Reference Dose and Relative Source Contribution

Molybdenum Standards Stakeholder Meeting

July 25, 2023

Reference Dose

Update on CRL Study

- F. Jay Murray et al., Sodium molybdate dihydrate does not exhibit developmental or reproductive toxicity in Sprague-Dawley rats maintained on a marginal copper diet, Reproductive Toxicology (published online 18 July 2023), https://doi.org/10.1016/j.reprotox.2023.108442

  *"**There was no evidence of copper depletion in serum at any dose level**. In conclusion, the no-observed-adverse-effect levels (NOAELs) for systemic, maternal reproductive, and developmental toxicity in this marginal Cu diet study are 40 mg Mo/kg bw/day, consistent with the results of guideline developmental and reproductive toxicity studies of SMD. **The results of Fungwe et al. were not replicated, even at higher dose levels of Mo, and their inconsistencies with guideline toxicity studies of Mo are not explained by the marginal dietary Cu level**."*

Modifying Factor (MF)

Issue: CDPHE policy about peer-reviewed RfD values

- We understand CDPHE's desire to use a federal peer-reviewed RfD value
- It is also important to use the best science available. *(See* EPA OSWER Directive 9285.7-53, *Human Health Toxicity Values in Superfund Risk Assessments* (Dec. 5, 2003))
- The 3-fold MF is based on the Fungwe (1990) study
- Without public review, ATSDR applied the MF to the NOAEL for minor kidney effects, not the NOAEL for developmental toxicity
- The recent CRL study demonstrates clearly that the Fungwe study is not credible

Modifying Factor (MF)

Issue: Other sources of data suggesting copper deficient diets could affect molybdenum toxicity

- “3 MF for concern that reproductive and/or developmental effects may be a more sensitive endpoint than kidney effects in populations with marginal copper intakes.” – ATSDR, 2020
- None of the other 5 studies cited in footnote 10 are developmental or reproductive toxicity studies
- These 5 studies do not support the need for a MF, and ATSDR stated these studies “were not considered relevant for MRL determination”

- "*Marked differences in the distribution of molybdenum and copper and the toxicity of molybdenum have been observed in rats exposed to high doses of molybdenum and maintained on a copper-deficient diet compared to those maintained on a copper-adequate diet (Brinkman and Miller 1961; Johnson et al. 1969; Nederbragt 1980, 1982; Sasmal et al. 1968).* **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.**" -- ATSDR (2020), p. 166 (A-15)

Additional Uncertainty Factors (UFs)

Issue: Is a subchronic-to-chronic UF needed?

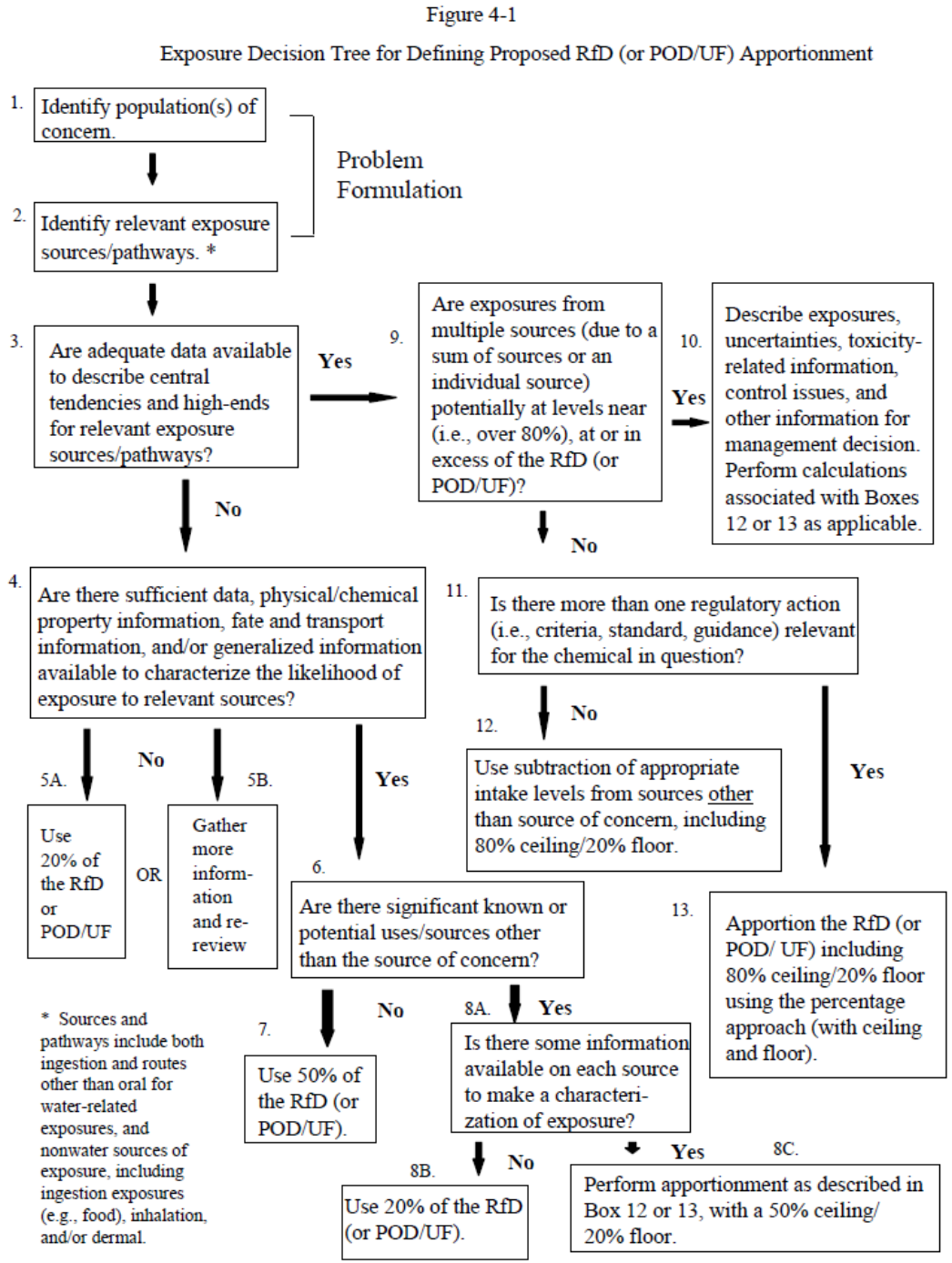
- It is inappropriate to use a subchronic-to-chronic UF for molybdenum or any essential element
- ATSDR, EPA and IOM saw no need for this UF in any of their risk assessments of Mo
- No UF for subchronic-to-chronic UF has ever been used for an essential element -- not in 22 risk assessments of 10 essential elements by ATSDR, EPA, and IOM
- Research indicates none are based on chronic toxicity studies
- Essential elements have short half-lives and do not bioaccumulate

Critical Low Flow relationship to UFs

- EPA recommends the harmonic mean flow as the critical low flow to implement human health criteria (Water Quality Standards Handbook, Ch. 5, pg. 13):
  - The EPA recommends the harmonic mean flow for implementing human health criteria. The concept of a harmonic mean is a standard statistical data analysis technique. The EPA's model for human health effects assumes that such effects occur because of a long-term exposure to low concentrations of a toxic pollutant (e.g., two liters of water per day for seventy years). The harmonic mean flow allows for estimating the concentration of toxic pollutant contained in those two liters of water per day when the daily variation in the flow rate is high. Therefore, the EPA recommends use of the harmonic mean flow in computing critical low flows for human health criteria rather than using other averaging techniques.
  - *See also* EPA, *Technical Support Document for Water Quality-based Toxics Control*, pp. 88-89 (1991); Advance Notice of Proposed Rulemaking, 53 Fed. Reg. 36742, 36793 (July 7, 1998)
- CO uses "the empirically based 30-day average low flow with an average 1-in-3 year recurrence interval (30E3) for chronic standards" (Reg. 31.9(1)(a)).
  - Use of this flow statistic is consistent with a shorter-term exposure of 30 days in duration, not a longer-term exposure over 70 years
- **Combining a subchronic-to-chronic UF *and* the 30E3 critical low flow for an essential element would be inappropriate and inconsistent with EPA guidance**

Relative Source Contribution

EPA's Exposure Decision Tree



Overview of RSC Analysis

- F. Jay Murray, PhD, *Application of the EPA Exposure Decision Tree for Defining the Relative Source Contribution (RSC) for Molybdenum in Drinking Water (Mar. 2023)*
  - Shared with stakeholders March 30, 2023
  - Conclusion: EPA's Exposure Decision Tree supports the use of the subtraction method for establishing an RSC of 80% for molybdenum
  - Consistent with EPA's conclusion in 2017 that RSC of 0.8 (i.e., 80%) is justified

- WQCD feedback received in June 2023

Step 1 of Decision Tree

Who are the sensitive subpopulations, and how have they been accounted for in the RSC?

- EPA Decision Tree on RSC doesn't mention sensitive subpopulations
- None were clearly identified
- All essential elements interact with other essential elements
- 10-fold intraspecies UF is adequate to protect potential sensitive individuals

Step 3 of Decision Tree

Why were data judged to be adequate under the EPA guidance?

- According to the EPA guidance: “The adequacy of data is a professional judgment for each individual chemical of concern, but EPA recommends that the minimum acceptable data for Box 3 are exposure distributions that can be used to determine, with an acceptable 95 percent confidence interval, the central tendency and high-end exposure levels for each source.”
- The data are adequate to describe the central tendency and the high-end of exposure to molybdenum based on professional judgment and the large number of scientific publications on dietary exposure to Mo with generally consistent results.

EPA Statement on Data Adequacy

"The EPA believes there are adequate data to describe central tendency and high-end exposure to molybdenum from food. Application of the Exposure Decision Tree gets into box 12 or 13 (see Figure 2). Calculations show that exposure to molybdenum from the diet remains only a small percentage of the above listed RfDs (this is discussed in more detail in our responsive comment letter). This justifies 0.8 as the value of the RSC to be used to calculate the Ambient Water Quality Standard."

-- US EPA Region 8 (2017) Letter from Sandra D. Spence, Chief, Water Quality Unit to David Baumgarten, Chair, Water Quality Control Commission. November 22, 2017.

Step 9 of Decision Tree

Did Climax generate the exposure estimates from the Total Diet Study results? If so, how do those compare with the other dietary exposure estimates presented?

- No, Climax did not generate exposure estimates from FDA's Total Diet Study, nor is that standard practice for an RSC analysis.

Step 9 of Decision Tree, Cont'd

What are the daily dietary intakes estimates for the sensitive subpopulations identified?

- No sensitive subpopulations were identified.
- Given the wide variety of sources of Mo in the diet, it is hard to imagine that the dietary exposure to Mo for any potential sensitive subpopulation is different than it is for the general population.

*"**EPA Region 8 proposes using data on the dietary intake of molybdenum as reported by the Institute of Medicine (National Academies Press, 2001) to calculate the RSC**. Data from the total diet study indicate an average intake of 0.109 mg/day for men and 0.076 mg/day for women. Another report (Tsongas et al., 1980) indicate intakes range from 0.12 to 0.24 mg/day, with an average intake of 0.18 mg/day. Using the maximum value of 0.24 mg/day and dividing by the body weight of 80 kg gives 0.003 mg/kg bw-day. Thus intake from the diet is only a small percentage (less than 1%) of the calculated RfD. . . . This justifies use of the RSC of 0.8, the maximum value permitted (U.S. EPA, 2000)."*

-- US EPA Region 8 (2017) Letter from Sandra D. Spence, Chief, Water Quality Unit to David Baumgarten, Chair, Water Quality Control Commission. October 27, 2017.

Step 9 of Decision Tree, Cont'd

Does Climax have any data on levels of molybdenum in drinking water in areas with elevated molybdenum and how this could impact levels in cooked foods?

- EPA's updated drinking water intake rate of 2.4 L/day accounts for exposure through direct and indirect means, including cooking *(See EPA Response to Scientific Views from the Public on Draft Updated National Recommended Water Quality Criteria for the Protection of Human Health, p. 11 (2015))*
- Data on the potential impact of elevated levels of substances in drinking water on cooked foods are uncommon.
- A study by Jaafar et al. (2017) reported that the Mo level in cooked rice doubled when using water containing 1300 mcg Mo/L
- Even if the daily dietary intake of Mo from all foods were doubled, the RSC of 80% would still be justified

"Although food cooked in molybdenum containing drinking water will increase the dietary contribution of molybdenum, ***the dietary molybdenum will still be only a small percentage of the RfD.*** *This justifies use of the RSC of 0.8, the maximum value permitted (U.S. EPA, 2000).*"

-- US EPA Region 8 (2017) Letter from Sandra D. Spence, Chief, Water Quality Unit to David Baumgarten, Chair, Water Quality Control Commission. October 27, 2017.