explained, so it is hard to determine if the UFs and MFs are adequate. There should be better explanation for it in Appendix A, and also given the importance of this issue, may I suggest inclusion of the reasoning for these factors also in the text itself of Chapter 1.

RESPONSE: *The relationship between dietary copper and molybdenum toxicity is discussed in several sections of the toxicological profile, including Sections 1.2 and 2.1. Additionally, there is a discussion included in the Selection of a Critical Effect subsection of the intermediate-duration oral MRL in Appendix A. The rationale for the modifying factor for the intermediate-duration oral MRL is also discussed in Appendix A. The modifying factor was used due to concern that reproductive/developmental endpoints may be a more sensitive endpoint than the kidney in populations with marginal copper intake. The rationale for the modifying factor is that the study reporting reproductive effects at a relatively low dose (Fungwe et al. 1990) utilized a diet with a copper content that was slightly higher than the dietary requirement. By comparison, the Murray et al. (2014b, 2019) studies, which did not find reproductive effects, utilized a commercial diet with a fairly high copper content. Consistent with ATSDR's profile guidance document, a discussion of uncertainty factors and modifying factors is not included in Section 1.3; the reader is directed to Appendix A for more information on the MRL derivation.*

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

COMMENT 6: No additional comments.

RESPONSE: *No response needed.*

Appendix A – MRL Worksheets

QUESTION: 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?

COMMENT 7: No additional comments.

RESPONSE: *No response needed.*

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 8 : 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? If study limitations were not adequately addressed, please suggest appropriate changes.

COMMENT 9: 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 10: Yes. The authors have exercised proper means to evaluate the adequacy of the studies. I concur with their assessments and the ultimate inclusion or exclusion criteria of the studies.

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 11: Yes.

RESPONSE: *No response needed.*

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

COMMENT 12: Yes.

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 the substance? Please provide a copy of each study and indicate where in the text each study should be included.

COMMENT 13: There are several studies on the neurotoxicity of molybdenum that should be included.

Molybdenum bupropion combined neurotoxicity in rats.
Helaly AM, Mokhtar N, Firgany AEL, Hazem NM, El Morsi E, Ghorab D.
Regul Toxicol Pharmacol. 2018 Oct;98:224-230. doi: 10.1016/j.yrtph.2018.08.001. Epub 2018 Aug 3.

Molybdenum cofactor deficiency is discussed throught the text (pages 7-8, etc.) but there is no mention of it on the section on the health effects of molybdenum in Chapter 2 as they related to neurological function.
It would seem adequate to include some of this information on p. 46, Section 2.15.

> S-sulfocysteine/NMDA receptor-dependent signaling underlies neurodegeneration in **molybdenum** cofactor deficiency.
> Kumar A, Dejanovic B, Hetsch F, Semtner M, Fusca D, Arjune S, Santamaria-Araujo JA, Winkelmann A, Ayton S, Bush AI, Kloppenburg P, Meier JC, Schwarz G, Belaidi AA.
> J Clin Invest. 2017 Dec 1;127(12):4365-4378. doi: 10.1172/JCI89885. Epub 2017 Nov 6.

RESPONSE: *The Helaly et al. (2018) study was added to Section 2.15:*

> In contrast, Helaly et al. (2018) reported dense inflammation and neurocyte degeneration in the cerebral cortex and hippocampus of rats receiving gavage doses of 30 mg molybdenum/kg/day as molybdenum dihydrate for 30 days; however, the study did not include incidence data.

The focus of the toxicological profile is on the toxicity of molybdenum. ATSDR did not identify studies that found a relationship between molybdenum cofactor deficiency and molybdenum-induced toxicity. Since the Kumar et al. (2017) study deals with molybdenum cofactor deficiency, it was not added to the profile.

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 14: See above (question 6).
There are also studies on molybdenum nanoparticles that the authors should consider including in the profile. One example is:

> Reproductive and developmental toxicity studies of manufactured nanomaterials.
> Ema M, Kobayashi N, Naya M, Hanai S, Nakanishi J.
> Reprod Toxicol. 2010 Nov;30(3):343-52. doi: 10.1016/j.reprotox.2010.06.002. Epub 2010 Jun 25. Review.

RESPONSE: *Studies evaluating molybdenum compounds that are predominantly comprised of nanoparticles (mean particle size ≤100 nm) are not included in the profile because the toxicokinetic and toxicodynamic properties can be substantially different from larger, respirable particles (Oberdorster 2010).*

Oberdorster G. 2010. Safety assessment for nanotechnology and nanomedicine: concepts of nanotoxicology. J Intern Med 267(1):89-105. http://doi.org/10.1111/j.1365-2796.2009.02187.x.

The following text was added to the profile:

> Section 1.1: Industrial applications of molybdenum nanoparticles have also been identified; however, molybdenum nanoparticle exposure is not discussed in this toxicological profile because their physical-chemical properties differ from that of larger molybdenum particles and the toxicological and toxicokinetic properties of nanoparticles can vastly differ from those of larger particles.

> Section 2.1: As illustrated in Figure 2-1, a number of human and laboratory animal studies have evaluated the toxicity of molybdenum following inhalation, oral, or dermal exposure; this

toxicological profile on molybdenum does not include discussion of the health effects of molybdenum nanoparticles which could have different toxicological and toxicokinetic properties than larger molybdenum particles.

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 15: Seems adequate, no changes recommended.

RESPONSE: *No response needed.*

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 16: 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. If citing a new reference, please provide a copy and indicate where (in the text) it should be included.

COMMENT 17: No. There is literature on the effects of molybdenum on various signal transduction pathways which is not included in the profile. The authors address mechanisms associated with metal competition, but at the molecular level they fail to allude to existing literature.

Examples include:

Cellular proliferation and differentiation induced by single-layer **molybdenum** disulfide and mediation mechanisms of proteins via the Akt-mTOR-p70S6K signaling pathway.
Zou W, Zhang X, Zhao M, Zhou Q, Hu X.
Nanotoxicology. 2017 Aug;11(6):781-793. doi: 10.1080/17435390.2017.1357213. Epub 2017 Aug 2.

Molybdenum induces pancreatic β-cell dysfunction and apoptosis via interdependent of JNK and AMPK activation-regulated mitochondria-dependent and ER stress-triggered pathways.
Yang TY, Yen CC, Lee KI, Su CC, Yang CY, Wu CC, Hsieh SS, Ueng KC, Huang CF.
Toxicol Appl Pharmacol. 2016 Mar 1;294:54-64. doi: 10.1016/j.taap.2016.01.013. Epub 2016 Jan 21.

RESPONSE: *As noted in a previous response, the profile does not include a discussion of nanoparticles, which have different toxicokinetic and toxicodynamic properties than respirable particles. The Zou et al. (2017) is a mechanistic study of a molybdenum disulfide nanosheet. The Yang et al. (2016) study was not added to the mechanism of action section because there are no data supporting the identification of the pancreas as a target of molybdenum toxicity. The mechanisms of action discussion in the profile is focused on mechanistic data related to the sensitive targets of toxicity.*

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 18: Yes.

RESPONSE: *No response needed.*

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

Toxicokinetics

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

COMMENT 19: Yes. But again, the authors may wish to include information of the kinetics of molybdenum nanoparticles.

RESPONSE: *The toxicological profile does not include a discussion of the toxicokinetic properties of molybdenum nanoparticles because the properties can be substantially different from larger, respirable particles (Oberdorster 2010).*

Oberdorster G. 2010. Safety assessment for nanotechnology and nanomedicine: concepts of nanotoxicology. J Intern Med 267(1):89-105. http://doi.org/10.1111/j.1365-2796.2009.02187.x.

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

COMMENT 20: Yes.

RESPONSE: *No response needed.*

Children and Other Populations that are Unusually Susceptible

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 21: It is noted in the Profile that molybdenum is essential because it is part of a complex called molybdenum cofactor that is required for the three mammalian enzymes xanthine oxidase (XO), aldehyde oxidase (AO), and sulfite oxidase (SO).

Inborn errors of deficiencies in XO, SO, and molybdenum cofactor have been described. Though relatively benign, patients with isolated deficiencies in SO or molybdenum cofactor exhibit mental retardation with neurologic problems.

Molybdenum deficiency has also been reported in a patient receiving prolonged total parenteral nutrition. The biochemical abnormalities in this acquired molybdenum deficiency include very low levels of uric acid in serum and urine (low XO activity) and low inorganic sulfate levels in urine (low SO activity).

Please refer to the following study:
Molybdenum: an essential trace element.
Sardesai VM.
Nutr Clin Pract. 1993 Dec;8(6):277-81.

RESPONSE: *The focus of the profile is the toxicity of molybdenum. The brief overview of molybdenum deficiency is intended to give the reader some background information. The Sardesai (1993) study was added to this discussion in Section 2.1:*

> Molybdenum, as a component of pterin-based cofactor, is an essential element. Historically, three molybdenum cofactor-containing enzymes have been identified: sulfite oxidase, xanthine oxidase, and aldehyde oxidase (NAS 2001; Sardesai 1993).

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 22: I believe there should be some discussion on molybdenum deficiency as well as molybdenum cofactor deficiency.

RESPONSE: *See response to the previous comment.*

Biomarkers of Exposure and Effect

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

COMMENT 23: Yes. Measuremnts of molybdenum in various tissues and biological media seem reasonable. Overall, the data seem to be quite scarce.

RESPONSE: *No response needed.*

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

COMMENT 24: Yes.

RESPONSE: *No response needed.*

Interactions with Other Chemicals

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 25: Yes

RESPONSE: *No response needed.*

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 26: Yes

RESPONSE: *No response needed.*

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 27: Seems adequate.

RESPONSE: *No response needed.*

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

COMMENT 28: Seems adequate.

RESPONSE: *No response needed.*

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 29: Yes.

RESPONSE: *No response needed.*

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 30: Yes.

RESPONSE: *No response needed.*

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 31: Yes.

RESPONSE: *No response needed.*

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 32: Yes to all. As far as other relevant information (last question), I am unaware of it.

RESPONSE: *No response needed.*

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 33: Yes.

RESPONSE: *No response needed.*

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 34: There are five technical reports on acute inhalation in rats among the 31 *unpublished studies for peer review* that should be included

RESPONSE: *The unpublished inhalation studies (Jackson et al. 1991a, 1991b, 1991c, 1991d; Leuschner 2010) are discussed in Chapter 2. Note that the Haferkorn (2010) study is the same study as the Leuschner (2010) study.*

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

COMMENT 35: No, I do not know of additional studies.

RESPONSE: *No response needed.*

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

COMMENT 36: Yes, I largely agree, but as stated above, I believe additional data on the neurological effects of molybdenum, especially as they relate to conditions of other metal deficiencies and genetic SNPs (molybdenum cofactor deficiency and others) are necessary and timely.

RESPONSE: *As noted in previous responses, the discussion of adverse health effects associated with molybdenum is limited to toxicity (doses exceeding nutritional requirements).*

Chapter 7. Regulations and Guidelines

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

COMMENT 37: No.

RESPONSE: *No response needed.*

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

COMMENT 38: No.

RESPONSE: *No response needed.*

Comments provided by Peer Reviewer #3:

ATSDR Charge Questions and Responses and Reviewer Comments

Chapter 1

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 1: I agree with the primary and secondaty health effects identified in Chapter 1.

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 2: Effects reported in animals following molybdenum exposure are relevant for hazard identification.

RESPONSE: *No response needed.*

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

COMMENT 3: Consider adding route(s) of exposure. Also consider normalizing the data to mg Mo/kg since there is a range of molecular weights for the different chemical forms that are considered in the profile.

RESPONSE: *There are separate LSE tables for inhalation, oral, and dermal exposure. Route information is also included in the discussion of health effects. All exposure concentrations and doses were expressed as mg Mo/m^3 (inhalation), mg Mo/kg/day (oral), or % Mo, mg Mo/kg, or mg Mo (dermal). It is noted that the LSE tables were revised to indicate that the inhalation concentrations were mg Mo/m^3 and oral and dermal doses were mg Mo/kg/day.*

Minimal Risk Levels (MRLs)

COMMENT 4: Inhalation exposure (mg molybdenum/m3)

- Acute Insufficient data for derivation of an MRL. I agree
- Intermediate Insufficient data for derivation of an MRL. I agree
- Chronic (molybdenum trioxide) 0.002 (provisional)
    - Squamous metaplasia of the epiglottis in female rats 0.071 (BMCLHEC)UF: 30 NTP 1997. See comments below regarding Appendix A.

RESPONSE: *No response needed.*

COMMENT 5: Oral exposure (mg/kg/day)

- Acute Insufficient data for derivation of an MRL. I agree
- Intermediate 0.06 (provisional) Renal proximal tubule hyperplasia 17 (NOAEL) UF: 100 MF: 3 Murray et al. 2014a.
    - It's unclear why reproductive effects were not considered – the selection of the specific endpoints could benefit from some additional rationale.
- ChronicInsufficient data for derivation of an MRL. I agree

RESPONSE: *As discussed in detail in Appendix A, ATSDR considered basing the MRL on reproductive effect points of departure. However, the studies that identified the lowest LOAELs for female reproductive effects (Fungwe et al. 1990) and male reproductive effects (Pandey and Singh 2002) were not considered adequate for MRL derivation. Fungwe et al. (1990) provided limited dose information and a comparison of serum molybdenum levels with the results from other intermediate-duration studies suggest that the animals may have been exposed to higher doses than estimated using reference values for body weight and drinking water consumption. The Pandey and Singh (2002) study did not provide information on the copper content of the diet. Additionally, reproductive effects were not observed in two studies conducted by Murray et al. (2014a, 2019), which tested higher doses.*

Appendix A – MRL Worksheets

QUESTION: 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?

COMMENT 6: See above. The presentation could be improved somewhat. The critical endpoint is identified early in the Appendix and based on the summary of the data its not immediately apparent why certain outcomes were selected (e.g., metaplasia of epiglottis vs. degeneration of nasal respiratory epithelium). The selection only becomes apparent based on the BMD models (e.g., Table A2) where the chosen endpoints were the most sensitive outcome – this however is not made explicit in the document since multiple outcomes occurred at the LOAEL. The authors state that: "Since the average copper intake of the U.S. population exceeds the dietary requirements (NAS 2001), studies in which animals were fed inadequate levels of copper were not considered relevant for MRL derivation and were excluded from further consideration". A significant weakness in the draft document is that dietary copper levels are not provided for the experimental studies cited in the profile. It is therefore difficult to assess whether or not adequate levels of copper (and other micronutrients) were fed. The authors have also not clearly defined what would consititute an inadequate level of dietary copper. The authors should also consider the fact that many trace minerals in common rodent chows are often supplemented at extremely high levels that far exceed NRC recommendations for rodent chow. Determining which diet(s) may or may not be relevant for hazard identification is difficult at best. I would encourage ATSDR to move forward all studies since the systematic review did not include diet as an inclusion/exclusion criteria. Likewise, the risk of bias does not seem to have considered copper in diet.

RESPONSE: *ATSDR will consider the Reviewer's comments regarding the format of the MRL worksheet in future updates to the toxicological profile guidance document.*

The dietary copper requirements for rats, mice, and rabbits are provided in Section 2.1 of the profile. Including the copper content of the diet for individual studies is beyond the scope of the toxicological profile. Rather, ATSDR has provided the dietary requirements and clearly identifies which studies provide inadequate dietary copper levels.

In Section C.4, ATSDR states that studies in which the diet did not contain adequate levels of copper or administered ammonium tetrathiomolybdate were excluded from the systematic review to identify potential health outcomes of concern.

COMMENT 7: Detailed risk of bias questions were not provided in the appendices (i.e., the OHAT items are provided; however, the specific questions used to assess each item were not provided). The use of the OHAT methods is a major strength of the profile.

RESPONSE: *The specific risk of bias questions are provided in Tables C-5, C-6, and C-7.*

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 8: Yes, they adequately reflect main findings and the results of the literature performed as part of the systematic review. The study descriptions are relatively sparse but do convey the critical findings.

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? If study limitations were not adequately addressed, please suggest appropriate changes.

COMMENT 9: "Goodness" of these studies was not a clear criteria for inclusion in the studies. In general studies found through the systematic review process would be kept. Poorer quality studies could have higher risk of bias that would lead to downgrades in subsequent analytical steps. 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. In general, the summary tables provide a bare minimum of the information from the cited studies. Strengths and weaknesses are not generally addressed. For example, most of the GLP studies cited in the document share common weaknesses including small group sizes, limited dose-response data, and limited number of outcomes were assessed.

RESPONSE: *The format of the toxicological profile does not allow for a discussion of the strengths and weaknesses of individual studies. A number of study limitations are pointed out in the health effects discussions in Chapter 2. Additionally, the results of the systematic review of studies examining sensitive endpoints are presented in Appendix C.*

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 10: See document concerning the peer review of the animal studies that were unpublished. No major concerns were noted. One issue that has not been addressed relates to particle size and solubility of certain molybdenum compounds used in the oral studies. Uptake of molybdenum is also influenced by surface area of the particles in the stomach and intestines. It's also unclear whether copper in rodent diets were reported in some of the older cited studies. Formulations of rodent diets can vary considerably. It's also unclear why changes in copper are not considered as potentially adverse if the animals are on a base diet (e.g., no additional copper is added). In general, mineral-mineral interactions are relevant for human risk assessment. Some of the rodent studies provided copper in the diet at levels that far exceed the NRC recommendations (e.g., 110 ppm). I would worry about additional changes in other trace minerals (e.g., iron, manganese) that may not have been considered in the analysis.

RESPONSE: *ATSDR did not identify studies that compared the relative bioavailability of different molybdenum compounds; this data need was added to Section 6.2 (Absorption, Distribution, Metabolism, and Excretion):*

> Limited information was identified on the relative bioavailability of different molybdenum compounds following inhalation or oral exposure. It is likely that the solubility of the molybdenum compound would greatly influence the amount that is absorbed through the lungs or gastrointestinal tract. Studies examining relative bioavailability would provide valuable information on extrapolating data across molybdenum compounds and species.

As discussed in Section 2.21, there are indications that the mode of action for molybdenum toxicity may involve altered copper utilization. However, it is difficult to categorize the adversity of changes in copper status without adequate information on the copper levels (serum levels or other biomarkers of copper status), which would be indicative of copper deficiency in a particular animal species. As discussed by NAS (2001), indicators of copper deficiency in humans may not be sensitive to marginal copper status. The same is likely true for other species.

ATSDR was able to estimate the copper content for many of the animal studies cited in the profile; this information was either provided by the investigators or ATSDR was able to estimate it based on feed information provided in the paper. The lack of information on the copper content of the diet was considered a major weakness of a study. ATSDR agrees with the Reviewer that some of the available studies utilized commercial diets that have copper contents far exceeding the NAS recommendations; these diets tended to be high in a number of mineral nutrients. Data were not identified to inform whether these mineral-mineral interactions would affect the toxicity of molybdenum.

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 11: Traditional laboratory animal species (rodents, rabbits) were used for studies cited in the hazard assessment. This is appropriate. To my knowledge studies in higher nonhuman primates have not been performed to suggest that species differences are operative.

RESPONSE: *No response needed.*

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

COMMENT 12: Yes, this issue has been addressed adequately.

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 the substance? Please provide a copy of each study and indicate where in the text each study should be included.

COMMENT 13: I am not aware of additional studies that were not identified by the literature search performed by ATSDR.

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 substance isomers? Please provide a copy if this is a new reference.

COMMENT 14: I am not aware of additional studies that would support derivation of a MRL.

RESPONSE: *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 15: The Tables appear complete.

RESPONSE: *No response needed.*

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 16: Clear definitions have been provided. The decreases in body weight in some studies was >15% (and in other > 25%) this would be considered evidence of systemic toxicity and could exceed an MTD which would be considered a serious effect. Increased postimplantation loss would also be considered a severe effect since it could reflect fetal death. Severe anemia can be life threatening – this should be qualified since it is currently considered a less serious effect. The tables also include negative findings from some (e.g., no alterations in blood triglyceride, glucose, or insulin levels) but not all studies. It's not clear why some negative results were provided for some studies only.

RESPONSE: *ATSDR has revised the categorization of the post-implantation losses observed in the Pandey and Singh (2002) to a serious LOAEL. Arrington and Davis (1953) did not provide information on the severity of the anemia observed in rabbits exposed to sodium molybdate and ATSDR categorized this effect as a less serious LOAEL.*

ATSDR has revised the format of the toxicological profile and the negative findings have been deleted for most entries in the LSE tables (Tables 2-1 and 2-2) with the exception of the other noncancer effects since this category is broad and ATSDR considered it important to include which endpoint was examined.

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 17: This issue has been addressed adequately.

RESPONSE: *No response needed.*

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 18: Conclusions are appropriate and supported.

RESPONSE: *No response needed.*

COMMENT 19: Figure 2.2 (and others) is missing a key – species (R or M) is identified but its not clear from the key what the numbers relate to. Not clear why ocular studies are included in the summary of dermal studies.

RESPONSE: *The number is related to the figure key in Table 2-1. Text in Section 2.1 refers the reader to the User's Guide in Appendix D for a guide on interpreting the LSE tables and figures.*

It is ATSDR's practice to include ocular effects due to direct contact in the dermal LSE table.

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

Toxicokinetics

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

COMMENT 20: Adequate descriptions provided.

RESPONSE: *No response needed.*

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

COMMENT 21: Appears complete.

RESPONSE: *No response needed.*

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 22: Adequate discussion provided.

RESPONSE: *No response needed.*

Children and Other Populations that are Unusually Susceptible

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 23: Appears complete.

RESPONSE: *No response needed.*

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 24: Discussion adequate.

RESPONSE: *No response needed.*

Biomarkers of Exposure and Effect

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

COMMENT 25: Measured molybdenum in biological samples can be affected by copper in diet and tissues – thus it may not always be a specific marker (albeit the relationship is inverse)

RESPONSE: *ATSDR agrees with the Reviewer that copper content in the diet needs to be taken into consideration when examining the relationship between molybdenum levels in biological samples and exposure levels. ATSDR also notes that the specific molybdenum compound may also affect this relationship.*

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

COMMENT 26: Not applicable.

RESPONSE: *No response needed.*

Interactions with Other Chemicals

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 27: Adequately addressed.

RESPONSE: *No response needed.*

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 28: Consider additional mineral interactions – e.g., iron and manganese can also be affected as copper levels change in the diet or tissues.

RESPONSE: *The intent of Section 3.4 is to evaluate how exposure to other chemicals can interfere with the toxicity of molybdenum. ATSDR did not identify studies that evaluated how alterations in mineral levels (with the exception of copper) influences the toxicity of molybdenum.*

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 29: Appears complete.

RESPONSE: *No response needed.*

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

COMMENT 30: Yes, information on different chemical forms was provided.

RESPONSE: *No response needed.*

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 31: Appears complete.

RESPONSE: *No response needed.*

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 32: Discussion is appropriate and complete. Yes, this information is provided and is sound. Appears complete.

RESPONSE: *No response needed.*

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 33: Yes, this information is provided and is sound. I'm unaware of additional information that should be completed in the profile.

RESPONSE: *No response needed.*

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 34: Yes, this information is provided and is sound. Yes. Yes. Yes, this information is provided and is complete. No, I am not aware of additional information that should be included in the profile.

RESPONSE: *No response needed.*

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 35: Yes. I do agree. People with high dietary molybdenum intake (e.g., supplements).

RESPONSE: *A statement was added to the discussion of other populations that are unusually susceptible (Section 3.2):*

> Additionally, individuals with high dietary molybdenum intake, including individuals taking supplements containing high levels of molybdenum, may be at an increased risk from exposure to high levels of molybdenum in the environment.

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 26: I am not aware of additional relevant information.

RESPONSE: *No response needed.*

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

COMMENT 37: I agree – however, research is needed to improve our understanding of mechanism(s) of action – this is a data gap that could be identified in the profile.

RESPONSE: *A need for additional mechanistic studies was added to Section 6.2 (Health Effects):*

Mechanisms of Action. The mechanisms of molybdenum toxicity are poorly understood. Although there are data suggesting that molybdenum toxicity may be related to alterations in copper utilization, it is also likely that other mechanisms, such as oxidative damage, are also involved. Studies examining the mode of action are needed to support the identification of critical endpoints and derivation of MRLs.

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

COMMENT 38: No bias detected.

RESPONSE: *No response needed.*

Chapter 7. Regulations and Guidelines

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

COMMENT 39: I am not aware of other regulations or guidelines.

RESPONSE: *No response needed.*

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

COMMENT 40: No.

RESPONSE: *No response needed.*

Peer Review Comments on Unpublished Studies

All of the unpublished studies were considered acceptable by a majority of the peer reviewers and were added to the appropriate sections of the toxicological profile.

General Comment From Peer Reviewer #2

COMMENT: Since the 31 papers/documents we were asked to review have not been peer-reviewed, the only condition I approve their inclusion in the Profile is that they are made available to the general public. If this cannot be accomplished, the unpublished papers/documents should not be included in the profile. I believe the genral public should have the right to scrutinize them, and assess their scientific merit.

ATSDR RESPONSE: *The unpublished studies will be part the toxicological profile docket files.*

ATSDR Charge Questions Reviewer Comments and Responses

Allan S. 1996a. Ammonium dimolybdate skin sensitisation in the guinea-pig. London, England: International Molybdenum Association.

QUESTION: Did the study use an adequate number of animals and practice good animal care?

PEER REVIEWER #1 COMMENT: Yes

PEER REVIEWER #2 COMMENT: Yes

PEER REVIEWER #3 COMMENT: N= 20/dose group – animal care described well and species appropriate. GLP study. YES

QUESTION: Did the study account for competing causes of death?

PEER REVIEWER #1 COMMENT: Not Applicable

PEER REVIEWER #2 COMMENT: Yes. Not an issue in this study.

PEER REVIEWER #3 COMMENT: Not Applicable

QUESTION: Did the study include a sufficient number of dose groups, and sufficient magnitude of dose levels?

PEER REVIEWER #1 COMMENT: Sufficient animals were used. Only a single dose was used, based on preliminary study and was the maximal practical concentration possible.

PEER REVIEWER #2 COMMENT: Yes, in this case 20 controls and 20 treated animals, with a single dose.

PEER REVIEWER #3 COMMENT: Single doses per route (dermal and intradermal) – author claims used maximum concentrations. Adequate.

QUESTION: If you think the study was not adequately designed or reported, does that negate the utility of the study? Please explain.

PEER REVIEWER #1 COMMENT: Not Applicable

PEER REVIEWER #2 COMMENT: Adequately designed, but the study lacks statistical analysis.

PEER REVIEWER #3 COMMENT: Not Applicable

QUESTION: Do you agree with the conclusions of the author? If not, please explain.

PEER REVIEWER #1 COMMENT: Yes. It should be noted that only female animals were used.

ATSDR notes that the LSE table (Table 2-3) indicates that only females were examined.

PEER REVIEWER #2 COMMENT: I do.

PEER REVIEWER #3 COMMENT: Tabulated data provided – no photographs of lesions. Based on tabulated data I agree with the conclusions.

Allan S. 1996b. Molybdenum oxide (pure). Skin sensitisation in the guinea-pig. London, England: International Molybdenum Association.

QUESTION: Did the study use an adequate number of animals and practice good animal care?

PEER REVIEWER #1 COMMENT: Yes.

PEER REVIEWER #2 COMMENT: Yes.

PEER REVIEWER #3 COMMENT: **N**= 20/dose group – animal care described well and species appropriate. GLP study. YES

QUESTION: Did the study account for competing causes of death?

PEER REVIEWER #1 COMMENT: Not Applicable

PEER REVIEWER #2 COMMENT: Yes. Not an issue in this study.

PEER REVIEWER #3 COMMENT: Not applicable

QUESTION: Did the study include a sufficient number of dose groups, and sufficient magnitude of dose levels?

PEER REVIEWER #1 COMMENT: Sufficient animals were used. Only a single dose was used for each exposure condition. For the topical application it was the maximal practical concentration possible. For the intradermal application the concentration was the highest that did not produce necrosis at the injection sites.

PEER REVIEWER #2 COMMENT: Yes, in this case 20 controls and 20 treated animals, with a single dose.

PEER REVIEWER #3 COMMENT: Single doses per route (dermal and intradermal) – author claims used maximum concentrations. Adequate.

QUESTION: If you think the study was not adequately designed or reported, does that negate the utility of the study? Please explain.

PEER REVIEWER #1 COMMENT: Not. Applicable

PEER REVIEWER #2 COMMENT: Adequately designed, but the study lacks statistical analysis.

PEER REVIEWER #3 COMMENT: Not applicable

QUESTION: Do you agree with the conclusions of the author? If not, please explain.

PEER REVIEWER #1 COMMENT: Yes. It should be noted that only female animals were used.

ATSDR notes that the LSE table (Table 2-3) indicates that only females were examined.

PEER REVIEWER #2 COMMENT: Yes.

PEER REVIEWER #3 COMMENT: Tabulated data provided – no photographs of lesions. Based on tabulated data I agree with the conclusions (negative study).

Allan S. 1996c. Molybdenum oxide (technical). Skin sensitisation in the guinea-pig. London, England: International Molybdenum Association.

QUESTION: Did the study use an adequate number of animals and practice good animal care?

PEER REVIEWER #1 COMMENT: Yes.

PEER REVIEWER #2 COMMENT: Yes, in this case 20 controls and 20 treated animals, with a single dose.

PEER REVIEWER #3 COMMENT: N= 20/dose group – animal care described well and species appropriate. GLP study. YES

QUESTION: Did the study account for competing causes of death?

PEER REVIEWER #1 COMMENT: Not Applicable.

PEER REVIEWER #2 COMMENT: Yes. Not an issue in this study.

PEER REVIEWER #3 COMMENT: Not applicable.

QUESTION: Did the study include a sufficient number of dose groups, and sufficient magnitude of dose levels?

PEER REVIEWER #1 COMMENT: Sufficient animals were used. For the topical application a single dose, which was the maximal practical concentration possible, was used. For the intradermal application one concentration was used; which was highest concentraation that did not produce necrosis at the injection sites.

PEER REVIEWER #2 COMMENT: Yes.

PEER REVIEWER #3 COMMENT: Single doses per route (dermal and intradermal) – author claims used maximum concentrations. Adequate.

QUESTION: If you think the study was not adequately designed or reported, does that negate the utility of the study? Please explain.

PEER REVIEWER #1 COMMENT: Not Applicable.

PEER REVIEWER #2 COMMENT: Adequately designed, but the study lacks statistical analysis.

PEER REVIEWER #3 COMMENT: Not applicable.

QUESTION: Do you agree with the conclusions of the author? If not, please explain.

PEER REVIEWER #1 COMMENT: No The report states that the test site was stained gray and they could not assess irritation in any test animal in the topical exposure group. The conclusion that Molybdenum Oxide (Technical) did not produce evidence of skin sensitization is misleading. Intradermal injections did not induce skin sensitization, but not conclusion can be made regarding topical exposure. It should be noted that only female animals were used.

The gray stained skin prevented an evaluation of skin irritation after topical application, but did preclude an evaluation of skin sensitization. ATSDR reported that molybdenum oxide did not result in skin sensitization and did not include this study in Section 2.11 (Dermal Effects). The Agency also notes that the LSE table (Table 2-3) indicates that only females were examined.

PEER REVIEWER #2 COMMENT: Yes.

PEER REVIEWER #3 COMMENT: Tabulated data provided – no photographs of lesions. Based on tabulated data I agree with the conclusions (negative study).

Allan S. 1996d. Sodium molybdate 241/32. Skin sensitisation in the guinea-pig. London, England: International Molybdenum Association.

QUESTION: Did the study use an adequate number of animals and practice good animal care?

PEER REVIEWER #1 COMMENT: Yes.

PEER REVIEWER #2 COMMENT: Yes, in this case 20 controls and 20 treated animals, with a single dose.

PEER REVIEWER #3 COMMENT: N= 20/dose group – animal care described well and species appropriate. GLP study. YES

QUESTION: Did the study account for competing causes of death?

PEER REVIEWER #1 COMMENT: Not Applicable.

PEER REVIEWER #2 COMMENT: Yes. Not an issue in this study.

PEER REVIEWER #3 COMMENT: Not applicable.

QUESTION: Did the study include a sufficient number of dose groups, and sufficient magnitude of dose levels?

PEER REVIEWER #1 COMMENT: Sufficient animals were used. For the topical application a single dose, which was the maximal practical concentration possible was used. For the intradermal application one concentration was used; one of which was highest that did not produce necrosis at the injection sites.

PEER REVIEWER #2 COMMENT: Yes.

PEER REVIEWER #3 COMMENT: Single doses per route (dermal and intradermal) – author claims used maximum concentrations. Adequate.

QUESTION: If you think the study was not adequately designed or reported, does that negate the utility of the study? Please explain.

PEER REVIEWER #1 COMMENT: Not Applicable.

PEER REVIEWER #2 COMMENT: Adequately designed, but the study lacks statistical analysis.

PEER REVIEWER #3 COMMENT: Not applicable.

QUESTION: Do you agree with the conclusions of the author? If not, please explain.

PEER REVIEWER #1 COMMENT: Yes. It should be noted that only female animals were used.

ATSDR notes that the LSE table (Table 2-3) indicates that only females were examined.

PEER REVIEWER #2 COMMENT: Yes.

PEER REVIEWER #3 COMMENT: Tabulated data provided – no photographs of lesions. Based on tabulated data I agree with the conclusions (negative study).

Baldrick P, Healing G. 1990a. Acute dermal toxicity to rats of ammonium molybdate. London, England: International Molybdenum Association.

QUESTION: Did the study use an adequate number of animals and practice good animal care?

PEER REVIEWER #1 COMMENT: Yes

PEER REVIEWER #2 COMMENT: Yes.

PEER REVIEWER #3 COMMENT: N= 5/sex/dose group – animal care described well and species appropriate. GLP study. Yes – acute rat dermal lethality study.

QUESTION: Did the study account for competing causes of death?

PEER REVIEWER #1 COMMENT: Not Applicable.

PEER REVIEWER #2 COMMENT: Yes. Not an issue in this study.

PEER REVIEWER #3 COMMENT: Not applicable.

QUESTION: Did the study include a sufficient number of dose groups, and sufficient magnitude of dose levels?

PEER REVIEWER #1 COMMENT: Sufficient animals of both genders were used. A single topical dose was used, 2000 mg/kg. There was no justification for this dose. It is not a concern.

PEER REVIEWER #2 COMMENT: Yes. Single dose.

PEER REVIEWER #3 COMMENT: Single dose study (2 g/kg). Adequate.

QUESTION: If you think the study was not adequately designed or reported, does that negate the utility of the study? Please explain.

PEER REVIEWER #1 COMMENT: Not Applicable.

PEER REVIEWER #2 COMMENT: Adequately designed, but the study lacks statistical analysis.

PEER REVIEWER #3 COMMENT: Not applicable.

QUESTION: Do you agree with the conclusions of the author? If not, please explain.

PEER REVIEWER #1 COMMENT: Yes.

PEER REVIEWER #2 COMMENT: Yes. There should be an explanation also, or consideration, on the potential effects of several metals on the outcome, as noted, lead, arsenic, and mercury levels in the diet, to name a few are quite high.

ATSDR notes that the analysis of the diet (Appendix 3 of the study report) does not report the levels of arsenic or mercury; the lead level is reported as <0.01%. The study report does list the maximum allowable concentrations of a number of contaminants (Appendix 1 of the report), however, it does not state that the levels of lead, arsenic, and mercury exceeded the maximum allowable concentrations. The investigators noted that "batches of the diet conformed with the acceptable standards agreed by the Study Director and Quality Assurance HRC [Huntington Research Center] as detailed below."

PEER REVIEWER #3 COMMENT: Tabulated data provided. Based on tabulated data I agree with the conclusions (negative study).

Baldrick P, Healing G. 1990b. Acute dermal toxicity to rats of pure molybdic oxide. London, England: International Molybdenum Association.

QUESTION: Did the study use an adequate number of animals and practice good animal care?

PEER REVIEWER #1 COMMENT: Yes

PEER REVIEWER #2 COMMENT: Yes.

PEER REVIEWER #3 COMMENT: N= 5/sex/dose group – animal care described well and species appropriate. GLP study. Yes – acute rat dermal lethality study.

QUESTION: Did the study account for competing causes of death?

PEER REVIEWER #1 COMMENT: Not Applicable

PEER REVIEWER #2 COMMENT: Yes. Not an issue in this study.

PEER REVIEWER #3 COMMENT: Not applicable.

QUESTION: Did the study include a sufficient number of dose groups, and sufficient magnitude of dose levels?

PEER REVIEWER #1 COMMENT: Sufficient animals of both genders were used. A single topical dose was used, 2000 mg/kg. There was no justification for this dose. It is not a concern.

PEER REVIEWER #2 COMMENT: Yes. Single dose.

PEER REVIEWER #3 COMMENT: Single dose study (2 g/kg). Adequate.

QUESTION: If you think the study was not adequately designed or reported, does that negate the utility of the study? Please explain.

PEER REVIEWER #1 COMMENT: Not Applicable.

PEER REVIEWER #2 COMMENT: Adequately designed, but the study lacks statistical analysis.

PEER REVIEWER #3 COMMENT: Not applicable.

QUESTION: Do you agree with the conclusions of the author? If not, please explain.

PEER REVIEWER #1 COMMENT: Yes.

PEER REVIEWER #2 COMMENT: Yes. There should be an explanation also, or consideration, on the potential effects of several metals on the outcome, as noted, lead, arsenic, and mercury levels in the diet, to name a few are quite high.

ATSDR notes that the analysis of the diet (Appendix 3 of the study report) does not report the levels of arsenic or mercury; the lead level is reported as <0.01%. The study report does list the maximum allowable concentrations of a number of contaminants (Appendix 1 of the report), however, it does not state that the levels of lead, arsenic, and mercury exceeded the maximum allowable concentrations. The investigators noted that "batches of the diet conformed with the acceptable standards agreed by the Study Director and Quality Assurance HRC [Huntington Research Center] as detailed below."

PEER REVIEWER #3 COMMENT: Tabulated data provided. Based on tabulated data I agree with the conclusions (negative study).

Baldrick P, Healing G. 1990c. Acute dermal toxicity to rats of sodium molybdate. London, England: International Molybdenum Association.

QUESTION: Did the study use an adequate number of animals and practice good animal care?

PEER REVIEWER #1 COMMENT: Yes

PEER REVIEWER #2 COMMENT: Yes.

PEER REVIEWER #3 COMMENT: N= 5/sex/dose group – animal care described well and species appropriate. GLP study. Yes – acute rat dermal lethality study.

QUESTION: Did the study account for competing causes of death?

PEER REVIEWER #1 COMMENT: Not Applicable

PEER REVIEWER #2 COMMENT: Yes. Not an issue in this study.

PEER REVIEWER #3 COMMENT: Not applicable.

QUESTION: Did the study include a sufficient number of dose groups, and sufficient magnitude of dose levels?

PEER REVIEWER #1 COMMENT: Sufficient animals of both genders were used. A single topical dose was used, 2000 mg/kg. There was no justification for this dose. It is not a concern.

PEER REVIEWER #2 COMMENT: Yes. Single dose.

PEER REVIEWER #3 COMMENT: Single dose study (2 g/kg). Adequate.

QUESTION: If you think the study was not adequately designed or reported, does that negate the utility of the study? Please explain.

PEER REVIEWER #1 COMMENT: Not Applicable

PEER REVIEWER #2 COMMENT: Adequately designed, but the study lack statistical analysis.

PEER REVIEWER #3 COMMENT: Not applicable.

QUESTION: Do you agree with the conclusions of the author? If not, please explain.

PEER REVIEWER #1 COMMENT: Yes.

PEER REVIEWER #2 COMMENT: Yes. There should be an explanation also, or consideration, on the potential effects of several metals on the outcome, as noted, lead, arsenic, and mercury levels in the diet, to name a few are quite high.

ATSDR notes that the analysis of the diet (Appendix 3 of the study report) does not report the levels of arsenic or mercury; the lead level is reported as <0.01%. The study report does list the maximum allowable concentrations of a number of contaminants (Appendix 1 of the report), however, it does not state that the levels of lead, arsenic, and mercury exceeded the maximum allowable concentrations. The investigators noted that "batches of the diet conformed with the acceptable standards agreed by the Study Director and Quality Assurance HRC [Huntington Research Center] as detailed below."

PEER REVIEWER #3 COMMENT: Tabulated data provided. Based on tabulated data I agree with the conclusions (negative study).

Baldrick P, Healing G. 1990d. Acute dermal toxicity to rats of technical molybdic oxide. London, England: International Molybdenum Association.

QUESTION: Did the study use an adequate number of animals and practice good animal care?

PEER REVIEWER #1 COMMENT: Yes

PEER REVIEWER #2 COMMENT: Yes.

PEER REVIEWER #3 COMMENT: N= 5/sex/dose group – animal care described well and species appropriate. GLP study. Yes – acute rat dermal lethality study.

QUESTION: Did the study account for competing causes of death?

PEER REVIEWER #1 COMMENT: Not applicable

PEER REVIEWER #2 COMMENT: Yes. Not an issue for this study.

PEER REVIEWER #3 COMMENT: Not applicable.

QUESTION: Did the study include a sufficient number of dose groups, and sufficient magnitude of dose levels?

PEER REVIEWER #1 COMMENT: Sufficient animals of both genders were used. A single topical dose was used, 2000 mg/kg. There was no justification for this dose. It is not a concern.

PEER REVIEWER #2 COMMENT: Yes. Single dose.

PEER REVIEWER #3 COMMENT: Single dose study (2 g/kg). Adequate.

QUESTION: If you think the study was not adequately designed or reported, does that negate the utility of the study? Please explain.

PEER REVIEWER #1 COMMENT: Not applicable.

PEER REVIEWER #2 COMMENT: Adequately designed, but the study lacks statistical analysis

PEER REVIEWER #3 COMMENT: Not applicable.

QUESTION: Do you agree with the conclusions of the author? If not, please explain.

PEER REVIEWER #1 COMMENT: Yes.

PEER REVIEWER #2 COMMENT: Yes. There should be an explanation also, or consideration, on the potential effects of several metals on the outcome, as noted, lead, arsenic, and mercury levels in the diet, to name a few are quite high.

ATSDR notes that the analysis of the diet (Appendix 3 of the study report) does not report the levels of arsenic or mercury; the lead level is reported as <0.01%. The study report does list the maximum

allowable concentrations of a number of contaminants (Appendix 1 of the report), however, it does not state that the levels of lead, arsenic, and mercury exceeded the maximum allowable concentrations. The investigators noted that "batches of the diet conformed with the acceptable standards agreed by the Study Director and Quality Assurance HRC [Huntington Research Center] as detailed below."

PEER REVIEWER #3 COMMENT: Tabulated data provided. Based on tabulated data I agree with the conclusions (negative study).

Baldrick P, Healing G. 1990e. Acute oral toxicity to rats of ammonium molybdate. London, England: International Molybdenum Association.

QUESTION: Did the study use an adequate number of animals and practice good animal care?

PEER REVIEWER #1 COMMENT: Yes

PEER REVIEWER #2 COMMENT: Yes

PEER REVIEWER #3 COMMENT: N= 5/sex/dose group – animal care described well and species appropriate. GLP study. Yes – acute rat oral lethality study.

QUESTION: Did the study account for competing causes of death?

PEER REVIEWER #1 COMMENT: No competing causes of death were noted.

PEER REVIEWER #2 COMMENT: Yes. Not an issue in this study

PEER REVIEWER #3 COMMENT: Not applicable- lethality study – deaths seen at higher two doses

QUESTION: Did the study include a sufficient number of dose groups, and sufficient magnitude of dose levels?

PEER REVIEWER #1 COMMENT: Sufficient animals of both genders were used. Three oral doses were used: 3200, 4000 and 5000 mg/kg. These doses were based on a small preliminary study using a single 250 mg/kg dose. It is unclear how the preliminary study informed the main study.

PEER REVIEWER #2 COMMENT: Yes. Single dose.

ATSDR notes that Baldrick and Healing (1990e) is a multi-dose study.

PEER REVIEWER #3 COMMENT: Multiple doses used (3.2, 4.0, and 5.0 g/kg). Adequate.

QUESTION: If you think the study was not adequately designed or reported, does that negate the utility of the study? Please explain.

PEER REVIEWER #1 COMMENT: Not applicable

PEER REVIEWER #2 COMMENT: Adequately designed, but the study lacks statistical analysis.

PEER REVIEWER #3 COMMENT: Not applicable.

QUESTION: Do you agree with the conclusions of the author? If not, please explain.

PEER REVIEWER #1 COMMENT: Yes

PEER REVIEWER #2 COMMENT: Yes. There should be an explanation also, or consideration, on the potential effects of several metals on the outcome, as noted, lead, arsenic, and mercury levels in the diet, to name a few are quite high.

ATSDR notes that the analysis of the diet (Appendix 3 of the study report) does not report the levels of arsenic or mercury; the lead level is reported as <0.01%. The study report does list the maximum allowable concentrations of a number of contaminants (Appendix 1 of the report), however, it does not state that the levels of lead, arsenic, and mercury exceeded the maximum allowable concentrations. The investigators noted that "batches of the diet conformed with the acceptable standards agreed by the Study Director and Quality Assurance HRC [Huntington Research Center] as detailed below."

PEER REVIEWER #3 COMMENT: Tabulated data provided. Based on tabulated data I agree with the conclusions (positive study).

Baldrick P, Healing G. 1990f. Acute oral toxicity to rats of pure molybdic oxide. London, England: International Molybdenum Association.

QUESTION: Did the study use an adequate number of animals and practice good animal care?

PEER REVIEWER #1 COMMENT: Yes

PEER REVIEWER #2 COMMENT: Yes

PEER REVIEWER #3 COMMENT: N= 5/sex/dose group with some exceptions – animal care described well and species appropriate. GLP study. Yes – acute rat oral lethality study.

QUESTION: Did the study account for competing causes of death?

PEER REVIEWER #1 COMMENT: No competing causes of death were noted.

PEER REVIEWER #2 COMMENT: Yes. Not an issue in this study.

PEER REVIEWER #3 COMMENT: Not applicable- lethality study – deaths seen at higher two doses

QUESTION: Did the study include a sufficient number of dose groups, and sufficient magnitude of dose levels?

PEER REVIEWER #1 COMMENT: Sufficient animals of both genders were used. Five oral doses were used: 2000, 2500, 3200, 4000 and 5000 mg/kg. These doses were based on a small preliminary study using three doses 126, 500 and 2500 mg/kg.

PEER REVIEWER #2 COMMENT: Yes. Single dose

ATSDR notes that Baldrick and Healing (1990f) is a multidose study.

PEER REVIEWER #3 COMMENT: Multiple doses used (2.0, 2.5, 3.2, 4.0, and 5.0 g/kg). Adequate.

QUESTION: If you think the study was not adequately designed or reported, does that negate the utility of the study? Please explain.

PEER REVIEWER #1 COMMENT: Not Applicable.

PEER REVIEWER #2 COMMENT: Adequately designed, but the study lacks statistical analysis.

PEER REVIEWER #3 COMMENT: There are some dose groups where a single sex was evaluated. This does not negate the findings.

QUESTION: Do you agree with the conclusions of the author? If not, please explain.

PEER REVIEWER #1 COMMENT: Yes.

PEER REVIEWER #2 COMMENT: Yes. There should be an explanation also, or consideration, on the potential effects of several metals on the outcome, as noted, lead, arsenic, and mercury levels in the diet, to name a few are quite high.

ATSDR notes that the analysis of the diet (Appendix 3 of the study report) does not report the levels of arsenic or mercury; the lead level is reported as <0.01%. The study report does list the maximum allowable concentrations of a number of contaminants (Appendix 1 of the report), however, it does not state that the levels of lead, arsenic, and mercury exceeded the maximum allowable concentrations. The investigators noted that "batches of the diet conformed with the acceptable standards agreed by the Study Director and Quality Assurance HRC [Huntington Research Center] as detailed below."

PEER REVIEWER #3 COMMENT: Tabulated data provided. Based on tabulated data I agree with the conclusions (positive study).

Baldrick P, Healing G. 1990g. Acute oral toxicity to rats of sodium molybdate. London, England: International Molybdenum Association.

QUESTION: Did the study use an adequate number of animals and practice good animal care?

PEER REVIEWER #1 COMMENT: Yes

PEER REVIEWER #2 COMMENT: Yes

PEER REVIEWER #3 COMMENT: N= 5/sex/dose group – animal care described well and species appropriate. GLP study. Yes – acute rat oral lethality study.

QUESTION: Did the study account for competing causes of death?

PEER REVIEWER #1 COMMENT: No competing causes of death were noted

PEER REVIEWER #2 COMMENT: Yes. Not an issue in this study.

PEER REVIEWER #3 COMMENT: Not applicable- lethality study – deaths seen at higher two doses

QUESTION: Did the study include a sufficient number of dose groups, and sufficient magnitude of dose levels?

PEER REVIEWER #1 COMMENT: Sufficient animals of both genders were used. Three oral doses were used: 3200, 5000 and 6400 mg/kg. These doses were based on a small preliminary study using two doses: 250 and 1000 mg/kg.

PEER REVIEWER #2 COMMENT: Yes. Single dose.

ATSDR notes that Baldrick and Healing (1990g) is a multi-dose study.

PEER REVIEWER #3 COMMENT: Multiple doses used (3.2, 5.0, and 6.4 g/kg). Adequate.

QUESTION: If you think the study was not adequately designed or reported, does that negate the utility of the study? Please explain.

PEER REVIEWER #1 COMMENT: Not Applicable.

PEER REVIEWER #2 COMMENT: Adequately designed, but the study lacks statistical analysis.

PEER REVIEWER #3 COMMENT: No issues identified.

QUESTION: Do you agree with the conclusions of the author? If not, please explain.

PEER REVIEWER #1 COMMENT: No. It is unclear how a dose-response could be calculated for males since more animals died at the 3200 mg/kg dose than the 5000 mg/kg dose (3 vs. 1 respectively). I agree that Risk Phases R22, R25 and R28 are not appropriate for either gender.

PEER REVIEWER #2 COMMENT: Yes. There should be an explanation also, or consideration, on the potential effects of several metals on the outcome, as noted, lead, arsenic, and mercury levels in the diet, to name a few are quite high.

ATSDR notes that the analysis of the diet (Appendix 3 of the study report) does not report the levels of arsenic or mercury; the lead level is reported as <0.01%. The study report does list the maximum allowable concentrations of a number of contaminants (Appendix 1 of the report), however, it does not state that the levels of lead, arsenic, and mercury exceeded the maximum allowable concentrations. The

investigators noted that "batches of the diet conformed with the acceptable standards agreed by the Study Director and Quality Assurance HRC [Huntington Research Center] as detailed below."

PEER REVIEWER #3 COMMENT: Tabulated data provided. Based on tabulated data I agree with the conclusions (positive study).

Baldrick P, Healing G. 1990h. Acute oral toxicity to rats of technical molybdic oxide. London, England: International Molybdenum Association.

QUESTION: Did the study use an adequate number of animals and practice good animal care?

PEER REVIEWER #1 COMMENT: Yes

PEER REVIEWER #2 COMMENT: Yes

PEER REVIEWER #3 COMMENT: N= 5/sex/dose – animal care described well and species appropriate. GLP study. Yes – acute rat oral lethality study.

QUESTION: Did the study account for competing causes of death?

PEER REVIEWER #1 COMMENT: Not applicable

PEER REVIEWER #2 COMMENT: Yes. Not an issue for this study.

PEER REVIEWER #3 COMMENT: Not applicable- no deaths seen at 5 g/kg.

QUESTION: Did the study include a sufficient number of dose groups, and sufficient magnitude of dose levels?

PEER REVIEWER #1 COMMENT: Sufficient animals of both genders were used. A single oral dose was used: 5000 mg/kg. This dose was based on a small preliminary study using a single dose of 126 mg/kg. It is unclear how the preliminary study informed the main study.

PEER REVIEWER #2 COMMENT: Yes. Single dose.

PEER REVIEWER #3 COMMENT: Single dose used (5.0 g/kg). Adequate.

QUESTION: If you think the study was not adequately designed or reported, does that negate the utility of the study? Please explain.

PEER REVIEWER #1 COMMENT: Not Applicable.

PEER REVIEWER #2 COMMENT: Adequately designed, but the study lacks statistical analysis.

PEER REVIEWER #3 COMMENT: No issues identified.

QUESTION: Do you agree with the conclusions of the author? If not, please explain.

PEER REVIEWER #1 COMMENT: Yes.

PEER REVIEWER #2 COMMENT: Yes. There should be an explanation also, or consideration, on the potential effects of several metals on the outcome, as noted, lead, arsenic, and mercury levels in the diet, to name a few are quite high.

ATSDR notes that the analysis of the diet (Appendix 3 of the study report) does not report the levels of arsenic or mercury; the lead level is reported as <0.01%. The study report does list the maximum allowable concentrations of a number of contaminants (Appendix 1 of the report), however, it does not state that the levels of lead, arsenic, and mercury exceeded the maximum allowable concentrations. The investigators noted that "batches of the diet conformed with the acceptable standards agreed by the Study Director and Quality Assurance HRC [Huntington Research Center] as detailed below."

PEER REVIEWER #3 COMMENT: Tabulated data provided. Based on tabulated data I agree with the conclusions (negative study).

Beevers C. 2009. Reverse mutation in five histidine-requiring strains of Salmonella typhimurium. London, England: International Molybdenum Association.

QUESTION: Did the study use an adequate number of animals and practice good animal care?

PEER REVIEWER #1 COMMENT: Not applicable

PEER REVIEWER #2 COMMENT: Yes

PEER REVIEWER #3 COMMENT: Not applicable. *Salmonella typhimurium* reverse mutation assay with metabolic activation

QUESTION: Did the study account for competing causes of death?

PEER REVIEWER #1 COMMENT: Not applicable

PEER REVIEWER #2 COMMENT: Yes

PEER REVIEWER #3 COMMENT: Not applicable.

QUESTION: Did the study include a sufficient number of dose groups, and sufficient magnitude of dose levels?

PEER REVIEWER #1 COMMENT: Yes. Seven concentrations were tested (156 – 5000 µg/ml) based on a six concentrations range finder study. All tests were performed in triplicate for each of the five strains (technical replicates) The entire study was performed in duplicate (biological replicate).

PEER REVIEWER #2 COMMENT: Multiple dose, yes.

PEER REVIEWER #3 COMMENT: Adequate

QUESTION: If you think the study was not adequately designed or reported, does that negate the utility of the study? Please explain.

PEER REVIEWER #1 COMMENT: Not applicable

PEER REVIEWER #2 COMMENT: Adequately designed, but the study lacks statistical analysis.

ATSDR notes that the study includes statistical analysis. The investigator reported that Dunnett's test was used to compare the counts at each concentration with the control.

PEER REVIEWER #3 COMMENT: No issues identified.

QUESTION: Do you agree with the conclusions of the author? If not, please explain.

PEER REVIEWER #1 COMMENT: Yes

PEER REVIEWER #2 COMMENT: Yes.

PEER REVIEWER #3 COMMENT: Tabulated data provided. Based on tabulated data I agree with the conclusions (negative study).

Fox V. 2005. Sublimed undensified molybdenum trioxide: in vitro micronucleus assay in human lymphocytes. London, England: International Molybdenum Association.

QUESTION: Did the study use an adequate number of animals and practice good animal care?

PEER REVIEWER #1 COMMENT: Not applicable

PEER REVIEWER #2 COMMENT: Yes

PEER REVIEWER #3 COMMENT: Not applicable. Micronucleus assay with metabolic activation.

QUESTION: Did the study account for competing causes of death?

PEER REVIEWER #1 COMMENT: Not applicable

PEER REVIEWER #2 COMMENT: Yes

PEER REVIEWER #3 COMMENT: Not applicable

QUESTION: Did the study include a sufficient number of dose groups, and sufficient magnitude of dose levels?

PEER REVIEWER #1 COMMENT: Yes. Four concentrations were tested (100, 250, 1000 and 1439 μg/ml) in three experiments using three of four concentrations per experiment. The highest concentration

was the limit for the assay using the accepted testing protocol. The test chemical was measured in duplicate (technical replicates). The entire study was performed in once.

PEER REVIEWER #2 COMMENT: Multiple doses, yes

PEER REVIEWER #3 COMMENT: Adequate

QUESTION: If you think the study was not adequately designed or reported, does that negate the utility of the study? Please explain.

PEER REVIEWER #1 COMMENT: The study should have been repeated at least two more time, in order to obtain biological replicates. This may further resolve the random positive results.

PEER REVIEWER #2 COMMENT: Adequately designed, but the study lacks statistical analysis

ATSDR notes that the investigator reported that Fisher Exact Probability Test was used to evaluate the percentage of binucleate cells with micronuclei.

PEER REVIEWER #3 COMMENT: No issues identified.

QUESTION: Do you agree with the conclusions of the author? If not, please explain.

PEER REVIEWER #1 COMMENT: Yes, within the limited scope of the study.

PEER REVIEWER #2 COMMENT: Yes

PEER REVIEWER #3 COMMENT: Tabulated data provided. Based on tabulated data I agree with the conclusions (negative study).

Haferkorn J. 2010. Acute inhalation study of molybdenum trioxide in rats. London, England: International Molybdenum Association.

ATSDR notes that this study is the same as the Leuschner (2010) study and was deleted from the profile.

QUESTION: Did the study use an adequate number of animals and practice good animal care?

PEER REVIEWER #1 COMMENT: Yes

PEER REVIEWER #2 COMMENT: Yes

PEER REVIEWER #3 COMMENT: N= 3/sex/dose– animal care described well and species appropriate. GLP study. Yes – acute rat inhalation lethality study.

QUESTION: Did the study account for competing causes of death?

PEER REVIEWER #1 COMMENT: Not applicable

PEER REVIEWER #2 COMMENT: Yes

PEER REVIEWER #3 COMMENT: Not applicable no deaths seen.

QUESTION: Did the study include a sufficient number of dose groups, and sufficient magnitude of dose levels?

PEER REVIEWER #1 COMMENT: Three male and three female rats were tested at two sites (total six of each gender). A single dose was used: 5.05 or 5.00 mg/L air, respectively. The δ50 particle size was ~3.1 μm. This size will not penetrate into the deep lung.

PEER REVIEWER #2 COMMENT: Multiple doses, yes

ATSDR notes that this was a single concentration study.

PEER REVIEWER #3 COMMENT: Single concentration used (5 mg/L, 4 hr). Adequate

QUESTION: If you think the study was not adequately designed or reported, does that negate the utility of the study? Please explain.

PEER REVIEWER #1 COMMENT: Not applicable

PEER REVIEWER #2 COMMENT: Adequately designed, but the study lacks statistical analysis. Authors state that since there was no mortality, no statistical analysis was necessary, but it is not clear why other endpoints were not statistically evaluated.

PEER REVIEWER #3 COMMENT: No issues identified.

QUESTION: Do you agree with the conclusions of the author? If not, please explain.

PEER REVIEWER #1 COMMENT: Yes

PEER REVIEWER #2 COMMENT: Yes

PEER REVIEWER #3 COMMENT: Tabulated data provided. Based on tabulated data I agree with the conclusions (negative study).

Jackson GC, Hardy CJ, Rupanagudi SR, et al. 1991a. Ammonium dimolybdate. Acute inhalation toxicity study in rats. 4 hour exposure. London, England: International Molybdenum Association.

QUESTION: Did the study use an adequate number of animals and practice good animal care?

PEER REVIEWER #1 COMMENT: Yes

PEER REVIEWER #2 COMMENT: Yes

PEER REVIEWER #3 COMMENT: N= 5/sex/dose– animal care described well and species appropriate. GLP study. Yes – acute rat inhalation lethality study.

QUESTION: Did the study account for competing causes of death?

PEER REVIEWER #1 COMMENT: Not applicable

PEER REVIEWER #2 COMMENT: Yes. Not an issue in this study.

PEER REVIEWER #3 COMMENT: Not applicable no deaths seen.

QUESTION: Did the study include a sufficient number of dose groups, and sufficient magnitude of dose levels?

PEER REVIEWER #1 COMMENT: Sufficient animals of both genders were used. A single mean dose was used: 2.08±24% mg/l. This dose was the maximum that could be generated.

PEER REVIEWER #2 COMMENT: Yes. Single dose.

PEER REVIEWER #3 COMMENT: Single concentration used (2.1 mg/L; 4 hr). Adequate.

QUESTION: If you think the study was not adequately designed or reported, does that negate the utility of the study? Please explain.

PEER REVIEWER #1 COMMENT: There is one issue with the study. There is no indication that following dust exposure the animals were cleaned. Particles in/on the fur could be consumed during normal grooming. This does not negate the utility of the study

PEER REVIEWER #2 COMMENT: Adequately designed, but the study lacks statistical analysis.

PEER REVIEWER #3 COMMENT: No issues identified.

QUESTION: Do you agree with the conclusions of the author? If not, please explain.

PEER REVIEWER #1 COMMENT: Yes. It should be noted that the majority of the particles were > 1.55 μm and will not penetrate deep into the lung. They will remain in the nasal and extra-thoracic areas.

PEER REVIEWER #2 COMMENT: Yes.

PEER REVIEWER #3 COMMENT: Tabulated data provided. Based on tabulated data I agree with the conclusions (negative study).

Jackson GC, Hardy CJ, Suttie AW, et al. 1991b. Pure molybdic. Oxide acute inhalation toxicity study in rats. 4-hour Exposure. London, England: International Molybdenum Association.

QUESTION: Did the study use an adequate number of animals and practice good animal care?

PEER REVIEWER #1 COMMENT: Yes

PEER REVIEWER #2 COMMENT: Yes

PEER REVIEWER #3 COMMENT: N= 5/sex/dose– animal care described well and species appropriate. GLP study. Yes – acute rat inhalation lethality study.

QUESTION: Did the study account for competing causes of death?

PEER REVIEWER #1 COMMENT: Not applicable.

PEER REVIEWER #2 COMMENT: Yes. Not an issue in this study.

PEER REVIEWER #3 COMMENT: Not applicable no deaths seen.

QUESTION: Did the study include a sufficient number of dose groups, and sufficient magnitude of dose levels?

PEER REVIEWER #1 COMMENT: Sufficient animals of both genders were used. A single mean dose was used: 5.84±23% mg/l. This dose was the maximum required for testing.

PEER REVIEWER #2 COMMENT: Yes. Single dose.

PEER REVIEWER #3 COMMENT: Single concentration used (5.8 mg/L; 4 hr). Adequate.

QUESTION: If you think the study was not adequately designed or reported, does that negate the utility of the study? Please explain.

PEER REVIEWER #1 COMMENT: There is one issue with the study. There is no indication that following dust exposure the animals were cleaned. Particles in/on the fur could be consumed during normal grooming. This does not negate the utility of the study

PEER REVIEWER #2 COMMENT: Adequately designed, but the study lacks statistical analysis

PEER REVIEWER #3 COMMENT: No issues identified.

QUESTION: Do you agree with the conclusions of the author? If not, please explain.

PEER REVIEWER #1 COMMENT: Yes. It should be noted that the majority of the particles were > 1.55 μm and will not penetrate deep into the lung. They will remain in the nasal and extra-thoracic areas.

PEER REVIEWER #2 COMMENT: Yes

PEER REVIEWER #3 COMMENT: Tabulated data provided. Based on tabulated data I agree with the conclusions (negative study).

Jackson GC, Hardy CJ, Suttie AW, et al. 1991c. Sodium molybdate. Acute inhalation toxicity study in rats. 4-hour exposure. London, England: International Molybdenum Association.

QUESTION: Did the study use an adequate number of animals and practice good animal care?

PEER REVIEWER #1 COMMENT: Yes

PEER REVIEWER #2 COMMENT: Yes

PEER REVIEWER #3 COMMENT: N= 5/sex/dose– animal care described well and species appropriate. GLP study. Yes – acute rat inhalation lethality study.

QUESTION: Did the study account for competing causes of death?

PEER REVIEWER #1 COMMENT: Not applicable

PEER REVIEWER #2 COMMENT: Yes. Not an issue in this study.

PEER REVIEWER #3 COMMENT: Not applicable no deaths seen.

QUESTION: Did the study include a sufficient number of dose groups, and sufficient magnitude of dose levels?

PEER REVIEWER #1 COMMENT: Sufficient animals of both genders were used. A single mean dose was used: 1.93±8% mg/l. This concentration was the maximum that could be generated.

PEER REVIEWER #2 COMMENT: Yes. Single dose.

PEER REVIEWER #3 COMMENT: Single concentration used (1.9 mg/L; 4 hr). Adequate.

QUESTION: If you think the study was not adequately designed or reported, does that negate the utility of the study? Please explain.

PEER REVIEWER #1 COMMENT: There is one issue with the study. There is no indication that following dust exposure the animals were cleaned. Particles in/on the fur could be consumed during normal grooming. This does not negate the utility of the study

PEER REVIEWER #2 COMMENT: Adequately designed, but the study lacks statistical analysis.

PEER REVIEWER #3 COMMENT: No issues identified.

QUESTION: Do you agree with the conclusions of the author? If not, please explain.

PEER REVIEWER #1 COMMENT: Yes. It should be noted that the all of the particles were > 1.55 μm, with the majority >69% >3.5 μm, and will not penetrate deep into the lung. They will remain in the nasal and extra-thoracic areas.

PEER REVIEWER #2 COMMENT: Yes

PEER REVIEWER #3 COMMENT: Tabulated data provided. Based on tabulated data I agree with the conclusions (negative study).

Jackson GC, Hardy CJ, Suttie AW, et al. 1991d. Technical molybdenum oxide acute inhalation toxicity study in rats: 4-Hour exposure. London, England: International Molybdenum Association.

QUESTION: Did the study use an adequate number of animals and practice good animal care?

PEER REVIEWER #1 COMMENT: Yes

PEER REVIEWER #2 COMMENT: Yes

PEER REVIEWER #3 COMMENT: N= 5/sex/dose– animal care described well and species appropriate. GLP study. Yes – acute rat inhalation lethality study.

QUESTION: Did the study account for competing causes of death?

PEER REVIEWER #1 COMMENT: Not applicable.

PEER REVIEWER #2 COMMENT: Yes. Not an issue in this study.

PEER REVIEWER #3 COMMENT: Not applicable no deaths seen.

QUESTION: Did the study include a sufficient number of dose groups, and sufficient magnitude of dose levels?

PEER REVIEWER #1 COMMENT: Sufficient animals of both genders were used. A single mean dose was used: 3.92±40% mg/l. This concentration was the maximum that could be generated.

PEER REVIEWER #2 COMMENT: Yes. Single dose.

PEER REVIEWER #3 COMMENT: Single concentration used (3.9 mg/L; 4 hr). Adequate.

QUESTION: If you think the study was not adequately designed or reported, does that negate the utility of the study? Please explain.

PEER REVIEWER #1 COMMENT: There is one issue with the study. There is no indication that following dust exposure the animals were cleaned. Particles in/on the fur could be consumed during normal grooming. This does not negate the utility of the study

PEER REVIEWER #2 COMMENT: Adequately designed, but the study lacks statistical analysis

PEER REVIEWER #3 COMMENT: No issues identified.

QUESTION: Do you agree with the conclusions of the author? If not, please explain.

PEER REVIEWER #1 COMMENT: Yes. It should be noted that the majority of the particles were > 1.55 µm and will not penetrate deep into the lung. They will remain in the nasal and extra-thoracic areas. They will remain in the nasal and extra-thoracic areas.

PEER REVIEWER #2 COMMENT: Yes

PEER REVIEWER #3 COMMENT: Tabulated data provided. Based on tabulated data I agree with the conclusions (negative study).

Jones E. 2004. Sublimes undensified pure molybdenum trioxide: Bacterial mutation assay in S. typhimurium and E. coli. London, England: International Molybdenum Association.

QUESTION: Did the study use an adequate number of animals and practice good animal care?

PEER REVIEWER #1 COMMENT: Not applicable.

PEER REVIEWER #2 COMMENT: Yes

PEER REVIEWER #3 COMMENT: Not applicable. *Salmonella typhimurium* reverse mutation assay and *E coli* assay both with metabolic activation.

QUESTION: Did the study account for competing causes of death?

PEER REVIEWER #1 COMMENT: Not applicable.

PEER REVIEWER #2 COMMENT: Yes

PEER REVIEWER #3 COMMENT: Not applicable

QUESTION: Did the study include a sufficient number of dose groups, and sufficient magnitude of dose levels?

PEER REVIEWER #1 COMMENT: Yes. Five bacterial strains were tested at six concentrations: 100, 200, 500, 1000, 2500 and 5000µg/plate. The experiment was repeated twice (biological replicates) and there were three technical replicates per experiment.

PEER REVIEWER #2 COMMENT: Multiple doses, yes

PEER REVIEWER #3 COMMENT: Adequate

QUESTION: If you think the study was not adequately designed or reported, does that negate the utility of the study? Please explain.

PEER REVIEWER #1 COMMENT: Not applicable.

PEER REVIEWER #2 COMMENT: Adequately designed, but the study lacks statistical analysis

PEER REVIEWER #3 COMMENT: No issues identified.

QUESTION: Do you agree with the conclusions of the author? If not, please explain.

PEER REVIEWER #1 COMMENT: Yes

PEER REVIEWER #2 COMMENT: Yes

PEER REVIEWER #3 COMMENT: Tabulated data provided. Based on tabulated data I agree with the conclusions (negative study).

Leuschner PJ. 2010. Acute inhalation toxicity study of molybdenum trioxide in rats - According to EC Method B.2 and OECD Guideline 403. London, England: International Molybdenum Association.

Peer Reviewer #1 noted that this was the same study as Haferkorn (2010) and did not provide additional comments on the Leuschner (2010) paper. ATSDR agrees with the Reviewer that the two papers are the same. In the toxicological profile, the data from this study are cited to Leuschner (2010). ATSDR used the comments on the Haferkorn (2010) paper from Peer Reviewer #1 to evaluate this study.

QUESTION: Did the study use an adequate number of animals and practice good animal care?

PEER REVIEWER #2 COMMENT: Yes

PEER REVIEWER #3 COMMENT: N= 3/sex/dose– animal care described well and species appropriate. GLP study. Yes – acute rat inhalation lethality study.

QUESTION: Did the study account for competing causes of death?

PEER REVIEWER #2 COMMENT: Yes

PEER REVIEWER #3 COMMENT: Not applicable no deaths seen.

QUESTION: Did the study include a sufficient number of dose groups, and sufficient magnitude of dose levels?

PEER REVIEWER #2 COMMENT: Multiple doses, yes

ATSDR notes that Leuschner (2010) is a single concentration study.

PEER REVIEWER #3 COMMENT: Single concentration used (5.1 mg/L; 4 hr). Adequate.

QUESTION: If you think the study was not adequately designed or reported, does that negate the utility of the study? Please explain.

PEER REVIEWER #2 COMMENT: Adequately designed, but the study lacks statistical analysis. Authors state that since there was no mortality, no statistical analysis was necessary, but it is not clear why other endpoints were not statistically evaluated.

PEER REVIEWER #3 COMMENT: No issues identified

QUESTION: Do you agree with the conclusions of the author? If not, please explain.

PEER REVIEWER #2 COMMENT: Yes

PEER REVIEWER #3 COMMENT: Tabulated data provided. Based on tabulated data I agree with the conclusions (negative study).

Liggett MP, McRae LA. 1990b. Irritant effects on the rabbit eye of pure molybdic oxide. London, England: International Molybdenum Association.

QUESTION: Did the study use an adequate number of animals and practice good animal care?

PEER REVIEWER #1 COMMENT: Yes

PEER REVIEWER #2 COMMENT: Yes

PEER REVIEWER #3 COMMENT: N= 6/dose– animal care described well and species appropriate. GLP study. Yes – acute rabbit eye irritation study.

QUESTION: Did the study account for competing causes of death?

PEER REVIEWER #1 COMMENT: Not applicable

PEER REVIEWER #2 COMMENT: Yes. Not an issue in this study.

PEER REVIEWER #3 COMMENT: Not applicable no deaths seen.

QUESTION: Did the study include a sufficient number of dose groups, and sufficient magnitude of dose levels?

PEER REVIEWER #1 COMMENT: Sufficient animals were used, however; only males were tested. A single dose was used: 100 mg/eye (OECD Guidelines #405). There was no indication of the solvent used.

ATSDR notes that the LSE table (Table 2-3) indicates that only males were examined.

PEER REVIEWER #2 COMMENT: Yes. Single dose.

PEER REVIEWER #3 COMMENT: Single dose (100 mg) used. Adequate.

QUESTION: If you think the study was not adequately designed or reported, does that negate the utility of the study? Please explain.

PEER REVIEWER #1 COMMENT: Not applicable.

PEER REVIEWER #2 COMMENT: Adequately designed, but the study lacks statistical analysis.

PEER REVIEWER #3 COMMENT: No issues identified.

QUESTION: Do you agree with the conclusions of the author? If not, please explain.

PEER REVIEWER #1 COMMENT: Yes.

PEER REVIEWER #2 COMMENT: Yes

PEER REVIEWER #3 COMMENT: Tabulated data provided. Based on tabulated data I agree with the conclusions (negative study).

Liggett MP, McRae LA. 1990c. Irritant effects on the rabbit eye of sodium molybdate. London, England: International Molybdenum Association.

QUESTION: Did the study use an adequate number of animals and practice good animal care?

PEER REVIEWER #1 COMMENT: Yes

PEER REVIEWER #2 COMMENT: Yes

PEER REVIEWER #3 COMMENT: N= 6/dose– animal care described well and species appropriate. GLP study. Yes – acute rabbit eye irritation study.

QUESTION: Did the study account for competing causes of death?

PEER REVIEWER #1 COMMENT: Not applicable.

PEER REVIEWER #2 COMMENT: Yes. Not an issue in this study.

PEER REVIEWER #3 COMMENT: Not applicable no deaths seen.

QUESTION: Did the study include a sufficient number of dose groups, and sufficient magnitude of dose levels?

PEER REVIEWER #1 COMMENT: Sufficient animals were used, both gender four males and two females were tested. A single dose was used: 100 mg/eye (OECD Guidelines #405). There was no indication of the solvent used.

PEER REVIEWER #2 COMMENT: Yes. Single dose.

PEER REVIEWER #3 COMMENT: Single dose (100 mg) used. Adequate.

QUESTION: If you think the study was not adequately designed or reported, does that negate the utility of the study? Please explain.

PEER REVIEWER #1 COMMENT: Not applicable.

PEER REVIEWER #2 COMMENT: Adequately designed, but the study lacks statistical analysis

PEER REVIEWER #3 COMMENT: No issues identified.

QUESTION: Do you agree with the conclusions of the author? If not, please explain.

PEER REVIEWER #1 COMMENT: Yes.

PEER REVIEWER #2 COMMENT: Yes

PEER REVIEWER #3 COMMENT: Tabulated data provided. Based on tabulated data I agree with the conclusions (negative study).

Liggett MP, McRae LA. 1990d. Irritant effects on the rabbit eye of technical molybdic oxide. London, England: International Molybdenum Association.

QUESTION: Did the study use an adequate number of animals and practice good animal care?

PEER REVIEWER #1 COMMENT: Yes

PEER REVIEWER #2 COMMENT: Yes

PEER REVIEWER #3 COMMENT: N= 6/dose– animal care described well and species appropriate. GLP study. Yes – acute rabbit eye irritation study**.**

QUESTION: Did the study account for competing causes of death?

PEER REVIEWER #1 COMMENT: Not applicable

PEER REVIEWER #2 COMMENT: Yes. Not an issue in this study.

PEER REVIEWER #3 COMMENT: Not applicable no deaths seen.

QUESTION: Did the study include a sufficient number of dose groups, and sufficient magnitude of dose levels?

PEER REVIEWER #1 COMMENT: Sufficient animals were used, however; only males were tested. A single dose was used: 100 mg/eye (OECD Guidelines #405). There was no indication of the solvent used.

ATSDR notes that the use of males only is indicated in the LSE table (Table 2-3).

PEER REVIEWER #2 COMMENT: Yes. Single dose.

PEER REVIEWER #3 COMMENT: Single dose (100 mg) used. Adequate

QUESTION: If you think the study was not adequately designed or reported, does that negate the utility of the study? Please explain.

PEER REVIEWER #1 COMMENT: Not applicable

PEER REVIEWER #2 COMMENT: Adequately designed, but the study lacks statistical analysis

PEER REVIEWER #3 COMMENT: No issues identified.

QUESTION: Do you agree with the conclusions of the author? If not, please explain.

PEER REVIEWER #1 COMMENT: Yes

PEER REVIEWER #2 COMMENT: Yes

PEER REVIEWER #3 COMMENT: Tabulated data provided. Based on tabulated data I agree with the conclusions (negative study).

Liggett MP, McRae LA. 1990e. Irritant effects on rabbit skin of ammonium molybdate. London, England: International Molybdenum Association.

QUESTION: Did the study use an adequate number of animals and practice good animal care?

PEER REVIEWER #1 COMMENT: Yes

PEER REVIEWER #2 COMMENT: Yes

PEER REVIEWER #3 COMMENT: N= 6/dose– animal care described well and species appropriate. GLP study. Yes – acute rabbit acute dermal toxicity study.

QUESTION: Did the study account for competing causes of death?

PEER REVIEWER #1 COMMENT: Not applicable.

PEER REVIEWER #2 COMMENT: Not an issue in this study.

PEER REVIEWER #3 COMMENT: Not applicable no deaths seen.

QUESTION: Did the study include a sufficient number of dose groups, and sufficient magnitude of dose levels?

PEER REVIEWER #1 COMMENT: Sufficient animals were used, however; only females were tested. A single dose was used: 0.5g as per OECD Guideline #404.

ATSDR notes that the LSE table (Table 2-3) indicates that only females were tested.

PEER REVIEWER #2 COMMENT: Yes. Single dose.

PEER REVIEWER #3 COMMENT: Single dose (500 mg) used. Adequate.

QUESTION: If you think the study was not adequately designed or reported, does that negate the utility of the study? Please explain.

PEER REVIEWER #1 COMMENT: Not applicable

PEER REVIEWER #2 COMMENT: Adequately designed, but the study lacks statistical analysis.

PEER REVIEWER #3 COMMENT: No issues identified.

QUESTION: Do you agree with the conclusions of the author? If not, please explain.

PEER REVIEWER #1 COMMENT: Yes

PEER REVIEWER #2 COMMENT: Yes

PEER REVIEWER #3 COMMENT: Tabulated data provided. Based on tabulated data I agree with the conclusions (negative study).

Liggett MP, McRae LA. 1990f. Irritant effects on rabbit skin of pure molybdic oxide. London, England: International Molybdenum Association.

QUESTION: Did the study use an adequate number of animals and practice good animal care?

PEER REVIEWER #1 COMMENT: Yes

PEER REVIEWER #2 COMMENT: Yes

PEER REVIEWER #3 COMMENT: N= 6/dose– animal care described well and species appropriate. GLP study. Yes – acute rabbit acute dermal toxicity study.

QUESTION: Did the study account for competing causes of death?

PEER REVIEWER #1 COMMENT: Not applicable

PEER REVIEWER #2 COMMENT: Yes. Not an issue in this study.

PEER REVIEWER #3 COMMENT: Not applicable no deaths seen.

QUESTION: Did the study include a sufficient number of dose groups, and sufficient magnitude of dose levels?

PEER REVIEWER #1 COMMENT: Sufficient animals were used, however; only females were tested. A single dose was used: 0.5 g as per OECD Guideline #404.

ATSDR notes that the LSE table (Table 2-3) indicates that only females were tested.

PEER REVIEWER #2 COMMENT: Yes. Single dose.

PEER REVIEWER #3 COMMENT: Single dose (500 mg) used. Adequate.

QUESTION: If you think the study was not adequately designed or reported, does that negate the utility of the study? Please explain.

PEER REVIEWER #1 COMMENT: Not applicable

PEER REVIEWER #2 COMMENT: Adequately designed, but the study lacks statistical analysis.

PEER REVIEWER #3 COMMENT: No issues identified.

QUESTION: Do you agree with the conclusions of the author? If not, please explain.

PEER REVIEWER #1 COMMENT: Yes

PEER REVIEWER #2 COMMENT: Yes

PEER REVIEWER #3 COMMENT: Tabulated data provided. Based on tabulated data I agree with the conclusions (negative study).

Liggett MP, McRae LA. 1990g. Irritant effects on rabbit skin of sodium molybdate. London, England: International Molybdenum Association.

QUESTION: Did the study use an adequate number of animals and practice good animal care?

PEER REVIEWER #1 COMMENT: Yes

PEER REVIEWER #2 COMMENT: Yes

PEER REVIEWER #3 COMMENT: N= 6/dose– animal care described well and species appropriate. GLP study. Yes – acute rabbit acute dermal toxicity study.

QUESTION: Did the study account for competing causes of death?

PEER REVIEWER #1 COMMENT: Not applicable.

PEER REVIEWER #2 COMMENT: Yes. Not an issue in this study.

PEER REVIEWER #3 COMMENT: Not applicable no deaths seen.

QUESTION: Did the study include a sufficient number of dose groups, and sufficient magnitude of dose levels?

PEER REVIEWER #1 COMMENT: Sufficient animals were used, however; only females were tested. A single dose was used: 0.5 g as per OECD Guideline #404.

ATSDR notes that the LSE table (Table 2-3) indicates that only females were tested.

PEER REVIEWER #2 COMMENT: Yes. Single dose.

PEER REVIEWER #3 COMMENT: Single dose (500 mg) used. Adequate.

QUESTION: If you think the study was not adequately designed or reported, does that negate the utility of the study? Please explain.

PEER REVIEWER #1 COMMENT: Not applicable.

PEER REVIEWER #2 COMMENT: Adequately designed, but the study lacks statistical analysis.

PEER REVIEWER #3 COMMENT: No issues identified.

QUESTION: Do you agree with the conclusions of the author? If not, please explain.

PEER REVIEWER #1 COMMENT: Yes.

PEER REVIEWER #2 COMMENT: Yes.

PEER REVIEWER #3 COMMENT: Tabulated data provided. Based on tabulated data I agree with the conclusions (negative study).

Lloyds M. 2009. Mutation at the thymidine kinase (tk) locus of mouse lymphoma L5178Y cells (MLA) using the Microtitre fluctuation technique. London, England: International Molybdenum Association.

QUESTION: Did the study use an adequate number of animals and practice good animal care?

PEER REVIEWER #1 COMMENT: Not applicable

PEER REVIEWER #2 COMMENT: Yes

PEER REVIEWER #3 COMMENT: Mouse lymphoma TK assay (MLA) with activation.

QUESTION: Did the study account for competing causes of death?

PEER REVIEWER #1 COMMENT: Not applicable

PEER REVIEWER #2 COMMENT: Yes

PEER REVIEWER #3 COMMENT: Not applicable

QUESTION: Did the study include a sufficient number of dose groups, and sufficient magnitude of dose levels?

PEER REVIEWER #1 COMMENT: Yes. A cytotoxicity Range-Finder Experiment, was performed using six test concentrations; 0, 64.38, 128.8, 257.8, 515, 1030 and 2060 μg/ml. 2060 μg/ml is the solubility limit in culture medium. Two mutation assay experiments were performed (biological replicates) using concentrations 200-2060 μg/ml

PEER REVIEWER #2 COMMENT: Multiple doses, yes

PEER REVIEWER #3 COMMENT: Adequate – multiple exposure concentrations.

QUESTION: If you think the study was not adequately designed or reported, does that negate the utility of the study? Please explain.

PEER REVIEWER #1 COMMENT: Not applicable

PEER REVIEWER #2 COMMENT: Adequately designed, but the study lacks statistical analysis.

PEER REVIEWER #3 COMMENT: No issues identified.

QUESTION: Do you agree with the conclusions of the author? If not, please explain.

PEER REVIEWER #1 COMMENT: Yes

PEER REVIEWER #2 COMMENT: Yes

PEER REVIEWER #3 COMMENT: Tabulated data provided. Based on tabulated data I agree with the conclusions (negative study).

Roper C. 2008. The in-vitro percutaneous absorption of molybdenum through human skin. London, England: International Molybdenum Association.

QUESTION: Did the study use an adequate number of animals and practice good animal care?

PEER REVIEWER #1 COMMENT: Not applicable.

PEER REVIEWER #2 COMMENT: Yes

PEER REVIEWER #3 COMMENT: In vitro human skin study (dermal absorption).

QUESTION: Did the study account for competing causes of death?

PEER REVIEWER #1 COMMENT: Not applicable.

PEER REVIEWER #2 COMMENT: Yes. Not an issue in this study.

PEER REVIEWER #3 COMMENT: Not applicable

QUESTION: Did the study include a sufficient number of dose groups, and sufficient magnitude of dose levels?

PEER REVIEWER #1 COMMENT: Yes. Two doses were tested in two separate experiments: 10.51 mg/ml and 54.20mg/ml; ca 100 and 500 μg/cm2, respectively. Twelve skin samples from four donors were dosed, with eight analyzed (biological replicates)

PEER REVIEWER #2 COMMENT: Yes. Two application rates.

PEER REVIEWER #3 COMMENT: Adequate – multiple exposure concentrations.

QUESTION: If you think the study was not adequately designed or reported, does that negate the utility of the study? Please explain.

PEER REVIEWER #1 COMMENT: The report uses the term "application rate" but the units are mg/cm2. Since there is no time component, it is unclear why "rate" is used. This does not negate the utility of the study.

PEER REVIEWER #2 COMMENT: Adequately designed, but the study lacks statistical analysis.

PEER REVIEWER #3 COMMENT: No issues identified.

QUESTION: Do you agree with the conclusions of the author? If not, please explain.

PEER REVIEWER #1 COMMENT: Yes

PEER REVIEWER #2 COMMENT: Yes

PEER REVIEWER #3 COMMENT: Tabulated data provided. Based on tabulated data I agree with the conclusions (in vitro pharmacokinetic study).

Taylor H. 2009. Induction of micronuclei in cultured human peripheral blood lymphocytes. London, England: International Molybdenum Association.

QUESTION: Did the study use an adequate number of animals and practice good animal care?

PEER REVIEWER #1 COMMENT: Not applicable.

PEER REVIEWER #2 COMMENT: Yes

PEER REVIEWER #3 COMMENT: Human peripheral blood lymphocyte micronuclei assay with activation.

QUESTION: Did the study account for competing causes of death?

PEER REVIEWER #1 COMMENT: Not applicable

PEER REVIEWER #2 COMMENT: Yes

PEER REVIEWER #3 COMMENT: Not applicable.

QUESTION: Did the study include a sufficient number of dose groups, and sufficient magnitude of dose levels?

PEER REVIEWER #1 COMMENT: Yes. Six concentrations were tested (340.4 – 2060 μg/ml) based on a 12 concentrations range finder study. The highest concentration is the maximum recommended using the accepted testing protocol. The test chemical was measured in duplicate (technical replicates). The entire study was performed in once.

PEER REVIEWER #2 COMMENT: Multiple doses, yes.

PEER REVIEWER #3 COMMENT: Adequate – multiple concentrations.

QUESTION: If you think the study was not adequately designed or reported, does that negate the utility of the study? Please explain.

PEER REVIEWER #1 COMMENT: The study should have been repeated at least two more time, in order to obtain biological replicates and the statically significant changes.

ATSDR notes that the study design was consistent with OECD guidelines for in vitro *mammalian cell micronucleus test (OECD Test #487) in that three concentrations were tested with replicate cultures.*

PEER REVIEWER #2 COMMENT: Adequately designed, but the study lacks statistical analysis.

PEER REVIEWER #3 COMMENT: No issues identified.

QUESTION: Do you agree with the conclusions of the author? If not, please explain.

PEER REVIEWER #1 COMMENT: Yes, within the limited scope of the study.

PEER REVIEWER #2 COMMENT: Yes.

PEER REVIEWER #3 COMMENT: Tabulated data provided. Based on tabulated data I agree with the conclusions (negative study).