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

November 2016

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

John Meeker, Sc.D., C.I.H.
Professor, Environmental Health Sciences
Associate Dean for Research, School of Public Health
University of Michigan
Ann Arbor, Michigan

Alexander V Lyubimov, M.D., Ph.D., D.A.B.T.
Toxicology Research Laboratory
Chicago, Illinois

Dagobert Heijerick
ARCHE consulting
Gent, Belgium

Comments provided by Peer Reviewer #1

General Comments

COMMENT 1: This is a well-written toxicological profile where the authors did a good job of covering the available literature and fitting it to the Tox Profile format. Overall it is my opinion that in the document as a whole, with some minor exceptions (see below in "specific comments"), the literature was categorized correctly, adequately described, well-formed into layman terms, and data needs were identified. The questions outlined in the "Guidelines for Peer Reviewers" were appropriately and adequately addressed aside for a few exceptions listed below in this document.

RESPONSE 1: *No revisions were suggested.*

COMMENT 2: In the Public Health Statement, there is no mention of human studies on reproduction, and the animal data on reproduction seems to be minimized in this section. Also some mention of nutrition supplements containing molybdenum may be important to include.

RESPONSE 2: *The intent of this section (How Can Molybdenum Affect Your Health) is to provide a list of primary health effects that may occur following exposure to molybdenum; none of the health effects are discussed in detail; the Reader is referred to Chapter 3 for more information on health effects. A statement was added that you may be exposed to molybdenum in some nutritional supplements.*

Specific Comments

COMMENT 1 (Section 3.2, Health Effects): The Meeker et al. (2008) study of semen quality also showed evidence for an interaction between molybdenum and copper, where the odds of below reference semen quality parameters were much greater in relation to Mo among men with low (below median) levels of copper in blood samples.

RESPONSE 1: *This possible interaction between molybdenum and copper found in Meeker et al. (2008) was added to Section 3.10 Interactions with Other Chemicals.*

COMMENT 2 (Section 3.2, Health Effects): Section 3, Health Effects: There is another paper showing no association between Mo and TSH among men in the Michigan study, but a significant inverse relationship between Mo and Prolactin: Meeker JD, Rossano MG, Protas B, et al. 2009. Multiple metals predict prolactin and thyrotropin (TSH) levels in men. Environ Res 109(7): 869-873.

RESPONSE 2: *The Meeker et al. (2009) study was added to Section 3.2.2.2 (Endocrine Effects).*

COMMENT 3 (Section 3.2, Health Effects): A recent human study of Mo and Testosterone among men in NHANES also found evidence for an inverse relationship: Lewis RC, Meeker JD. 2015. Biomarkers of exposure to molybdenum and other metals in relation to testosterone among men from the United States National Health and Nutrition Examination Survey 2011-2012. Fertil Steril 193:172-178.

RESPONSE 3: *The Lewis and Meeker (2015) study was added Section 3.2.2.5.*

COMMENT 4 (Section 6, Human Exposures and Public Health Statement): For "other media" as well as the discussion of food as the primary source of Mo exposure for the general population, it seems as though at least mention of vitamin/mineral supplements that may contain high levels of molybdenum. For example: Momcilovic B. 1999. A case report of acute human molybdenum toxicity from a dietary molybdenum supplement—a: new member of the "Lucor metallicum" family. Arch Hig Rada Toksikol 50:289-297.

RESPONSE 4: *The Momcilovic (1999) study suggested by the Reviewer, as well as data from another source, were added to Section 6.5 to address vitamin and mineral supplement concentrations and exposure. Section 6.4.4 addresses levels monitored in "other environmental media." The concentrations in food in this section refer to natural food sources (e.g., plants and grains). Since vitamins and supplements are not naturally found in the environment, this information was not added to this section.*

COMMENT 5 (Section 6, Occupation Exposure): Mining is mentioned, but what about metal work, such as steel production, stainless steel welding, etc.? Example: Kucera J, Bencko V, Papavova A. 2000. Monitoring of occupational exposure in manufacturing of stainless steel constructions, Part I: chromium, iron, manganese, molybdenum, nickel, and vanadium in the workplace air of stainless steel welders. Cent Eur J Public Health 9:171-175.

RESPONSE 5: *The Kucera et al. (2000) study suggested by the Reviewer was added to Sections 6.5 and 6.7 to address exposure via metal work.*

Annotated Comments

COMMENT 1 (Page 29, line 30): The reviewer questioned whether the sentence was referring to humans.

RESPONSE 1: *ATSDR believes that it is implied that general population is humans.*

COMMENT 2 (page 30, line 2): "Old study, anything more recent?"

RESPONSE 2: *The more recent Biego et al. (1998) study was added as a reference.*

COMMENT 3 (page 31, line 22): The Reviewer questioned whether this should be copper rather than molybdenum.

RESPONSE: *The statement was corrected to indicate adequate copper intake.*

COMMENT 4 (page 31, line 34): The Reviewer noted that there is a paper showing Mo related to lower testosterone in men from NHANES (Lewis and Meeker 2015, Fertility and Sterility). There is also a paper (Meeker et al. 2009, Environmental Research) showing no association between Mo and TSH among men in the Michigan study, but a significant inverse relationship between Mo and Prolactin.

RESPONSE 4: *The Lewis and Meeker (2015) study was added to the discussion of reproductive effects; the Meeker et al. (2009) study was included in Chapter 3 in the discussion of endocrine effects.*

COMMENT 5 (page 32, line 4): The Reviewer noted that Meeker et al. (2008) also looked at interaction with low copper.

RESPONSE 5: *The discussion of the interaction between molybdenum and copper was added to the interaction section of Chapter 3.*

COMMENT 6 (page 41, line 25): The Reviewer comments "Median, but are individuals on the low end of the distribution at risk of being copper deficient? What about children?"

RESPONSE 6: *Based on the third National Health and Nutrition Examination Survey (NHANES III), the mean copper intake in adults is 1.30 mg/day; the 5^{th} and 10^{th} percentiles are 0.72 and 0.82 mg/day, respectively. As discussed in the National Academy of Sciences (NAS 2001), a study of men fed 0.79 mg/day copper for 42 days did not have alterations in indices of copper status. Thus, it is reasonable to assume that copper deficiency is not an issue for most of the U.S. adult population. The mean (5^{th} and 10^{th} percentiles) copper intakes for children 1–3 and 4–8 years old are 0.74 mg/day (0.30 and 0.40 mg/day) and 0.97 mg/day (0.70 and 0.75 mg/day), respectively. The Recommended Daily Allowances (RDAs) are 0.34 and 0.44 mg/day for these two age groups. Given the unlikelihood that the general population is copper deficient, ATSDR believes that it is reasonable to question the relevance of animal studies utilizing copper-deficient studies.*

COMMENT 7 (page 47, line 34): The Reviewer suggested adding studies looking at testosterone or thyroid hormones to the discussion of endocrine effects in Section 3.2.2.2.

RESPONSE 7: *The Meeker et al. (2009) study examining prolactin and thyroid stimulating hormone was added to this section.*

COMMENT 8 (page 48, line 9): The Reviewer questioned whether this was an appropriate assumption that the copper intake was low based on the severe decrease in body weight, hematological parameters, and increased mortality.

RESPONSE 8: *Given that these effects and mortality were also observed at 59 mg molybdenum/kg/day, it seems reasonable to assume that the copper content of the diet was low. These severe effects have not been observed in other studies in which the copper content of the diet was sufficient.*

COMMENT 9 (page 51, line 19): The Reviewer noted that there was a double negative.

RESPONSE 9: *This has been corrected.*

COMMENT 10 (page 51, line 33): The Reviewer commented that Meeker et al. 2008 study also showed evidence for interaction between high molybdenum and low copper.

RESPONSE 10: *The interaction between high molybdenum and low copper discussed in the Meeker et al. (2008) study was added to Interactions with Other Chemicals section (Section 3.10).*

COMMENT 11 (page 63, line 6): The Reviewer commented that is would be useful to present blood concentrations corresponding to those exposure levels.

RESPONSE 11: *The blood molybdenum levels were added to the profile.*

COMMENT 12 (page 63, line 16): The Reviewer asked "what about urine excretion?"

RESPONSE 12: *Urinary excretion would not be included because this would represent absorbed molybdenum, whereas the fecal excretion was unabsorbed molybdenum.*

COMMENT 13 (page 65, line 13): The Reviewer asked how long after exposure did the tissue levels decrease.

RESPONSE 13: *The text was revised to indicate that tissue levels were monitored in a 2-week postexposure period.*

COMMENT 14 (page 78, line 27): The Reviewer suggested adding a statement about why ruminant data was excluded in case someone does not read all the previous sections.

RESPONSE 14: *A note was added to see Section 3.5.2.*

COMMENT 15 (page 88, line 18): The Reviewer asked what type of human study would qualify for this section, "not semen quality or testosterone?"

RESPONSE 15: *This statement is referring to studies that provide evidence that molybdenum mimics androgens or thyroid hormones or interferes with endogenous hormones. On their own, studies examining testosterone levels in humans would not be sufficient to determine whether molybdenum acts as an endocrine disruptor since there can be numerous mechanisms that could alter testosterone levels.*

COMMENT 16 (page 92, line 33): The Reviewer noted that it might be useful to report additional values in the distribution, such as 95^{th} percentile.

RESPONSE 16: *This information is provided in Section 6.5; a statement was added referring the Reader to this section for additional information.*

COMMENT 17 (page 93, line 6): The Reviewer noted that the last sentence of the paragraph does not make sense.

RESPONSE 17: *The sentence was revised.*

COMMENT 18 (page 103, lines 22-25): The Reviewer asked "how do you know about the IMOA study?"

RESPONSE 18: *This information was provided to ATSDR by IMOA.*

COMMENT 19 (page 136, line 1): The Reviewer noted that some vitamin/mineral supplements may also contain high levels of Mo.

RESPONSE 19: *The Momcilovic (1999) study suggested by the Reviewer was added to Section 6.5 to address vitamin and mineral supplement concentrations and exposure. Section 6.4.4 addresses levels monitored in "other environmental media." The concentrations in food in this section refer to natural food sources (e.g., plants and grains). Since vitamins and supplements are not naturally found in the environment, this information was not added to this section.*

COMMENT 20 (page 144, line 20): The Reviewer questioned "what about metal work, such as steel production, stainless steel welding, etc?"

RESPONSE 20: *The Kucera et al. (2000) study suggested by the Reviewer was added to Sections 6.5 and 6.7 to address exposure via metal work.*

COMMENT 21 (page 145, line 33): The Reviewer noted that nutritional supplements could add a lot to body burden.

RESPONSE 21: *The text was revised to include the exposure to the general population from vitamins and nutritional supplements.*

COMMENT 22 (page 146, line 25): The Reviewer noted that the NHANESIII was quite a while ago, it now runs in 2-year cycles and that they measure Mo in urine and not blood.

RESPONSE 22: *The text was revised to delete the reference to NHANES III and to correct blood to urine.*

Comments provided by Peer Reviewer #2:

General Comments

COMMENT 1: The Reviewer noted that there are no unpublished studies included in the profile and suggested that there was an advantage for using two studies published as abstracts in Teratology and Birth Defects as they may significantly increase the weight of evidence about potential teratology effect of tetrathiomolybdate. The Reviewer noted that the birth defects in rabbit legs were remarkably similar with muscular skeletal findings in Arrington and Davis (1953).

> Lyubimov AV, Merceica MD, Tomaszewski JE, et al. The developmental toxicity of tetrathiomolybdate (TTM, NSC-714598) and protective effect of copper in rats.
>
> Lyubimov AV, Mercieca MD, Smith AC, et al. Oral developmental toxicity study of ammonium tetrathiomolybdate (NSC-714598) in rabbits.

RESPONSE 1: *The information from these abstracts was added to the profile.*

COMMENT 2: The Reviewer suggested that the following paper may be beneficial to be included in Section 3.2.2.4:

> Armstrong C, Leong W, Lees GJ. 2001. Comparative effects of metal chelating agents on the neuronal cytotoxicity induced by copper (Cu+2), iron (Fe+3) and zinc in the hippocampus. Brain Res 18:51-62.

RESPONSE 2: *Section 3.2.2.4 discusses neurological effects following oral exposure; the route of exposure in the Armstrong et al. (2001) study was intrahippocampal injection. The relevance of this study assessing the potential neurotoxicity of molybdenum following inhalation, oral, or dermal exposure (environmentally routes of exposure) is not known. Additionally, it is noted that intermediate- and chronic-duration inhalation (NTP 1997) and oral (Murray et al. 2013) studies did not find histological alterations in the brain of rats or mice.*

Annotated Comments

The Reviewer made several editorial suggestions to the profile; unless otherwise noted, the suggested revisions were made.

COMMENT 1 (page 23, line 8): The Reviewer questioned whether there is a known molybdenum intake deficit and how this would affect health.

RESPONSE 1: *As noted by NAS (2001), molybdenum deficiency has not been observed in healthy individuals. Only one case of molybdenum deficiency resulting from dietary inadequacy has been identified in a man on total parenteral nutrition for 18 months.*

COMMENT 2 (page 23, line 16): The Reviewer asked what molybdenum concentrations resulted in lung cancer in rats and mice.

RESPONSE 2: *An increase in lung tumors was observed in mice exposed to ≥6.7 mg molybdenum/m^3; the increase in lung tumors in rats did not exceed historical controls and the reference to rats was deleted.*

COMMENT 3 (page 27, line 21): The Reviewer asked the source of the statement that molybdenum levels as high as 500 µg/L have been detected and also asked where and when this occurred and what populations were exposed. The Reviewer also noted that this is a potentially harmful concentration.

RESPONSE 3: *The text was revised with updated references and more detail as to the circumstances surrounding the measured molybdenum levels. A statement referring to the health-based screening-level concentration for molybdenum in water was also added.*

COMMENT 4 (page 29, lines 30-31): The Reviewer suggested adding the statement "in 4 men dosed with high and low molybdenum diet" to clarify that this is a human experimental study rather than an animal study.

RESPONSE 4: *The text was revised in indicate that the Deosthale and Gopalan (1974) study was conducted in men.*

COMMENT 5 (page 3, lines 5-6): The Reviewer suggested adding that the MRL was also based on alveolar epithelial metaplasia and histiocytic cellular infiltration in rats because on page 36, it is stated that the same effects were observed in rats and mice.

RESPONSE 5: *The suggested revision was not made because the MRL is only based on the squamous metaplasia in the epiglottis because the human equivalent concentrations of the points of departure for the other respiratory effects were higher than for the epiglottal effect in mice.*

COMMENT 6 (page 31, line 10): The Reviewer questioned why LOAEL was plural.

RESPONSE 6: *LOAEL values were identified in rats and mice.*

COMMENT 7 (page 36, line 13): The Reviewer asked why it wasn't noted that no hematological effects were observed after 2 years.

RESPONSE 7: *Hematological parameters were not assessed in the 2-year NTP (1997) study.*

COMMENT 8 (page 36, line 18): The Reviewer asked whether this was at 13 weeks or 2 years.

RESPONSE 8: *The sentence notes that bone density was measured after chronic exposure, which is the 2-year study; the 13-week study is considered intermediate duration.*

COMMENT 9 (page 37, line 23): The Reviewer asked whether peripheral nerves were evaluated.

RESPONSE: *The NTP (1997) study did not include an examination of peripheral nerves.*

COMMENT 10 (page 46, line 21): The Reviewer questioned whether the copper insufficiency was due to molybdenum and whether a copper-sufficient diet was used.

RESPONSE 10: *A statement was added that the copper insufficiency was possibly due to the molybdenum exposure.*

COMMENT 11 (page 49, line 18): The Reviewer asked what other studies.

RESPONSE 11: *The sentence was revised to indicate that no overt signs of toxicity were observed in laboratory animal studies.*

COMMENT 12 (page 50, line 20): The Reviewer noted "This can be explained by the difference in the Mo form (sodium molybdate vs. ammonium tetrathiomolybdate in Murray et al. vs. Lyubimov et al. papers, respectively. Ammonium tetrathiomolybdate is a powerful copper chelator (Brewer GJ, Askari F, Dick RB, et al. Treatment of Wilson's disease with tetrathiomolybdate: V. Control of free copper by tetrathiomolybdate and a comparison with trientine. Transl Res. 2009; 154(2):70-77) while to the contrary, the copper levels were increased in the work presented by Murray. Spermotoxicity effects observed by Lyubimov et al. were likely the results of a secondary effect, i.e., copper deficiency. The other major difference was a gavage vs. diet administration."

RESPONSE 12: *A statement was added that the administration of tetrathiomolybdate resulted in a secondary copper insufficiency.*

COMMENT 13 (page 62, line 1): The Reviewer questioned whether the results of the Mills et al. (1981a) study suggest that tetrathiomolybdate is well absorbed.

RESPONSE 13: *The results of the Mills et al. (1981b) study (citation was corrected in profile) suggest that tetrathiomolybdate is not as well absorbed as other molybdenum compounds. The profile was revised to include this information.*

COMMENT 14 (page 75, line 8): The Reviewer noted that "There is an intensive literature from Brewer whose group uses tetrathiomolybdate for antiangiogenosis compound for cancer treatment. Description of copper chelation mechanisms and effect on ceruloplasmin in animals and human from these papers are probably beneficial to be included here."

RESPONSE 14: *Information from Brewer et al. (2000) was added to the discussion in Section 3.5.2 on the interaction of copper and tetrathiomolybdate.*

COMMENT 15 (page 76, line 19): The Reviewer noted that it may depend on the different molybdenum form (salt) used in different studies.

RESPONSE 15: *The data were considered not classifiable based on the inconsistency of results of studies in which sodium molybdate was administered with adequate copper (Jeter and Davis 1954; Murray et al. 2014; Pandey and Singh 2002).*

COMMENT 16 (page 79, line 20): The Reviewer noted that on page 29, it is stated that the study was 14 days long.

RESPONSE 16: *The study was 10 days in length, the profile was corrected.*

COMMENT 17 (page 96, line 17): The Reviewer questioned whether peripheral nerves or sciatic nerve were tested.

RESPONSE 17: *Neither study (Murray et al. 2013; NTP 1997) examined nerves.*

COMMENT 18 (page 97, line 23): The Reviewer suggested reviewing Brewer's paper on tetrathiomolybdate.

RESPONSE 18: *Although the Brewer papers provide information on the interaction of molybdenum in the form of tetrathiomolybdate and copper, they do not provide information on the toxicokinetics of molybdenum in terms of absorption, distribution, or excretion. As noted in the Response to Comment 14, this interaction between copper and tetrathiomolybdate was added to Section 3.5.2.*

COMMENT 19 (page 122, line 14): The Reviewer asked what geographical areas was the molybdenum content in the water that high.

RESPONSE 19: *The text was revised to include this information.*

Comments provided by Peer Reviewer #3:

General Comments

COMMENT 1: The Reviewer commented "Overall the draft profile is very well presented and gives a concise and extensive overview of the toxicological profile for Molybdenum and by and large the studies are accurately reported. However, there does seem to be a lack of differentiation between poor quality and better quality studies overall and inconsistencies in the way certain studies are dealt with in different sections."

RESPONSE 1: *ATSDR strives to report data from peer-reviewed articles and authoritative reports issued by agencies such as the Environmental Protection Agency (EPA). In doing so, it does not attempt to rank the studies; however, attempts are made to address any issues that may require clarification or have contradictory conclusions to other studies.*

Specific Comments

COMMENT 1 (Section 1, What is Molybdenum?): The Reviewer commented "It is important to note that exposure is to molybdenum compounds and not molybdenum metal itself and the text does not make it clear enough. While it has not been highlighted by this reviewer throughout the document it should be emphasized throughout the document as the important information could be lost in the detail later on. Suggested text has been added to Page 21: Lines 22-28."

RESPONSE 1: *The suggested text was added to Chapter 1 as recommended by the Reviewer. It was also added to Sections 2.1 and 6.5 to clarify the nature of exposure throughout the document.*

COMMENT 2: Regarding the quality and relevance of human epidemiology studies, the Reviewer commented "Starting in Section 2.2 Summary Of Health Effects. With regards to the human epidemiology studies reported and observation was made as follows 'Although the observational epidemiology studies have found statistically significant associations, they do not establish causality and it is possible that the effects are not due to molybdenum exposure.' However this evaluation is not reflected in the later text throughout the review when referring to the human epidemiology studies. This has been highlighted where noted. It is important that such limitations are noted and such studies are not used out of context (for instance see Page 30: lines 10-12). For instance, despite the noted limitations in studies such as Meeker, a Moderate level of evidence of male reproductive effects in cross-sectional studies was concluded based on Meeker et al. 2008, 2010. (Section B.8 Integrate Evidence To Develop Hazard Identification Conclusions).

Another example is the Koval'skiy et al 1961 study where it is noted (Page 81: Lines 11-18 that the study has a number of deficiencies that limit the interpretation of the results: (1) the control group consisted of 5 individuals compared to 52 subjects in the exposed group; (2) no information was provided on the controls to assess whether they were matched to the exposed group; (3) it does not appear that the study controlled for potential confounders, such as diet and alcohol, which can increase uric acid levels; and (4) NAS (2001) noted that there were potential analytical problems with the measurement of serum and urine copper levels. These limitations cast doubt upon the data and there should be a qualification wherever the data is mentioned and used especially where the data is used to support other data (e.g., Page 88 Lines 21-24.)

In addition the confidence in these studies is indicated as being very low to moderate (see Table B-19) but this is not reflected adequately in the text. Since each study is mentioned several times in different contexts, without such qualifications the impression is given that the studies are adequate to draw conclusions."

RESPONSE 2: *ATSDR disagrees with the Reviewer that the limitations of the human studies should be discussed every time the study is cited. In numerous places in the profile, the limitations of the human studies are discussed, including Sections 2.2, 3.2.2.2 (Cardiovascular Effects), 3.2.2.2 (Hepatic Effects), and 3.6.2.2 (Chronic-Duration Oral MRL). Discussions of the limitations of the observational studies were added to Section 3.2.2.2 (Other Systemic Effects) (Koval'skiy et al. 1961 study), 3.2.2.5 (Meeker et al. 2008, 2010 studies), and 3.2.2.6 (Vazquez-Salas et al. 2014 and Shirai et al. 2010 studies).*

COMMENT 3: Regarding the quality of animal data, the Reviewer commented "While there is some evaluation of the quality of the data in the appendices this is not reflected in the text. For endpoints such as reproductive effects there is a wide diversity of studies of different types and age, for instance there are very old studies such as Fungwe et al. 1990; Jeter and Davis 1954. There appears to be no differentiation in the text as to which studies are most reliable and which may be inaccurate and equal weight appears to be given to studies that are of moderate and very low confidence with those of high confidence and indeed an MRL has been set on a study of only moderate confidence (Fungwe et al. 1990) when another study of initial high confidence level (Murray et al. 2013) was ignored for setting the MRL.

Another example is regarding Pandey and Singh (2002) where on page 50 lines 11-14 it notes 'Degeneration of the seminiferous tubules was also reported by Pandey and Singh (2002) for intermediate-duration (60 days) exposures in rats administered molybdenum at doses up to 24 mg molybdenum/kg/day (sodium molybdate); however, the dose(s) producing the effects are unclear and incidence data were not reported'. The question has to be asked if the dosing was unclear for these and other effects seen by Pandey and Singh."

RESPONSE 3: *A number of factors are considered in selecting the key study for an MRL; these include the quality of the study, relevance of the animal species, relevance of the endpoint to humans, and NOAEL and/or LOAEL values identified in the study. The Fungwe et al. (1990) study was selected over other studies, particularly the Murray et al. (2013) study, because it identified a LOAEL for a relevant end point; the highest dose tested in the Murray et al. (2013) study was a NOAEL. Regarding the Pandey and Singh (2002) study, the study only provided qualitative data for the histological alterations in the seminiferous tubules; no information on incidence was provided. However, the investigators provided quantitative data (including statistical analysis) for other reproductive effects.*

COMMENT 4: Regarding the physiochemical properties, the Reviewer commented "Some comments/corrections were made to the Tables that report on the physico-chemical properties (pages 100-105) of the different molybdenum compounds. There are some discrepancies noted between e.g., CAS numbers that are reported in this document, and the CAS-numbers that have been used in e.g., REACH registration dossiers. The CAS-number for MoS2, for example, is different for the natural and the chemically produced form. For some compounds there is also a difference between the hydrated and non-hydrated form. Please double-check that the correct CAS –number is used (or make reference to both). It is also worth mentioning that e.g., molybdenum pentachloride – when in contact with moisture – will form hydrochloric acid. Consequently, all hazardous properties of this substance are related to the formed HCl, and NOT due to molybdenum."

RESPONSE 4: *The CAS number for chemically reduced MoS_2 was added to the table and reference was made to which CAS number was for each different species.*

The Reviewer noted that the CAS number for ammonium heptamolybdate was 12027-67-7 in the EU Reach Dossier; however, this CAS number is for the anhydrous or unspecified hydrate compound. The chemical listed in the profile is the tetrahydrate, which has a CAS number of 12054-85-2, as stated in the profile, but as CAS 12027-67-7 may also refer to this chemical, it was added as well.

The Reviewer stated that the melting point for molybdenum in Table 4-2 of 2,622°C is reported as 2,623°C in some handbooks. The melting point in the profile comes from the Hazardous Substances Data Bank (HSDB), which cited the CRC Handbook of Chemistry and Physics. As the value of 2,622°C was confirmed in CRC, and only one melting point is listed in the profile, no change was made.

The Reviewer noted that molybdenum disulfide in Table 4-2 has no definitive melting point and that it will oxidize to MO_3 when heated. Given that the compound sublimes at 450 °C, it is agreed that a definitive melting point would be inaccurate. The text was revised.

The Reviewer stated that the melting point for molybdenum trioxide in Table 4-2 of 795°C is reported as 802°C in some handbooks. The melting point in the profile comes from HSDB, which cited the Merck Index. The value of 795°C was confirmed in CRC Handbook of Chemistry and Physics. No change was made.

The Reviewer noted that the density of molybdenum disulfide in Table 4-2 is slightly variable (c.a. 4.8–5.1 g/cm^3) based on the nature of the product. While this statement is accurate, the density given in the profile comes from a reliable source (HSDB citing the Merck Index) and was verified as 5.06 g/cm^2. No change was made.

The Reviewer stated that the density for molybdenum trioxide in Table 4-2 of 4.69 (26°C/4°C) is reported as 4.66 at 20°C in an available study. The density in the profile comes from HSDB, which cited the Merck Index and was confirmed. No change was made.

The Reviewer noted that for odor in Table 4-2, molybdenum and molybdenum disulfide should be documented as "odorless." Odorless was listed for molybdenum disulfide. ATSDR did not locate a source for stating that molybdenum was odorless. The Reviewer was contacted to provide a source for this information. The information had not been received at the time of this report. If the information is received, it will be considered for future drafts of the profile.

The Reviewer stated that the water solubility for molybdenum trioxide in Table 4-2 of 490 mg/L at 28°C is reported as 1 g/L at 20°C in another source. This information was not located by ATSDR. The Reviewer was contacted to provide a source for this information. The information had not been received at the time of this report. If the information is received, it will be considered for future drafts of the profile.

The Reviewer noted that flammability in Table 4-2 for molybdenum noted as "flammable" should be changed to "not flammable," based on an available study result (EU A.10 method; fine molybdenum powder, FSSS=4.8µm). This information was not located by ATSDR. The Reviewer was contacted to provide a source for this information. The information had not been received at the time of this report. If the information is received, it will be considered for future drafts of the profile. For now, the "flammable" designation comes from two separate sources in HSDB citing molybdenum powder and dust as flammable. No change was made for this draft of the profile, until the study mentioned by the Reviewer is provided.

The Reviewer stated that the melting point for ammonium heptamolybdate tetrahydrate in Table 4-2 of 1,235.8°C becomes 1,163.5°C if the four water molecules are not taken into account. Since the chemical

listed in the table is the tetrahydrate, the melting point for the anhydrous form was not listed. No changes were made.

The Reviewer agreed that the boiling point for anhydrous sodium molybdate in Table 4-2 is 687°C. The Reviewer also stated that sodium molybdate dihydrate decomposes at ca. 100°C and, therefore, a boiling point is not relevant. The boiling point in the profile is listed as "No data." Given the information provided by the reviewer, the text was revised to state "Not applicable."

In Table 4-2, the Reviewer provided an experimentally derived water solubility for sodium molybdate dihydrate. Since the chemical properties listed in the table are for the anhydrous form of sodium molybdate, the water solubility for the dihydrate was not listed. No changes were made.

COMMENT 5: Regarding the environmental concentration levels, the Reviewer commented "With regard to exposure data, some additional data have been added as comments (pages 123-124) on baseline levels of molybdenum in the marine environment, in soil and in sediment. This information is merely supportive as it confirms the reported Mo-levels that are currently used in the document."

RESPONSE 5: *The profile has been revised to include these data that were available to ATSDR.*

COMMENT 6: The Reviewer noted "I am aware that IMOA has submitted a number of recent GLP compliant studies to ATSDR (late 2015) which have not been reviewed yet in the current Toxicological Profile: this information can assist in filling some of the data gaps such as for sensitization and *in vitro* genotoxicity."

RESPONSE 6: *The studies submitted by IMOA to ATSDR are proprietary and cannot be released to the public. Since the studies are not publically available and cannot undergo independent peer review, they were not added to the profile.*

COMMENT 7: The Reviewer provided some additional references regarding environmental concentration levels:

Salminen R, Batista MJ, Bidovec M, et al. (2005). Geochemical Atlas of Europe - Part 1: Background information, Methodology and Maps. EuroGeoSurveys.

Allaway WH, 1968. Adc Agron. 20, 235.

Brewer PG (1975). In: Riley JP, Skirrow G (Eds), Chemical Oceanography. Academic Press, New York, p. 415.

Brooks RR, Rumsby MG (1965). The biogeochemistry of trace element uptake by some New Zealand bivalves. Limnol Oceanogr 10:521-527.

Chan KM, Riley JP (1966). Anal Chim Acta 36, 220.

Goldberg ED (1965). Minor elements in seawater. In: Riley JP, Skirrow G (Eds), Chemical Oceanography, Academic Press, London, p 163-196.

Kappanna AN, Gadre GT, Bhavnagary HM, Joshi JM (1962). Minor constituents of seawater; Current Science (India) 31, 273.

Kawabuchi K, Kuroda R (1969). Anal Chim Acta 46, 23. In: Crompton TR (Ed.), Analysis of Seawater: a guide for the analytical and environmental chemist. Springer, 2006.

Kiriyama T, Kuroda R (1984). Talanta 31, 472. In: Crompton TR (Ed.), Analysis of Seawater: a guide for the analytical and environmental chemist. Springer, 2006.

Kulathilake AI, Chatt A (1980). Anal Chem. 52, 828. In: Crompton TR (Ed.), Analysis of Seawater: a guide for the analytical and environmental chemist. Springer, 2006.

Kuroda R, Tarui T (1974). Fresen Z Anal Chem 269, 22. In: Crompton TR (Ed.), Analysis of Seawater: a guide for the analytical and environmental chemist. Springer, 2006.

Morris AW (1975). Dissolved molybdenum and vanadium in Northeast Atlantic Ocean. Deep Sea Res. 22, 49-54.

Nakata R, Okazaki S, Hori T, Fujinaga T (1983). Anal Chim Acta 149, 67.

Parker GA (1986). Molybdenum. In: Handbook of Environmental Chemistry, 3rd Ed., 217-240.

Riley JP, Taylor D (1968). The use of chelating ion exchange in the determination of molybdenum and vanadium in sea water. Anal Chim Acta 41, 175-178.

Rollinson CR (1970). Chromium, molybdenum and tungsten. In: Comprehensive Inorganic Chemistry.

Bailar JC, Emeléus HJ, Nyholm R, Trotman-Dickenson AP (Eds).

Schriadah MMA, Kataoka M, Ohzeki K (1985). Analyst (London), 110, 125.

Schutz DF, Turokian KK (1965). The investigation of the geographical and vertical distribution of several trace elements in sea water using neutron activation analysis. Geochim Cosmochim Acta, 29, 259-313.

Sugawara K, Okabe S (1968). J Tokyo Univ Fish Spec Ed 8, 165.

Tao H, Miyazaki A, Bansho K, Umezaki Y (1984). Anal Chim Acta 156, 159.

Tuit B, Ravizza G (2003). The marine distribution of molybdenum. Goldschmidt Conference Abstracts.

Van den Berg CMG (1985). Anal Chem 57, 1532. Reported In: Crompton TR (Ed.), Analysis of Seawater: a guide for the analytical and environmental chemist. Springer, 2006.

Young EG, Smith DG, Langille WM (1959) J Fish Res Board Can 16, 7.

RESPONSE 7: *ATSDR was able to locate the following papers suggested by the Reviewer: Chan and Riley (1966); Kawabuchi and Kuroda (1969); Kiriyama and Kuroda (1984); Kulathilake and Chatt (1980); Nakata et al. (1983); Riley and Taylor (1968); Schutz and Turokian (1965); and Tao et al.*

(1984). The data from these references were added to the profile, except for Schutz and Turokian (1965), in which data referring to molybdenum concentrations were not located. The Reviewer was contacted to provide the additional papers. The information had not been received at the time of this report. If the information is received, it will be considered for future drafts of the profile.

Annotated Comments

COMMENT 1 (page 21, line 21-28): The Reviewer commented "It is important to note that exposure is to molybdenum compounds and not molybdenum metal itself and the text does not make it clear enough. While it has not been highlighted by this reviewer throughout the document it should be emphasized throughout the document as the important information could be lost in the detail later on."

RESPONSE 1: *The suggested text was added to Chapter 1 as recommended by the Reviewer. It was also added to Sections 2.1 and 6.5 to clarify the nature of exposure throughout the document.*

COMMENT2 (page 22, line 32): The Reviewer commented "As consultant to IMOA, and being part of the scientific team that supported IMOA in their discussion and information exchange with the Canada-US Regulatory Cooperation Council (RCC) Initiative (meeting at the end of October 2015), I am aware that IMOA has submitted a number of recent GLP complaint studies to ATSDR including an in vitro percutaneous absorption study."

RESPONSE 2: *IMOA provided ATSDR's contractor copies of several studies; however, as per a non-disclosure agreement, these studies are considered confidential and cannot be cited in the profile.*

COMMENT 3 (page 30, line 7-8): The Reviewer commented "This evaluation is not really reflected in the later text throughout the review."

RESPONSE 3: *As noted in the Response to Specific Comment 2, the limitations of the observational epidemiology studies are discussed in numerous sections in Chapter 3.*

COMMENT 4 (page 30, lines 12-14): The Reviewer suggested deleting the following sentence "Based on the available animal data, the reproductive effects appear to be the most sensitive targets. Consistent with the findings in the Meeker et al. (2008) epidemiology study."

RESPONSE 4: *Based on the systematic review of the available data, ATSDR concluded that reproductive toxicity is a suspected health effect of molybdenum exposure. Several animal studies (Beresenyi et al. 2008; Fungwe et al. 1990; Lyubimov et al. 2004; Pandey and Singh 2002; Zhai et al. 2013) have alterations in sperm parameters. Meeker et al. (2008) also found significant associations between sperm parameters and molybdenum. Only one animal study (Murray et al. 2013) did not find significant alterations in sperm parameters.*

COMMENT 5 (page 30, lines 20-21): The Reviewer commented "There appears to be no comments at all about the quality of studies."

RESPONSE 5: *These studies are discussed in greater detail in Section 3.2.*

COMMENT 6 (page 48, line 13): The Reviewer commented "Later in this document it is noted on Page 81: Lines 11-18: that the Koval'skiy (1961) study has a number of deficiencies that limit the interpretation of the results: (1) the control group consisted of 5 individuals compared to 52 subjects in the exposed group; (2) no information was provided on the controls to assess whether they were matched to the exposed group; (3) it does not appear that the study controlled for potential confounders, such as diet and alcohol, which can increase uric acid levels; and (4) NAS (2001) noted that there were potential analytical problems with the measurement of serum and urine copper levels."

RESPONSE 6: *A discussion of the limitations of the Koval'skiy et al. (1961) study was added to this section of the profile.*

COMMENT 7 (page 28, line 34): The Reviewer commented "This sentence is unclear. It relates to Table 22 in EPA 1979. A slight rewording should be made."

RESPONSE 7: *The text was revised to clarify that increases in uric acid were found in residents with low molybdenum levels and in residents with high molybdenum levels in the drinking water.*

COMMENT 8 (page 49, lines 23-25): The Reviewer commented "It is noted on Page 30: lines 6-7 'Although the observational epidemiology studies have found statistically significant associations, they do not establish causality and it is possible that the effects are not due to molybdenum exposure.' This statement should also be added in this paragraph to be consistent but also to point out that the effects may not be due to molybdenum exposure. This statement should also be added in this paragraph to be consistent but also to point out that the effects may not be due to molybdenum exposure. The assessment perhaps could be made at the end of the paragraph."

RESPONSE 8: *A discussion of the limitations of observational epidemiology studies was added to this section of the profile.*

COMMENT 9 (page 51, lines 5-7): The Reviewer commented "On page 50 lines 11-14 it notes 'Degeneration of the seminiferous tubules was also reported by Pandey and Singh (2002) for intermediate-duration (60 days) exposures in rats administered molybdenum at doses up to 24 mg molybdenum/kg/day (sodium molybdate); however, the dose(s) producing the effects are unclear and incidence data were not reported.' The question has to be asked if the dosing was unclear for these and other effects seen by Pandey and Singh."

RESPONSE 9: *Pandey and Singh (2002) provided quantitative data and statistical analysis for the other end points examined.*

COMMENT 10 (page 53, lines 10-12): The Reviewer commented "Molybdenum pentachloride fumes in air and reacts with moisture and give off hydrogen chloride. In contact with skin, the formed HCl will cause inflammation and damage. Therefore, when evaluating the hazardous properties of molybdenum pentachloride, one should be aware that harmful properties are due to the hydrogen chloride (hydrochloric acid) liberated by contact with moisture (in the air, perspiration), and NOT due to molybdenum."

RESPONSE 10: *Sensitization was also observed in guinea pigs exposed to sodium molybdate, suggesting that molybdenum contributed to the sensitization.*

COMMENT 11 (page 53, line 13): The Reviewer commented "I am aware that IMOA has submitted up to date, GLP complaint new studies on various molybdenum compounds indicating no sensitization effects. (cfr comment on Page 22)."

RESPONSE 11: *As noted in the Response to Comment 2, IMOA considered these studies to be confidential and ATSDR is currently unable to cite them in the profile.*

COMMENT 12 (page 59, lines 7-9): The Reviewer commented "I am aware that IMOA has submitted a number of up to date, GLP complaint in vitro studies which should be considered (cfr comment on Page 22)."

RESPONSE 12: *See Response to Comment 11.*

COMMENT 13 (page 75, line 16): The Reviewer commented "It would be preferable to indicate that ceruloplasmin is the major copper-carrying protein in the blood. This is important for those who do not understand the significance of a "tightly bound form" that is not associated with ceruloplasmin. There is an explanation in lines 24-26 but there should be an earlier explanation."

RESPONSE 13: *Parenthetical text was added indicating that ceruloplasmin is a major copper-carrying protein in blood.*

COMMENT 14 (page 77, line 14): The Reviewer commented "It is noted on Page 30: lines 6-7. 'Although the observational epidemiology studies have found statistically significant associations, they do not establish causality and it is possible that the effects are not due to molybdenum exposure'. This would not seem to support a moderate level of evidence in humans and would be more appropriate to say 'inadequate level of evidence' or 'low level of evidence'."

RESPONSE 14: *ATSDR has re-evaluated the initial confidence rating of the epidemiology studies examining reproductive effects and downgraded them to low confidence. Thus, there is low level of evidence in humans.*

COMMENT 15 (page 82, lines 17-18): The Reviewer commented "Fungwe et al 1990 has only been assigned a study of moderate confidence while other studies, Murray et al 2013 and Lyubimov et al. 2004 have been assigned high confidence and it seems that it would be more appropriate to use the NOAELs from one of these studies of higher confidence."

RESPONSE 15: *As per ATSDR guidance, the MRL is based on the study that identified the lowest reliable point of departure for the most sensitive end point. Fungwe et al. (1990) identified the lowest LOAEL (1.5 mg molybdenum/kg/day) for reproductive effects. The NOAELs identified in the Lyubimov et al. (2004) study and Murray et al. (2013) studies are equal to or higher than this LOAEL.*

COMMENT 16 (page 90, lines 22-25): The Reviewer commented " It is noted on Page 81: Lines 11-18: that the Koval'skiy (1961) study has a number of deficiencies that limit the interpretation of the results: (1) the control group consisted of 5 individuals compared to 52 subjects in the exposed group; (2) no

information was provided on the controls to assess whether they were matched to the exposed group; (3) it does not appear that the study controlled for potential confounders, such as diet and alcohol, which can increase uric acid levels; and (4) NAS (2001) noted that there were potential analytical problems with the measurement of serum and urine copper levels."

RESPONSE 16: *The limitations of the Koval'skiy et al. (1961) study are discussed in several places in the profile.*

COMMENT 17 (page 94, lines 9-10): The Reviewer commented "As indicated on Page 53: Lines 8-12. I am aware that IMOA has submitted to ATSDR up to date, GLP compliant new studies on various molybdenum compounds indicating no sensitization effects."

RESPONSE 17: *See Response to Comment 11.*

COMMENT 18 (page 94, lines 31-34): The Reviewer commented "As indicated on Page 53: Lines 8-12. I am aware that IMOA has submitted to ATSDR up to date, GLP compliant new studies on various molybdenum compounds indicating no sensitization effects. In addition acute dermal and irritation studies were submitted."

RESPONSE 18: *See Response to Comment 11.*

COMMENT 19 (page 96, line 21): The Reviewer commented "am aware that IMOA has submitted to ATSDR up-to-date and GLP compliant new studies on a number of in vitro studies that should be included."

RESPONSE 19: *See Response to Comment 11.*

COMMENT 20 (page 97, lines 11-12): The Reviewer commented "As indicated on Page 53: Lines 8-12. I am aware that IMOA has submitted to ATSDR up to date, GLP compliant new studies on various molybdenum compounds indicating no sensitization effects."

RESPONSE 20: *See Response to Comment 11.*

COMMENT 21 (page 97, line 34 – page 98, line 1): The Reviewer commented "It is noted on Page 81: Lines 11-18: that the Koval'skiy (1961) study has a number of deficiencies that limit the interpretation of the results: (1) the control group consisted of 5 individuals compared to 52 subjects in the exposed group; (2) no information was provided on the controls to assess whether they were matched to the exposed group; (3) it does not appear that the study controlled for potential confounders, such as diet and alcohol, which can increase uric acid levels; and (4) NAS (2001) noted that there were potential analytical problems with the measurement of serum and urine copper levels. This deficiency should be noted here."

RESPONSE 21: *The limitations of the Koval'skiy et al. (1961) are discussed in numerous places in the profile.*

COMMENT 22 (page 100, line 21): The Reviewer suggested adding the following text "Under physiological conditions (pH > 6.5) the sole molybdenum species in aqueous media is the molybdate anion, [MoO4]2- (Cruywagen, 2000; Cruywagen et al, 2002). Molybdenum compounds, e.g., molybdenum trioxide and polymolybdates, transform rapidly to the [MoO4]2- ion under environmental relevant test conditions (Greenwood and Earnshaw, 1987)."

RESPONSE 22: *The suggested statement was added to Section 4.1; information from the Cruywagen (2000) and Cruywagen et al. (2002) papers was also added to Section 6.3.2.2.*

COMMENT 23 (page 102): The Reviewer commented "Molybdenite is the natural mineral form of MoS2; this substance can also be produced chemically, but this form never occurs in isolation as the substance as such, i.e., it is always included in or adsorbed onto a matrix."

RESPONSE 23: *Section 4.1 and Table 4-2 were revised to include mention of the synthetically produced form of molybdenum sulfide.*

COMMENT 24 (page 102): The Reviewer commented "The CAS number for chemically produced MoS2 is 12612-50-9."

RESPONSE 24: *The CAS number for chemically reduced MoS_2 was added to the table, and reference was made to which CAS number was for each different species.*

COMMENT 25 (page 103): The Reviewer commented "The CAS number in the EU REACH Registration dossier for ammonium hexamolybdate is 12027-67-7."

RESPONSE 25: *The CAS number 12027-67-7 is for the anhydrous or unspecified hydrate compound. The chemical listed in the profile is the tetrahydrate, which has a CAS number of 12054-85-2, as stated in the profile, but as CAS 12027-67-7 may also refer to this chemical, it was added as well.*

COMMENT 26 (page 105): The Reviewer noted that some handbooks list the melting point for molybdenum as 2623°C.

RESPONSE 26: *The melting point in the profile comes from HSDB, which cited the CRC Handbook of Chemistry and Physics and was confirmed in the CRC reference. No change was made.*

COMMENT 27 (page 105): Regarding the melting point for molybdenite, the Reviewer noted "MoS2 has no melting point in air, as it oxidises to MoO3 when heated to ca. 500-600°C. The reaction is exothermic and used on a commercial scale to convert MoS2 to technical MoO3. In the vacuum MoS2 dissociates to the elements from ca. 1000°C. Definitive melting points as reported in some factual handbooks and older literature are most likely incorrect."

RESPONSE 27: *Given that the compound sublimes at 450°C, it is agreed that a definitive melting point would be inaccurate. The text was revised.*

COMMENT 28 (page 105): The Reviewer noted that some handbooks list the melting point for molybdenum trioxide as 802°C.

RESPONSE 28: *The melting point in the profile comes from HSDB, which cited the Merck Index and was confirmed in the Merck Index. No change was made.*

COMMENT 29 (page 105): Regarding the density of molybdenite, the Reviewer noted "The density of MoS2 is slightly variable (ca. 4.8-5.1 g/cm³) depending on the nature of the product (natural molybdenite ore, degree of purification, or chemically produced form)."

RESPONSE 29: *While this statement is accurate, the density given in the profile comes from a reliable source (HSDB citing the Merck Index) and was confirmed in the Merck Index. No change was made.*

COMMENT 30 (page 105): Regarding the density of molybdenum trioxide, the Reviewer noted "Available study result: 4.66 at 20°C."

RESPONSE 30: *The density in the profile comes from HSDB, which cited the Merck Index and was confirmed in the Merck Index. No change was made.*

COMMENT 31 (page 105): The Reviewer noted that molybdenum and molybdenite are odorless.

RESPONSE 31: *This information was not located by ATSDR. The Reviewer was contacted to provide a source for this information. The information had not been received at the time of this report. If the information is received, it will be considered for future drafts of the profile.*

COMMENT 32 (page 105): Regarding the water solubility of molybdenum trioxide, the Reviewer noted "1 g/L at 20°C has been reported."

RESPONSE 32: *This information was not located by ATSDR. The Reviewer was contacted to provide a source for this information. The information had not been received at the time of this report. If the information is received, it will be considered for future drafts of the profile.*

COMMENT 33 (page 105): Regarding the flammability limits for molybdenum, the Reviewer noted "Study result available for flammability (EU A.10 method; fine molybdenum powder, FSSS=4.8µm); it was concluded that molybdenum was not flammable."

RESPONSE 33: *This information was not located by ATSDR. The Reviewer was contacted to provide a source for this information. The information had not been received at the time of this report. If the information is received, it will be considered for future drafts of the profile. For now, the "flammable" designation comes from two separate sources in HSDB citing molybdenum powder and dust as flammable. No change was made for this draft of the profile, until the study mentioned by the Reviewer is provided.*

COMMENT 34 (page 106): Regarding the molecular weight of ammonium heptamolybdate tetrahydrate, the Reviewer noted "MM becomes 1163.5 if the four water molecules are not taken into account."

RESPONSE 34: *Since the chemical listed in the table is the tetrahydrate, the melting point for the anhydrous form was not listed. No changes were made.*

COMMENT 35 (page 106): Regarding the boiling point of sodium molybdate, the Reviewer noted "The melting point of anhydrous sodium molybdate is 678°C. Sodium molybdate dihydrate decomposes at ca. 100°C. Therefore, a boiling point is not relevant."

RESPONSE 35: *The boiling point in the profile is listed as "No data." Given the information provided by the reviewer, the text was revised to state "Not applicable."*

COMMENT 36 (page 106): Regarding the water solubility of sodium molybdate, the Reviewer noted "The water solubility of sodium molybdate dihydrate has been determined experimentally to be ca. 654 g/L at 20°C."

RESPONSE 36: *In Table 4-2, the Reviewer provided an experimentally derived water solubility for sodium molybdate dihydrate. Since the chemical properties listed in the table are for the anhydrous form of sodium molybdate, the water solubility for the dihydrate was not listed. No changes were made.*

COMMENT 37 (page 115, line 17): The Reviewer noted that molybdate is the only relevant form in the aqueous environment.

RESPONSE 37: *The text was revised to add this information.*

COMMENT 38 (page 115, lines 27-28): The Reviewer noted "Micò C, Zhao FJ, McGrath SP (2010) conducted chronic toxicity tests with five plant species in 10 different types of soil. They concluded that the organic carbon content of the soils consistently yielded the best correlations with EC_{50} values for the various species tested. These regressions were however strongly affected by the presence of an organic soil. Except for ryegrass, the Feox content of the soils was also significantly correlated with Mo toxicity thresholds. In the strong multiple relationship with pH and clay, clay content is a good surrogate for the actual binding surfaces that are present on clays, including oxides and organic matter. Similarly, in the multiple regressions with pH and CEC, which is theoretically a measure for binding of cations, the CEC is probably a measurement that integrates clay and organic matter in soil, which both have binding sites for molybdate. Because of the large R^2 values and good predictions of EC_{50} values based on pH and clay content for all 5 plant species, these multiple regression models can be used for normalisation of the plant data to specific soil conditions."

RESPONSE 38: *Ecotoxicity and the correlation to soil properties is beyond the scope of this section in the profile. While not included to a high degree of detail in the Overview (Section 6.1), data regarding soil properties and their impact on molybdenum binding are noted in Section 6.3.1.*

COMMENT 39 (page 122, lines 29-32): The Reviewer noted that this specific paragraph has been repeated several times in the document.

RESPONSE 39: *The paragraph was revised.*

COMMENT 40 (page 123, line 10): The Reviewer noted "Under physiological conditions (pH > 6.5) the sole molybdenum species in the aqueous environment is the molybdate anion, [MoO4]2- (Cruywagen, 2000; Cruywagen et al, 2002). Molybdenum compounds, e.g., molybdenum trioxide and polymolybdates, transform rapidly to the [MoO4]2- ion under environmental relevant test conditions (Greenwood and Earnshaw, 1987)."

RESPONSE 40: *The papers cited by the Reviewer (Cruywagen 2000; Cruywagen et al. 2002; Greenwood and Earnshaw 1987) were unable to be located by ATSDR. The Reviewer was contacted to provide a source for this information. The information had not been received at the time of this report. If the information is received, it will be considered for future drafts of the profile.*

COMMENT 41 (page 125, lines 7-8): The Reviewer noted "Average concentrations of molybdenum as a minor seawater constituent of 1 and 10 µg Mo/L are reported by Brooks (1965) and Kappanna (1962), respectively. Tuit et al (2003) reported averaged salinity (35 ppt) normalized concentration of Mo for the Arabian Sea and Sargasso Sea of respectively 10.6 µg Mo/L and 10.6 µg Mo/L (average density of sea water: 1.025 g/mL). Rollinson (1970) reported Mo concentrations in seawater that ranged from 8.3 to 13.5 µg Mo/kg, i.e., from 9.12 to 13.8 µg Mo/L. Parker (1986) reviewed the concentration of Mo in seawater that varied within the range of 10-12 µg Mo/L (Morris, 1975) or 2-19 µg Mo/L (Brewer, 1975). A worldwide mean value in seawater of 10 µg Mo/L is cited by one investigator (Allaway, 1968). Mo concentration in the Atlantic Ocean ranged from 7.3 µg Mo/L to 7.9 µg Mo/L (Kulathilake et al, 1980). Mo concentration in the Eastern Atlantic and Western Atlantic was 7.5 µg Mo/L (Ternero et al, 1983) and a range of 6.3 - 14.0 µg Mo/L (Young et al, 1959), respectively. Mo concentration in the North Atlantic varied from ranges 0.5 - 1.0 µg Mo/L (Chan et al, 1966) to 12.8 - 13.2 µg Mo/L (van den Berg, 1985). Mo concentration in the Pacific Ocean varied between the Eastern Pacific (8.8 µg Mo/L; Kiriyama, 1984) and the Western Pacific (1.5 µg Mo/L; Nakata, 1983). In the Indian Ocean Mo concentration ranged from 9.5 µg Mo/L to 13.3 µg Mo/L (Sugawara, 1966). In the Japan Sea a concentration of 11.5 µg Mo/L is reported (Shriadah et al, 1985). Different Mo concentrations are reported for Tokyo Bay, and were situated between 7.7 µg Mo/L (Kawabuchi et al, 1969), 10 - 13 µg Mo/L (Kuroda et al, 1974) and 9.3 µg Mo/L (Tao et al, 1984). Mo concentration in the English Channel are situated between 12 and 16 µg Mo/L (Chan et al, 1966). Two different Mo concentrations in the Irish Sea are reported: 8.4 µg Mo/L (Riley et al, 1968) and 11.8 µg Mo/L (van den Berg, 1985). Finally, Goldberg (1965) and Schutz et al (1965) reported a Mo concentration of 0.01 ppm i.e. 10.25 µg Mo/L. With this data, a 90^{th} percentile of 13.6 µg Mo/L can be calculated (Non-parametric Distribution). It should be noted, however, that it is not always clear from the data whether the reported values represent the total or the dissolved fraction."

RESPONSE 41: *ATSDR was able to locate the following papers suggested by the Reviewer: Chan and Riley (1966); Kawabuchi and Kuroda (1969); Kiriyama and Kuroda (1984); Kulathilake and Chatt (1980); Nakata et al. (1983); Riley and Taylor (1968); Schutz and Turokian (1965); and Tao et al. (1984). The data from these references were added to the profile, except for Schutz and Turokian (1965), in which data referring to molybdenum concentrations were not located. The Reviewer was contacted to provide a source for this information. The information had not been received at the time of this report. If the information is received, it will be considered for future drafts of the profile.*

COMMENT 42 (page 126, line 15): The Reviewer commented "Additional info: A total of 840 pristine European top soil samples (FOREGS survey) were analysed ICP-MS, detection limit 0.12 mg/kg dry wt.

Reported total molybdenum levels in the top soil layer ranged between 0.05 (DL / 2) and 21.3 mg Mo/kg dry wt, with 50th/90th percentiles of 0.62 and 1.81 mg Mo/kg dry wt. This analysis confirms the proposed average concentrations of 1-2 ppm of Mo in soils."

RESPONSE 42: *The text was revised to include these data.*

COMMENT 43 (page 126, line 28): The Reviewer noted "Additional info: A total of 848 pristine European freshwater sediment samples (FOREGS survey) were analysed ICP-MS, detection limit 0.05 mg Mo/kg dry wt. Total molybdenum levels in the sediment layer ranged between 0.12) [sic] and 1173 mg Mo/kg dry wt, with 50th/90th percentiles of 0.63 and 1.89 mg Mo/kg dry wt."

RESPONSE 43: *The text was revised to include these data.*

COMMENT 44 (page 143): The Reviewer suggested that all detection limits in the sediments be expressed in the same unit, i.e., ng/L or μg/L.

RESPONSE 44: *According to ATSDR guidelines, units are reported as cited by the original author. However, units were converted in the text to provide consistency.*

COMMENT 45 (page B-34): Regarding the reproductive effects, the Reviewer commented "As noted on Page 30 (Lines 6-7) the epidemiology data does not establish causality therefore this should not reflect a moderate level of evidence."

RESPONSE 45: *ATSDR has re-evaluated the initial confidence rating for these studies; the revised confidence rating is "low."*

COMMENT 46 (page B-35): Regarding the level of evidence for reproductive effects in human studies, the Reviewer noted "As noted on Page 30 (Lines 6-7) the epidemiology data does not establish causality therefore this does not reflect a moderate level of evidence."

RESPONSE 46: *See Response to Comment 45.*

COMMENT 47 (page B-36): Regarding the level of evidence for reproductive effects in human studies, the Reviewer noted "As noted on Page 30 (Lines 6-7) the epidemiology data does not establish causality therefore this does not reflect a moderate level of evidence."

RESPONSE 47: *See Response to Comment 45.*