IMOA
THE VOICE OF THE MOLYBDENUM INDUSTRY

14 November 2024

TO: Illinois Pollution Control Board

FR: International Molybdenum Association

RE: R2022-18 - Groundwater – Molybdenum – Proposed Rule – Proposed second notice

IMOA thanks the IPCB both for this further opportunity to comment on the proposed Class I Molybdenum groundwater quality standard of 23 µg Mo/L, and for their decision to base calculations on the scientific dataset in the US ATSDR 2020 Toxicological Profile for Molybdenum.

Having reflected upon the contents of the Molybdenum section of the IPCB Opinion and Order document dated 17 October 2024 in relation to the R22-18 proposed rule/proposed second notice, we summarize below four key insights for your consideration, the first of which we assert is a sufficient basis to further review and revise the unwarranted low current proposed Mo value of 23 µg/L.

Insight 1: Why a sub-chronic to chronic Uncertainty Factor (UF) of 10 is demonstrably unwarranted:

- Molybdenum is an essential element for all humans (plants and animals). Internal exposures are regulated by homeostatic mechanisms, that exist for all essential elements. Thus the intake requirements for essential elements and vitamins do not change based on the duration of exposure. The body regulates these substances in a manner that the recommended daily allowance is the same, whether exposure is sub-chronic or chronic, unless the exposures greatly exceed the daily requirements. The molybdate ion $(MoO_4)^{2-}$ is the form in which molybdenum is taken up into the human body by all routes of exposure.

- According to the National Academy of Sciences Institute of Medicine (IOM, 2001), "Stable isotope studies showing molybdenum intakes and rapid excretion at high intakes suggest the kidney is the primary site of molybdenum homeostatic regulation."[1] Similarly, IOM (2001) noted that balance studies in humans have established homeostasis is maintained over a wide range of dosage. Homeostatic mechanisms prevent overexposures and underexposures to essential elements over a lifetime, obviating the need for a sub-chronic to chronic UF.

- IEPA assert that 'ATSDR's sub-chronic toxicity value should not be used without applying an additional uncertainty factor of 10 for sub-chronic to chronic extrapolation'. The RfD of 0.006 mg/kg-day proposed by IEPA by adding an additional 10-fold uncertainty factor to the ATSDR MRL, *which already has a 300-fold combined uncertainty/modifying factor,*

[1] Institute of Medicine. 2001. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. Washington, DC: National Academies Press

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represents a combined uncertainty/modifying factor of 3000. Applying a 3000-fold combined factor in a risk assessment of an essential element is unprecedented and unwarranted, when in fact, a sub-chronic to chronic UF has never been used for a risk assessment of any essential element, based on the 22 risk assessments of essential elements by EPA, ATSDR, and the IOM.

- ATSDR's MRL of 0.06 mg Mo/kg/day is indeed based on the *sub-chronic* 90-day repeated dose toxicity study (Murray et al. 2014a), *but* it must be recognised and taken into account by IEPA/IPCB that there also exists a highly relevant *chronic* inhalation toxicology study conducted and published by the NTP In 1997. The test item was molybdenum trioxide which converts to bioavailable molybdate in the respiratory tract. Rats and mice were exposed to molybdenum trioxide via inhalation at 100 mg/m^3 for 2 years. The key take-away is that the *NOAEL in the chronic toxicity study of molybdenum is not lower than the NOAEL in the sub-chronic toxicity study*, as determined by comparable blood molybdenum concentrations:
    - NTP 2-year study: 2.41 ± 0.48 µg/g among female rats at the NOAEL at the end of the chronic study.[2]
    - Murray et al 2014a: 2.63 ± 0.48 µg/g among female rats at the NOAEL at the end of the sub-chronic study[3]

- The NOAEL (17 mg Mo/kg bw/day) in the Murray sub-chronic study (i.e., the critical study used to develop the ATSDR MRL) is based on the most sensitive endpoint of renal tubule hyperplasia. According to the NTP (1997), the male and female rats exposed to molybdenum trioxide at concentrations up to 100 mg/m^3 for 2 years (a dose level that produced a blood molybdenum level comparable to that seen at the NOAEL in the sub-chronic toxicity study) "did not show any signs or symptoms of renal effects,"[4], or indeed any systemic toxicity.

- These results indicate the NOAEL for kidney effects for molybdenum was the same after a 2-year chronic exposure as it was after a 90-day sub-chronic exposure at comparable systemic (internal) doses of molybdenum. *In short, the NOAEL for chronic systemic exposure to molybdenum is <u>not lower</u> than it is for sub-chronic systemic exposure.* ***This is compelling molybdenum-specific evidence that no sub-chronic to chronic UF is required.***

- It should also be borne in mind that an "ATSDR MRL may already be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals"[5]. This is because "ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive[4]", hence the already embedded level of precaution within the MRL value. In the case of molybdenum the ATSDR modifying factor (MF) of 3 means it is 300-fold.

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[2] NTP (1997) NTP Technical Report on the Toxicology and Carcinogenesis of Studies of Molybdenum Trioxide. TR 462. Appendix G.
[3] Murray et al 2014a, Regulatory Toxicology & Pharmacology 70 (2014) p.585, Table 5
[4] NTP (1997) NTP Technical Report on the Toxicology and Carcinogenesis of Studies of Molybdenum Trioxide. TR 462. p. 56.
[5] ATSDR 2020 Toxicological Profile for Molybdenum, p. A-1.

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- We bring to your attention that EPA Region 8 diligently reviewed the data from the NTP chronic toxicity, as well as the details of the 90-day sub-chronic toxicity study of molybdenum, in its recent rebuttal comments in Colorado. EPA Region 8 concluded:

    - "The evidence available from molybdenum studies for kidney health effects, the most sensitive endpoint reported following repeated molybdenum exposure (ATSDR, 2020), supports the conclusion that **application of an uncertainty factor to account for sub-chronic to chronic exposures is unnecessary for the intermediate duration oral MRL.** However, it would not be constructive or appropriate to broadly apply this conclusion to evaluations of other agents as an *a priori* assumption; rather, the database for each compound should be evaluated appropriately according to current Agency guidance (e.g., USEPA 2002; USEPA, 2012). "[6] [emphasis added].

- Also worthy of note is that EPA's practices also do not support the application of a sub-chronic to chronic UF for essential elements. While EPA often uses sub-chronic to chronic UFs for non-essential substances, EPA has never used a sub-chronic to chronic uncertainty factor for any essential element, including molybdenum.[7] As already commented, in fact a sub-chronic to chronic UF has never been used for a risk assessment of any essential element, based on the 22 risk assessments of essential elements by EPA, ATSDR, and the IOM. Only two of the 22 risk assessments of essential elements are based on a chronic toxicity study, and none is based on a 2-generation reproductive toxicity study. *In other words, 20 out of 22 risk assessments of essential elements by ATSDR, EPA, and IOM chose not to use a sub-chronic to chronic uncertainty factor (UF) even though the critical study was neither a chronic toxicity study nor 2-generation reproductive toxicity study.* These results reflect that the default practice of IOM, EPA and ATSDR is not to use a sub-chronic to chronic UF for essential elements in the absence of a chronic toxicity study.

For all the above reasons, *IMOA's clear and substantiated position is that an UF10 is demonstrably unwarranted and should not be included in the calculation method.*

IMOA therefore respectfully requests IPCB to further review this aspect of the Mo WQS derivation calculation and to eliminate the UF10 for sub-chronic to chronic. This is supported by a high-quality chronic study with Mo blood level evidence that demonstrates the *NOAEL for chronic systemic exposure to molybdenum is not lower than it is for sub-chronic systemic exposure*, which compellingly obviates the need for a UF10.

Insight 2: The most recent EPA RSC-determination guidance derives an RSC of 0.8:

- IEPA commented: "If exposure is almost entirely from food, an RSC value representing 80% of molybdenum human exposure via drinking water is not appropriate. An RSC value of 20%

[6] EPA Region 8 (2024) Rebuttal Comments, p. 5
[7] Written testimony of Dr. Murray, March 6, 2024, pp 17-

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(0.2) is the more appropriate value for molybdenum's contribution to human exposure via water ingestion." IMOA respectfully disagrees on the following basis:

- The purpose of the Relative Source Contribution (RSC) is to determine what percentage of exposure to a substance is safely permitted in drinking water while taking into account the acceptable daily exposure and the amount of exposure that occurs from food. With an essential element, it is important to prevent too little as well as too much exposure because both inadequate and excessive intake may pose health risks. It is widely acknowledged that the dietary intake of molybdenum in the U.S. is adequate to meet the minimum daily requirements for molybdenum. However, the determinant of the RSC is not how much additional exposure to molybdenum via drinking water is needed to meet the recommended daily allowance (RDA). *Rather, the issue for determining the RSC is how much additional exposure to molybdenum can a person have from drinking water without posing a risk of overexposure to molybdenum.* In other words, an RSC for an essential element is determined the same way as an RSC for a non-essential substance.

- To determine the RSC for molybdenum, it is appropriate to use the most recent EPA guidance, which appears in its "Methodology for deriving ambient water quality criteria for the protection of human health" dated October 2000 (the "EPA Methodology Guidance"). EPA's Methodology Guidance provides a detailed Decisions Tree for determining the RSC.

- In 2024, as part of the proceedings in Colorado, the RSC for molybdenum was determined to be 0.8 based on the EPA Methodology Guidance and its RSC Decision Tree based on the ATSDR MRL. The details of each step in the Decision Tree are presented in a report entitled 'Application of the EPA Exposure Decision Tree for Defining the Relative Source Contribution (RSC)for Molybdenum in Drinking Water" dated March 6, 2024, and a copy is attached as Appendix 2. The evaluation supports the use of EPA's subtraction method for establishing a RSC of 0.8 for molybdenum.

- The Colorado Department of Public Health and Ecology (CDPHE) agreed with the choice of a RSC of 0.8 for molybdenum. Together with extensive involvement of EPA Region 8, they spent 7+ years and major resources on establishing their water supply standard (530 µg Mo/L). Stakeholder concern was particularly high in Colorado given the mining of large natural molybdenum deposits, which is not a concern in Illinois.

- A further supportive example of a significantly higher RSC than 20% can be found in the groundwater calculation methodology of Wisconsin state that goes beyond 80% and uses ***100% as the RSC:***

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Standard Selection

DHS recommends an enforcement standard of 60 µg/L for molybdenum.

Basis for Enforcement Standard
☐ Federal Number
☐ Cancer Potential
☐ EPA Acceptable Daily Intake
☑ Technical information

The current enforcement standard for molybdenum is based on a lifetime health advisory set by the EPA in 1993. Since this time, a number of studies have been published evaluating the health risk of molybdenum. In 2020, the Agency for Toxic Substances and Disease Registry (ATSDR) updated their intermediate-duration oral miniumum risk level to be based on a 2014 subchronic toxicity study in rats by Murray et al.[2, 14, 15]

DHS calculated the recommended enforcement standard (ES) using ATSDR's intermediate-duration oral minimum risk level for molybdenum (0.06 mg/kg-d), an average body weight of 10 kg, a water consumption rate of 1 liter per day (L/d), and a relative source contribution of 100% as specified in Chapter 160 of Wisconsin Statute.

Also a very significant note in the red box above, in relation to Insight 1, is that the Wisconsin calculation methodology applies no sub-chronic to chronic UF of 10.

Insight 3: Since US ATSDR published their 2020 Toxicological Profile for Molybdenum, it is the preferred choice of risk assessment basis for US states seeking to determine potable water standards:

- IEPA, in their September 2024 response, provided a table showing six out of eight states contacted by IEPA as using EPA's IRIS as the RfD source to determine potable water standards. What is not clear is whether any of these six states have actually established a potable water standard for molybdenum. For example, California, one of the states reported to rely on EPA IRIS, has never established a drinking water primary or secondary Maximum Contaminant Level (MCL) or a Public Health Goal (PHG) for molybdenum.

- By contrast, what is clear is that to the best of our knowledge only two states, Colorado and Wisconsin, have determined a potable water standard for molybdenum since 2020, and both relied upon the more recent science in the 2020 ATSDR Tox Profile for Molybdenum. Colorado concluded on 530 µg Mo/L, and Wisconsin on 600 µg Mo/L, which contrast markedly with IEPA/IPCB's current proposal of 23 µg Mo/L. Without the UF10, a 230 µg Mo/L value would still be very precautionary, being less than half the derived values in the two afore-mentioned states.

Insight 4: Koval'skiy 1961 is the basis for the >30 years-outdated 1992 US IRIS RfD, and a new epidemiologic study, Joun et al 2024, demonstrates the opposite of what Koval'skiy reported:

A newly published study provides additional support for IPCB's decision to use ATSDR as the scientific basis for its assessment, and not the vastly outdated US IRIS database for molybdenum:

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- Very recently (August 2024), a high-quality epidemiologic study using data from the US National Health & Nutrition Examination Survey (NHANES) was published in peer-reviewed scientific literature.

- This study by Joun et al. (2024) "found molybdenum in the human kidney proximal tubular epithelial cells provided antioxidative benefits in the presence of oxidative stress and that urinary molybdenum-to-creatinine ratio is associated with lower levels of systemic inflammation and oxidative stress and a reduced prevalence of hyperuricemia and gout in the general U.S. adult population."[8] Based on over 15,000 participants in the U.S., Joun et al. (the "Joun study) provides convincing evidence in humans that increasing levels of exposure to molybdenum are statistically significantly associated with a ***decreased*** prevalence of hyperuricemia and gout (whereas Koval'skiy reported the opposite). The Joun study also showed that higher urinary molybdenum levels are associated with lower levels of systemic oxidative stress using human kidney proximal tubular epithelial cells *in vitro*. The authors hypothesized that "Molybdenum's antioxidative properties might have acted as an important mechanism for the reduction of systemic inflammation, ROS and uric acid levels." In other words, the Joun study offers a possible explanation for the beneficial effect of molybdenum on the kidneys.

- ATSDR (2021) was highly critical of the Koval'skiy et al. study. For example, ATSDR noted the outdated colorimetric analytical methods for molybdenum and uric acid used by Koval'skiy et al. In the Joun study, the measurement of urinary levels of molybdenum was conducted by inductively coupled plasma mass spectrometry (ICPMS), which is the current state-of-the art analytical method for measuring molybdenum.

In conclusion, IMOA thanks IPCB for its in-depth consideration of the insights contained in this document. Based on its substantiated technical content we respectfully request IPCB further review the Illinois calculation method, deleting the unnecessary UF10 for sub-chronic to chronic exposure, and likewise adjusting the RSC upwards well beyond its current 20%.

With kind regards.

Sandra Carey

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Enc.

Annex 1

Annex 2

[8] Joun JH, Lillin L, An JN, Jang J, Oh YK et al. (2024) Antioxidant effects of molybdenum and its association with reduced prevalence of hyperuricemia in the adult population. Plos One 19(8):e0306025.

Table 2. Summary of intraspecies uncertainty factors (UF), modifying factors, and subchronic to chronic UF used in 22 risk assessments of essential elements conducted by the IOM, US EPA, and ATSDR

Essential Element	Effect	Intraspecies UF	Modifying Factor (MF)	Subchronic to chronic UF	Intraspecies UF x MF
Calcium: IOM UL (1997)	Hypercalcemia and renal insufficiency	2	1	—	2
Copper: IOM UL (2001)	Liver damage in adult volunteers	1	1	—	1
Copper: ATSDR MRL (2004)	GI disturbances in humans	3	1	—	3
Fluoride: IOM UL (1997)	Moderate enamel fluorosis in humans	1	1	—	1
Fluoride: EPA RfD (1997)	Dental fluorosis in humans	1	1	—	1
Fluoride: ATSDR MRL (2003)	Hip fractures in humans	3	1	—	3
Iodine: IOM UL (2001)	TSH secretion in humans	1.5	1	—	1.5
Iodine: ATSDR MRL (2004)	Subclinical hypothyroidism in humans	1	1	—	1
Iron: IOM UL (2001)	GI effects in humans	1.5	1	—	1.5
Magnesium: IOM UL (1997)	Diarrhea in some adults	1	1	—	1
Manganese: IOM UL (2001)	Increase in SOD in humans	1	1	—	1
Manganese: EPA RfD (1995)	CNS effects in humans	1	1[a]	—	1
Molybdenum: IOM UL (2001)	Repro effects in rats	3	1	—	3
Molybdenum: EPA RfD (1992)	Increased uric acid in volunteers	3	1	—	3
Molybdenum: ATSDR MRL (2020)	Kidney effect in rats	10	3[b]	—	30
Phosphorus: IOM UL (1997)	Hyperphosphatemia in humans	2.5	1	—	2.5
Selenium: IOM UL (2000)	Selenosis in humans	2	1	—	2
Selenium: EPA RfD (1991)	Symptoms of selenosis in humans	3	1	—	3
Selenium: ATSDR MRL (2003)	Symptoms of selenosis	3	1	—	3
Zinc: IOM UL (2001)	Human RBC Cu-Zn SOD	<1.5[c]	1	—	1.5
Zinc: EPA RfD (2005)	Human RBC Cu-Zn SOD	3	1	—	3
Zinc: ATSDR MRL (2005)	Human RBC Cu-Zn SOD	3	1	—	3

[a] MF of 3 recommended for drinking water and soil ingestion (total UF/MF would = 3). EPA (1995) described four reasons for the MF of 3. EPA Drinking Water Health Advisory for Manganese (2004) said the MF of 3 was "mainly for bioavailability concerns" in food vs. water.
[b] MF of 3 for concern that reproductive and/or developmental effects may be a more sensitive endpoint than kidney effects in populations with marginal copper intakes.
[c] UF of 1.5 based on both interindividual variability and to extrapolate from LOAEL to NOAEL
IOM = Institute of Medicine; UL = Upper Limit; ATSDR = Agency for the Toxic Substances and Disease Registry; MRL = Minimal Risk Level; EPA RfD = US EPA Reference Dose; TSH = thyroid stimulating hormone; SOD = superoxide dismutase; CNS = central nervous system; RBC = red blood cell; Cu = copper; Zn = zinc

Appendix B

Application of the EPA Exposure Decision Tree for Defining the Relative Source Contribution (RSC) for Molybdenum in Drinking Water

By F. Jay Murray, Ph.D.

Summary

The purpose of this report is to evaluate the appropriate relative source contribution (RSC) factor for molybdenum for a Colorado water supply standard that is protective statewide and in Summit County. For this evaluation, I used the most recent guidance from the US Environmental Protection Agency (EPA), which appears in its “Methodology for deriving ambient water quality criteria for the protection of human health” dated October 2000 (the “EPA Methodology Guidance”).[1] This report uses EPA’s Exposure Decisions Tree for apportionment of a proposed Reference Dose (RfD) that is described in Figure 4-1 of the EPA Methodology Guidance, as shown on the next page. The ATSDR Minimal Risk Level (MRL) was chosen herein as the Reference Dose in order to calculate the RSC. The current report describes the steps and pathway in EPA’s Exposure Decision Tree that supports the use of the subtraction method for establishing a RSC of 0.8 (80%) for molybdenum.

Importantly, EPA Region 8 came to the same conclusion in 2017 in “EPA’s Rebuttal Comments on the Proposed Revisions to Regulation 31 and 33 (Molybdenum).”[2] EPA Region 8 employed the subtraction method to establish an RSC for molybdenum in drinking water. Both EPA Region 8 and the current evaluation used the conservative “high-end exposure to molybdenum from food” estimate of 240 mcg/day in its calculation of the RSC.[3] To calculate the RSC, EPA Region 8 used the yet-to-be-published 2-generation reproductive toxicity study by Murray et al. (2019) to establish a Reference Dose for molybdenum.[4] Both EPA Region 8 and the current report came to the same conclusion: the RSC of 0.8 (i.e., 80%) is justified using EPA’s Exposure Decision Tree methodology because dietary intake remains only a small percentage of the total allowable daily intake of molybdenum.

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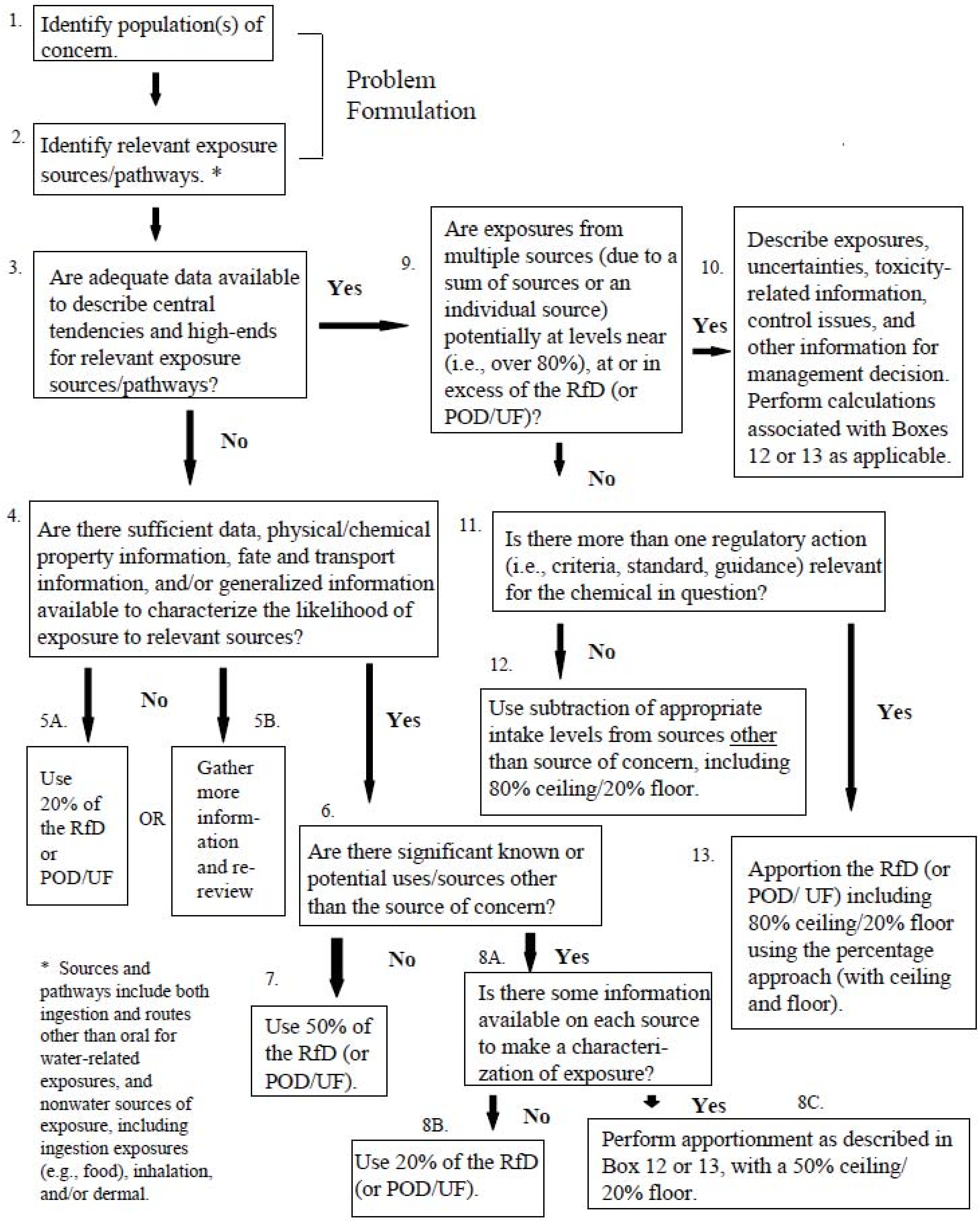
[1] US EPA (2000) Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health. Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health (2000) (epa.gov)
[2] EPA Region 8 (2017) Letter from Sandra D. Spence, Chief, Water Quality Unit to David Baumgarten, Chair, Water Quality Control Commission. November 22, 2017.
[3] Id.
[4] Id.

Figure 4-1

Exposure Decision Tree for Defining Proposed RfD (or POD/UF) Apportionment



Step 1: Identify population(s) of concern for a drinking water standard in Colorado

The population of concern for molybdenum (Mo) in drinking water is the general population of Colorado. No sensitive subpopulations were clearly identified. Because the richest sources of molybdenum in the diet are legumes, grains, and leafy vegetables (and not meat), vegans are expected to ingest more molybdenum than meat-eaters. The estimated increased intake of molybdenum associated with a Vegan diet was taken into consideration in the current evaluation, and the difference is not enough to change the RSC. The potential impact of a Vegan diet on dietary exposure to molybdenum is discussed in greater detail in Step 3 herein.

Step 2: Identify relevant exposure sources/pathways

Food

Molybdenum is a naturally occurring trace element that can be found extensively in nature. Biologically, it plays an important role as a micronutrient in plants and animals, including humans. For most of the general population of the United States (U.S.), the exposure to molybdenum occurs primarily through food. Foods derived from above-ground plants, such as legumes, leafy vegetables, and cauliflower, generally have a relatively higher concentration of molybdenum in comparison to food from tubers or animals. Beans, cereal grains, leafy vegetables, legumes, liver, and milk are reported as the richest sources of molybdenum in the average diet (Barceloux 1999).[5] The dietary intake of molybdenum has been studied and defined. Daily consumption of molybdenum has been estimated in multiple studies in the U.S. and internationally. Molybdenum is an essential element for humans, and the daily dietary intake is similar around the world. The U.S. Food and Drug Administration (FDA) has measured the molybdenum content of hundreds of foods as recently as 2018-2020 as part of the FDA Total Diet Study.

Drinking water

The other relevant exposure pathway to molybdenum is drinking water. For the vast majority of the general population in the U.S., molybdenum exposure via drinking water is very low (<1 to 40 µg/L). However, in certain states, including Colorado, drinking water coming from sources near natural molybdenum deposits, molybdenum mining or industrial effluents may contain a higher concentration of molybdenum.

Mining molybdenum is economically and environmentally important. Molybdenum is used primarily in metallurgical applications, including as an alloying agent in stainless steel, cast iron, and superalloys to enhance properties such as hardenability, strength, toughness, and wear- and corrosion-resistance. As green technology is becoming more popular, molybdenum has become

[5] Barceloux, DG (1999) Molybdenum. J Toxicol Clin Toxicol 37(2):231-7.

increasingly important in areas like biofuels, catalysts, ethanol, solar panels, and wind power (USGS 2015a).

Colorado plays a unique role in molybdenum mining. Colorado has large, high-quality deposits of molybdenum ore. Historically, the Climax Mine in Colorado was the largest source of mined molybdenum in the world, and currently Colorado is the only place outside of China that has primary production of high-purity molybdenum concentrates. The Climax mine employs more than 400 people and is a significant contributor to the rural communities in which it operates.

Inhalation

For the general population, exposure to molybdenum by inhalation is negligible compared to dietary intake.[6] According to the ATSDR, molybdenum is infrequently detected in the ambient air.[7] EPA reported molybdenum concentrations in ambient air range from below detection limits to 0.03 $\mu g/m^3$.[8] A person inhaling ambient air containing 0.03 $\mu g/m^3$ for 24 hours per day would inhale only about 0.6 mg per day. Concentrations of molybdenum in ambient air of urban areas, 0.01-0.03 $\mu g/m^3$, are higher than those found in rural areas, 0.001-0.0032 $\mu g/m^3$.[9] According to ATSDR, EPA's Air Quality System Database reported 24-hour concentrations of molybdenum in locations in several states (CA, MI, TX, VT) for 2018; the results are summarized in Table 5-7 in the ATSDR Tox Profile.[10, 11] The vast majority of these molybdenum air concentrations were well below 0.03 $\mu g/m^3$.[12] In summary, inhalation of molybdenum is not a relevant exposure pathway for the general population.

Dermal contact

For the general population, exposure to molybdenum by dermal contact is negligible. Molybdenum is poorly absorbed through the skin.[13,14] The amount of exposure to molybdenum from skin contact is insignificant compared to the molybdenum exposure from food and drinking water. Therefore, dermal contact is not a relevant exposure pathway for the general population.

[6] ATSDR (2020) Toxicological Profile for Molybdenum. p. 104. Toxicological Profile for Molybdenum (cdc.gov)
[7] Id., p. 84.
[8] US EPA (1979) Human health effects of molybdenum in drinking water. U.S. Environmental Protection Agency. EPA600179006. PB292755.
[9] Barceloux DG. 1999. Molybdenum. J Toxicol Clin Toxicol 37(2):231-237.
[10] US EPA. 2018c. EPA Air Quality System database: Molybdenum. Washington, DC: U.S. Environmental Protection Agency. https://www.epa.gov/outdoor-air-quality-data. June 10, 2019.
[11] ATSDR (2020) Toxicological Profile for Molybdenum. p. 104. Toxicological Profile for Molybdenum (cdc.gov)
[12] US EPA reported higher air concentrations of molybdenum at a single location in Michigan, with an arithmetic mean concentration of 3.08 $\mu g/m^3$ and a 99th percentile concentration of 49.5 $\mu g/m^3$. The highest value appears to be an outlier. Another possibility is that the sampling at this single location in Michigan was not an ambient air sample or an ambient air sample at an unusual location. ATSDR (2020) did not discuss EPA's individual sample results.
[13] Teasdale A, Ulman K, Walsh P, Domoradzi J (2015) Establishing limits for dermal absorption of elemental impurities. Pharm Technol 39(9):44-51.
[14] ATSDR (2020) Toxicological Profile for Molybdenum. p. 64. Toxicological Profile for Molybdenum (cdc.gov)

Soil ingestion

Most, if not all, essential elements are present in the soil because they are essential to plants. The potential exposure to molybdenum in soil is expected to be small in relationship to the dietary intake of molybdenum. The average concentration of molybdenum in soils is generally 1–2 ppm.[15] In the United States, it has been reported that the median concentration of molybdenum in soils is 1.2–1.3 ppm, with a range of 0.1–40 ppm (EPA 1979).[16] Conservative default daily soil, dust, and sediment ingestion rates in ATSDR's Public Health Assessment Guidance Manual (PHAGM) are: (1) 100 mg/day for adults and children age 11 and up, and (2) 200 mg/day for children under 11 years of age; these values are Reasonable Maximum Exposures (RME), which refers to people who are at the high end of the exposure distribution (approximately the 95th percentile).[17] According to ATSDR, the Central Tendency Exposure (CTE) values are 30 mg/day for adults and children age 11 and up, and 60 mg/day for children under 11 years of age; the CTE refers to individuals who have average or typical exposure to a contaminant.

A child under 11 years of age ingesting the ATSDR's RME (200 mg/day) at a median concentration of 1.3 ppm of molybdenum would ingest 0.26 µg Mo/day (0.0000013 mg Mo/mg of soil x 200 mg soil/day = 0.00026 mg Mo/day = 0.26 µg Mo/day). An adult or a child of at least 11 years would ingest half this amount (0.13 µg Mo/day) at the RME of 100 mg/day. These are tiny amounts compared to dietary intake of molybdenum based on a conservative default estimate of the amount of soil ingested at approximately the 95th percentile. Even at the highest soil concentration of molybdenum of 40 ppm reported by EPA (1979), the amount of molybdenum ingested at approximately the 95th percentile for soil ingestion would be 8.0 and 4.0 mcg/day per day for a child under 11 year and an adult, respectively. Importantly, these exposure estimates assume that 100% of the molybdenum ingested on soil is ingested. However, it is likely that only a portion that is not adsorbed to soil is available for absorption across the GI tract.

Summary

For determining the RSC for a water supply standard for molybdenum in Colorado for the general population, there are two relevant exposure pathways: food and drinking water. Exposures via inhalation, dermal contact, and soil ingestion are negligible and not relevant exposure pathways for the general population.

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[15] Id.

[16] EPA (1979) Human health effects of molybdenum in drinking water. U.S. Environmental Protection Agency. EPA600179006. PB292755. http://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=2000Z0FV.txt. October 2, 2015.

[17] ATSDR (2018) Exposure Dose Guidance for Soil and Sediment Ingestion, V1 – Sept 25, 2018 ATSDR EDG for Soil and Sediment Ingestion (cdc.gov)

Step 3. Are adequate data available to describe central tendencies and high-ends for relevant exposure sources/pathways?

Yes. Adequate data exist to describe the central tendencies and the high end of the range for exposures to molybdenum in both food and drinking water.

According to 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."[18] The data are adequate to describe the central tendency and the high-end exposure to molybdenum based on professional judgment and the large number of scientific publications on dietary exposures to molybdenum with generally consistent results.

The determination that there are adequate data is consistent with EPA positions in 2017, where it said: "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."[19]

Food

As noted earlier, for the majority of the general population in the U.S., food is the largest source of exposure to molybdenum. According to the National Academy of Sciences (NAS) Food and Nutrition Board (2001), the average dietary intake of molybdenum in the U.S. by adult men and women are 109 and 76 µg/day, respectively.[20] The dietary intake of molybdenum ranged from 74 to 126 µg molybdenum in a study of older children and adults in the northeastern U.S.[21]

Based on a review article by Barceloux (1999), the ATSDR Toxicological Profile for Molybdenum (2020) reported that a study of the dietary intake of adult residents in Denver, Colorado had an average molybdenum ingestion rate of 180 µg/day, with a range of 120 to 240 µg/day.[22] However, the study described by Barceloux was actually conducted by Tsongas et

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[18] US EPA (2000) Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health. Pages 4-10 to 4-12 [Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health (2000) (epa.gov)]
[19] EPA Region 8 (2017) Letter from Sandra D. Spence, Chief, Water Quality Unit to David Baumgarten, Chair, Water Quality Control Commission, p. 16. November 22, 2017
[20] NAS. (2001) Molybdenum. In: Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. Washington, DC: National Academies Press, 420-439.
[21] Pennington JAT, Young BE, Wilson D. (1989) Nutritional elements in U.S. diets: Results from the total diet study, 1982–1986. *J Am Diet Assoc* **89**:659–664.
[22] Barceloux DG (1999) Molybdenum. J Toxicol Clin Toxicol 37(2):231-237.

al. (1980), and it did not evaluate the dietary intake of molybdenum among adult residents in Denver.[23] The authors of the Tsongas et al. (1980) study were investigators at the University of Colorado School of Medicine, and they estimated that the average daily dietary intake of molybdenum ***for the average person in the United States***. Foods were purchased from five major supermarket chains in the Denver area between 1975-1977 and analyzed for molybdenum content using the colorimetric thiocyanate analytical method, which is a primitive analytical standard by current standards. According to the investigators, "Several buyers from supermarkets serving the Denver metropolitan area were interviewed to determine what foods were purchased most frequently and in greatest bulk." However, foods purchased most frequently from supermarket chain stores in Denver are probably similar to those purchased in other regions of the United States, and the investigators used these results to estimate the average dietary intake for the average person in the United States. Tsongas et al. also used U.S. government databases to estimate the serving size and the frequency of consumption of each food. In other words, Tsongas et al. did not evaluate the serving size and the frequency of consumption of foods by residents of Denver. These investigators estimated that the average dietary consumption for the average person in the United States varies between 120 and 240 µg/day, depending on age, sex, and income.[24]

The dietary intake of molybdenum has been evaluated in other countries, and the results are similar to those in the U.S. For example, the average dietary intake of molybdenum in men and women in Germany was reported to be 100 and 89 µg/day, respectively.[25] The daily dietary intake of molybdenum was higher among German vegetarians: 170 and 179 µg/day among vegetarian men and vegetarian women, respectively.[26] Among the general population in Mexico, the daily dietary intake of molybdenum was estimated to be 208 and 162 µg/day for men and women, respectively.[27] In Japan, the average daily dietary consumption of molybdenum was estimated to be 225 µg/day for men and women combined based on the levels of Mo in foods and Japan's National Nutrition Survey of food consumption in Japan.[28] The principal source of molybdenum in the Japanese diet was rice followed by soybean products, and approximately 90% of the Mo intake was derived from plant foods.[29]

In addition to the above estimates of dietary intake, a summary of molybdenum concentrations positively identified in foods analyzed during the FDA Total Diet Study (TDS) of 2006–2011,

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[23] Tsongas TA, Meglen RR, Walravens PA, Chappell WR (1980) Molybdenum in the diet: an estimate of average daily intake in the United States. Am J Clin Nutr 33(5): 1103-7.
[24] Id.
[25] Holzinger S. Anke M, Rohrig B, Gonzalez D (1998) Molybdenum intake of adults in Germany and Mexico. Analyst 123(3):447-50.
[26] Id.
[27] Id.
[28] Hattori H, Ashida A, Ito C, Yoshida M (2004) Determination of molybdenum in foods and human milk, and an estimate of average molybdenum intake in the Japanese population. J Nutr Sci Vitaminol 50(6):404-9. doi: 10.3177/jnsv.50.404
[29] Id.

2013–2014, and now 2018–2020 are available.[30] The data for molybdenum arose from Market Basket Surveys in which 382 store-bought foods purchased in up to six geographic regions of the United States were analyzed. These data can be used in combination with serving size and frequency of consumption, to estimate dietary exposure to molybdenum.

Another survey of levels of molybdenum in food found the highest molybdenum concentrations in legumes; grains and grain products; nuts; meat, fish, and poultry (including liver); eggs; and milk, yogurt, and cheese (76.7, 30.0, 29.5, 8.9, 6.3, and 4.6 μg/100 g, respectively).[31]

The European Food Safety Authority (EFSA) used dietary intake studies to derive estimates of which foods were most responsible for molybdenum intake in European populations.[32] Cereals and cereal-based products (including bread) are the largest contributors to molybdenum intake in a Western diet; these products contribute one-third to one-half of the total molybdenum intake. Other contributors to total molybdenum intake include dairy products and vegetables.

A survey of locally grown produce in Summit County, Colorado, near a large molybdenum mine found no evidence to suggest that local residents were exposed to more molybdenum in their diet than the average person in Colorado, or nationally (Climax Molybdenum Company 2021).[33] There is little produce grown in Summit County due to climate. Produce that is being locally grown is grown with non-native soils (i.e., soils that would have average Mo concentrations), and with water that has Mo concentrations below 210 μg/L.

A question was raised about likely increases in dietary intake of molybdenum among vegetarians and vegans. Vegans do not eat meat, fish, dairy and eggs, and they are expected to ingest greater amounts of the foods that are rich in molybdenum, such as grains, legumes, nuts, and leafy green vegetables. The EPA methodology for calculating RSCs does not call for distinguishing between meat-eaters, vegetarians, and vegans. Such data generally do not exist, and I did not find any studies in the scientific literature that directly estimated the dietary intake of molybdenum for vegetarians or vegans. However, there is a way to estimate the dietary intake of molybdenum among vegetarians and vegans, as described below.

A recent scientific publication evaluated the nutrient intake of essential elements, vitamins and other dietary constituents among adults and adolescents consuming plant-based diets compared to meat-eaters.[34] This study reported increased intakes of fiber, polyunsaturated fatty acids,

[30] FDA (2022) Total Diet Study: FY2018-FY2020 TDS Elements Report Supplement: Summary of Analytical Results. FDA Total Diet Study (TDS): Results | FDA
[31] Pennington JA, Jones JW (1987) Molybdenum, nickel, cobalt, vanadium and strontium in total diets. J Am Diet Assoc 87(12):1644-50.
[32] EFSA (2013) Scientific opinion on dietary reference values for molybdenum. EFSA Panel on Dietetic Products, Nutrition, and Allergies (NDA). EFSA Journal 11(8):3333
[33] Climax Molybdenum Company. Summit County Produce Study. June 2021.
[34] Neufingerl N and Eilander A (2022) Nutrient intake and status in adults and adolescents consuming plant-based diets compared to meat-eaters: a systematic review. Nutrients. 14(1):29.

folate, Vitamin C, Vitamin E, iron and magnesium among vegans compared to meat-eaters (Table 1). The ratio of the intake by vegans relative to meat-eaters ranged from 2.08-fold (fiber) to 1.27-fold (iron).

Table 1. Comparison of average intake of various dietary substances that were observed to be greater among vegans based on 141 studies mostly from Europe, South/East Asia and North America (Neufingerl N and Eilander A, 2022)[a][35]

Dietary Substance	Average Intake			Vegetarian/M.E.	Vegan/M.E.
	Meat-eaters (M.E.)[a]	Vegetarian[b]	Vegan[c]		
Fiber	14.3 g/d	15.5 g/d	29.8 g/d	1.08	2.08
PUFA[d]	4.6%	6.8%	8.0%	1.48	1.74
Folate	199 µg/d	247 µg/d	362 µg/d	1.24	1.82
Vitamin C	83 mg/d	85 mg/d	120 mg/d	1.02	1.45
Vitamin E	7.1 mg/d	8.0 mg/d	13.3 mg/d	1.13	1.87
Iron	10.6 mg/d	10.5 mg/d	13.5 mg/d	0.99	1.27
Magnesium	292 mg/d	271 mg/d	398 mg/d	0.93	1.36

[a] Meat eating is defined as “consuming meat > once per week OR self-defined.”
[b] Vegetarian is defined as “consuming no meat and fish at all/not during the days of dietary assessment OR ≤ once per month OR self-defined vegetarians.”
[c] Vegan is defined as “consuming no meat, fish, dairy, and eggs at all/not during the days of dietary assessment OR ≤ once per month OR self-defined vegans.”
[d] PUFA = polyunsaturated fatty acids

Perhaps the best predictor of the likely increased intake of molybdenum among vegans is magnesium. Good dietary sources of magnesium include leafy green vegetables, legumes (e.g., beans, lentils), whole grains, and nuts. These are the very same foods that are rich in molybdenum. The intake of magnesium was 36% greater in vegans compared to meat-eaters. It is likely that the intake of molybdenum among vegans is about 36% higher than among meat-eaters. The largest difference in dietary intake occurred with fiber, which was approximately twice as much among vegans compared to meat-eaters. To be conservative, if the highest estimate of molybdenum for the general population of 240 µg/day is doubled using fiber as a conservative marker for molybdenum, the average dietary intake of molybdenum among vegans would be about 480 µg/day. Even if this value were used as the estimated dietary intake for purposes of calculating a RSC (which is not what EPA does), it would still justify an RSC of 0.8. In fact, the RSC would still be 0.8 unless the dietary consumption of molybdenum exceeded 960 µg/day based on the current ATSDR MRL. In short, even if the RSC were calculated based on a conservative estimate of the dietary intake of molybdenum by vegans, which is not the approach EPA uses, the RSC would be 0.8.

I also reviewed the most current (2018-2020) version of the FDA Total Diet Study (TDS) for information on the molybdenum levels in various foods. The FDA TDS analyzed multiple samples of approximately 900 different food products collected at grocery stores across the U.S.

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[35] Id.

for 21 different elements, including molybdenum.[36] The FDA TDS is designed to provide information about the average and range of concentrations of these elements in a large variety of foods. The FDA TDS does not estimate the daily exposure to molybdenum or other elements from typical dietary consumption because it does not contain information about the serving size or frequency of consumption of each food. Serving sizes are available on the package labels of most foods, but it is important to note that the serving sizes are estimates used to standardize the nutritional information on the product label. Serving sizes do not always reflect customers' actual serving size for various foods. There are government databases that can be used to estimate average frequencies of consumption of foods, such as NHANES and CSFII, but I am not aware of any such databases that summarize frequency of consumption for vegans only.

Based on the approximately 900 foods tested by the FDA Total Diet Study (2018-2020), the food with the highest concentration of molybdenum is "cereal, oat ring" (Cheerios or similar product) with an average concentration of 1276 ppb of molybdenum. This is not surprising since oat ring cereal is made from grain. The serving size on the label for oat ring cereal is typically 2 ounces, which amounts to a bowl of cereal since oat ring cereal is light. A 2-ounce serving of oat ring cereal containing 1276 ppb molybdenum would provide an intake of 76 µg molybdenum per serving.

Another one of the other foods with the highest average concentration of molybdenum is "black beans, canned" with 753 ppb of molybdenum. This amounts to 98 µg molybdenum per serving (130 grams or approximately 4.6 ounces based on the label). Other examples of molybdenum levels identified by the FDA TDS include: peanuts (737 ppb), lima beans (390 ppb), white bread (209 ppb), American cheese (177 ppb), eggs (173 ppb), and milk (40 ppb). At a concentration of 40 ppb, a 12-ounce glass of milk would contain approximately 14 µg of molybdenum. Meat products generally contain the lowest levels of molybdenum.

Most studies that evaluate the dietary intake of essential elements base their estimates on the elemental content of the raw foodstuff. However, washing and cooking certain foods in water can theoretically decrease or increase the content of essential elements. In order to evaluate the impact of food preparation (e.g., washing and cooking food with water containing various levels of molybdenum) on the dietary intake of molybdenum from food, a literature search was conducted. One relevant study was found, as described below.

Jaafar et al. (2018) published a study on the effect of food preparation using naturally-occurring groundwater from La Pampa, Argentina on the elemental dietary intake from rice.[37] The primary reason for conducting this study was to evaluate the effect of washing and cooking rice in

[36] FDA (2022) FDA Total Diet Study FDA Total Diet Study (TDS) FY2018-020 TDS Elements Report Supplement: Summary of Analytical Results. FY2018-FY2020 TDS Elements Report Supplement: Summary of Analytical Results (in PDF) and (in Excel)

[37] Jaafar M, Marcilla AL, Felipe-Sotelo M, Ward NI (2018) Effect of food preparation using naturally-occurring groundwater from La Pampa, Argentina: estimation of elemental dietary intake from rice and drinking water. Food Chem 246:258-265.

groundwater with arsenic contamination of natural origin on the level of arsenic in rice. However, in addition to arsenic, the groundwater in La Pampa also exhibited elevated levels of several elements due to natural origin (volcanic soil), including vanadium, iron, and molybdenum. The highest concentration of molybdenum in the groundwater studied by Jaafar et al. (2018) was 1332 µg Mo/L.

Using groundwater containing 1332 µg Mo/L to cook a sample of Argentinian rice using a rice cooker and a conventional recipe (2 cups of water to 1 cup of rice) doubled the concentration of molybdenum in the rice compared to rice cooked in tap water containing 32 µg Mo/L. According to the National Institute of Health's (NIH) Molybdenum Fact Sheet for Health Professionals, the dietary intake of molybdenum in a serving of white rice, long grain, cooked, ½ cup is 13 µg.[38] Based on Jaafar et al. (2018), if this rice were cooked in water containing 1332 µg Mo/L, the dietary intake of molybdenum would be doubled to 26 µg of molybdenum.

As noted earlier, the highest estimate of the U.S. average dietary intake of molybdenum is 240 µg per day. If this estimated average diet had included a serving of rice, cooking the rice in water containing 1334 µg/L of molybdenum would have increased this dietary intake of molybdenum from 240 to 253 µg/day. Rice was selected by Jaafar et al. (2018) "because it provides a good model to show how preparation methods may affect the chemical composition of food as consumed." Rice appears to be a worse case cooking example because most of the water used to cook rice is taken up into the rice. After cooking, little water is left in the bottom of the rice cooker. The water content of cooked rice is 60-68%, whereas there is little, if any, water in dried rice before cooking. Compared to rice, most foods are not cooked in water, and those foods that are cooked in water are not cooked to the point that little water is left in the cooking pot.

Later, in Step 12 below, it will be shown that the dietary consumption of molybdenum would need to be higher than 960 µg/day in order to exceed the 20% default RSC based on the current ATSDR MRL. Considering the estimates of dietary intake of molybdenum and any potential impact of molybdenum in water used for food preparation on foods, it is inconceivable that dietary consumption of molybdenum could come close to exceeding 960 µg/day.

Of note, washing and cooking foods in water with low levels of essential elements can reduce the levels of essential elements in foods. In the Jaafar et al. (2018) study, washing rice up to three times with tap water reduced the molybdenum content of the rice. For example, washing rice once in tap water containing 32 µg Mo/L reduced the concentration of molybdenum in the rice by about 7%. Washing rice three time with tap water containing 32 µg Mo/L reduced the concentration of molybdenum in the rice by about 21%.

[38] NIH (2021) Molybdenum Fact Sheet for Health Professionals. March 30, 2021. Molybdenum - Health Professional Fact Sheet (nih.gov)

Drinking water

In January of 2017, the EPA published the final results of the third Unregulated Contaminant Monitoring Rule (UCMR 3) program.[39] According to the EPA, "EPA uses the Unregulated Contaminant Monitoring Rule (UCMR) to collect data for contaminants that are suspected to be present in drinking water and do not have health-based standards set under the Safe Drinking Water Act (SDWA)."[40] Molybdenum levels >1 µg/L were measured in 25,377 out of 62,981 analyzed drinking water samples, and 151 samples had levels greater than 40 µg/L. In 40 of the 4,922 public water systems (PWS) tested, at least one measurable level above 40 µg/L was found (EPA 2017b); thus, in 99% of PWS tested, no water sample exceeded 40 µg/L.

According to the U.S. Geological Survey (USGS), concentrations of molybdenum as high as 1,400 µg/L have been detected in drinking waters in areas impacted by mining and milling operations.[41] In a study of finished drinking water supplies from the 100 largest cities in the United States in 1964, median and maximum molybdenum concentrations of 1.4 and 68 µg/L, respectively, were reported.[42] An older study reported a mean molybdenum concentration of 8 µg/L in samples collected from 161 drinking water sources from 44 states in the United States. (Hadjimarkos 1967).[43]

A comprehensive ***groundwater*** monitoring study was conducted from 1992 to 2003 by the USGS of 5,183 monitoring and drinking-water wells representative of over 40 principal aquifers in humid and dry regions and in various land-use settings.[44] Wells included in this study are from USGS NAWQA studies designed to describe the quality of water withdrawn from major aquifers and used for drinking (termed major aquifer studies) and studies of shallow groundwater within specific land-use settings (termed land-use studies or LUSs). The locations of the NAWQA wells appeared to include most, if not all, states, including Colorado. Trace elements were analyzed at the USGS National Water Quality Laboratory in Denver, CO. The USGS reported that the median concentration of molybdenum in 3,063 samples was 1.0 µg/L, with a maximum value of 4,700 µg/L. Approximately 1.5% of the groundwater samples had molybdenum levels exceeding the screening level of 40 µg/L.[45]

Climax has monitored the molybdenum concentrations in the surface water and effluent from the outfall at the Climax facility to the Blue River at the Dillon Dam. The results of this monitoring

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[39] EPA. (2017) The third unregulated contaminant monitoring rule (UCMR 3): Data summary, January 2017. U.S. Environmental Protection Agency. EPA815S17001. https://www.epa.gov/sites/production/files/2017-02/documents/ucmr3-da ta-summary-january2017.pdf. June 10, 2019

[40] EPA (2021) Learn About the Unregulated Contaminant Monitoring Rule | US EPA

[41] USGS. 2011. Trace elements and radon in groundwater across the United States, 1992-2003. Scientific investigations report 2011-5059. U.S. Geological Survey.

[42] USGS. 1964. Public water supplies of the 100 largest cities in the United States, 1962. Geological survey water-supply paper 1812. Washington, DC: U.S. Geological Survey. http://pubs.usgs.gov/wsp/1812/report.pdf.

[43] Hadjimarkos DM. (1967) Effect of trace elements in drinking water on dental caries. J Pediatr 70(6):967- 969.

[44] USGS. 2011. Trace elements and radon in groundwater across the United States, 1992-2003. Scientific investigations report 2011-5059. U.S. Geological Survey.

[45] Id.

from January 2013 through February 2024 are available online.[46] Note that these surface waters are not drinking water supplies.

Climax has also monitored municipal water in Summit County at public buildings, as well as a surface water location on the North Fork at the Roberts Tunnel Outlet. All data samples were well below the current water quality standard of 210 μg/L, with many below 1 μg/L.

Because there are adequate data available to describe central tendencies and high-ends for relevant exposure sources/pathways, the answer to Step 3 is "yes," and the Exposure Decision Tree moves to Step 9.

Step 9. Are exposures from multiple sources (due to a sum of sources or an individual source) potentially at levels near (i.e., over 80%), at or in excess of the RfD or (POD/UF)?

No. Conservative estimates of the exposure to molybdenum from both food and drinking water do not come close to exceeding 80% of the ATSDR (2020) oral intermediate duration Minimal Risk Level (MRL) of 0.06 mg molybdenum/kg bw/day. The ATSDR MRL is overly conservative because it employed a modifying factor (MF) of 3 "to address concern that reproductive/developmental alterations may be sensitive outcomes in populations with marginal copper intakes." However, a recent developmental/reproductive toxicity study of molybdenum in rats maintained on a marginal copper diet sponsored by Climax and conducted at Charles River Laboratories (Murray et al. 2023) did not confirm the findings of the Fungwe et al. (1990) study, which formed the basis of ATSDR's concern for populations with marginal copper intakes. For purposes of evaluating the RSC using EPA's Exposure Decision Tree herein, it is conservatively assumed that the current ATSDR MRL is the appropriate point of departure (POD) for risk assessment.

It is more appropriate to use the ATSDR MRL than the EPA Reference Dose (RfD) for evaluating the RSC. The EPA RfD is based on an outdated environmental epidemiological study of gout and exposure to molybdenum in residents living in an area of Armenia with high molybdenum levels in the soil by Koval'skiy et al. (1961).[47] Due to this study's multiple limitations, ATSDR (2020) excluded this study from consideration for establishing the MRL:

> "Although the Koval'skiy et al. (1961) study provided an estimated dose, the study was not considered suitable for derivation of a chronic-duration oral MRL for molybdenum. 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

[46] www.ClimaxMOinCO.com

[47] Koval'skiy VV, Yarovaya GA, Shmavonyan DM. (1961) Changes of purine metabolism in man and animals under conditions of molybdenum biogeochemical provinces. Zh Obshch Biol 22(3):179-191.

> 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."[48]

In contrast to the Koval'skiy study, no significant increases in urinary uric acid levels were found in a clinical study with four male volunteers (Deosthale and Gopalan 1974).[49] The subjects were exposed to a low molybdenum diet for 10 days followed by a high molybdenum diet with an ammonium molybdate supplement for 7 days (time-weighted average molybdenum intake was 0.014 mg molybdenum/kg/day), as compared to uric acid levels when the subjects were fed a low molybdenum diet. In other words, each participant served as his own control. The fact that no increase in uric acid was observed under these carefully controlled conditions indicates that molybdenum does not increase uric acid in the urine or cause gout.

A series of studies in Colorado investigated uric acid levels in communities with high molybdenum levels in the drinking water from mine tailings pollution (EPA 1979).[50] Comparisons between subjects living in areas with high molybdenum in the drinking water (80–200 µg/L; approximately 0.002–0.006 mg/kg/day) to those living in areas with lower levels (<40 µg/L; <0.001 mg/kg/day) did not result in any significant differences in serum uric acid levels or urinary molybdenum levels.

In summary, it has been clearly established that molybdenum does not cause gout. No study since the Koval'skiy study in 1961 has confirmed that molybdenum causes gout.

For purposes of this document, it is assumed that the most relevant risk assessment of molybdenum is the oral intermediate-duration MRL developed by ATSDR in its recent Toxicological Profile for Molybdenum (2020).[51] ATSDR (2020) described the basis for its MRL as follows.

> "An intermediate-duration oral MRL of 0.06 mg molybdenum/kg/day was derived for molybdenum based on an increased incidence of renal proximal tubule hyperplasia in rats exposed to sodium molybdate in the diet for 90 days (Murray et al. 2014a). The MRL is based on a NOAEL of 17 mg molybdenum/kg/day, a total uncertainty factor of 100 (10 for extrapolation from animals to humans, and 10 for human variability), and a modifying

[48] ATSDR (2020) Toxicological Profile for Molybdenum. p. 104. Toxicological Profile for Molybdenum (cdc.gov)
[49] Deosthale YG, Gopalan C (1974) The effect of molybdenum levels in sorghum (Sorghum vulgare Pers.) on uric acid and copper excretion in man. Br J Nutr 31(3):351-5.
[50] EPA.(1979). Human health effects of molybdenum in drinking water. U.S. Environmental Protection Agency. EPA600179006. PB292755.
[51] Climax continues to disagree with the ATSDR's use of a modifying factor (MF) of 3 "to address concern that reproductive/developmental alterations may be sensitive outcomes in populations with marginal copper intakes." A recent developmental/reproductive toxicity study of molybdenum in rats maintained on a marginal copper diet sponsored by Climax and conducted at Charles River Laboratories did not confirm the findings of the Fungwe et al. (1990) study, which formed the basis of ATSDR's concern for populations with marginal copper intakes.

> factor of 3 (to address concern that reproductive/developmental alterations may be sensitive outcomes in populations with marginal copper intakes)."[52]

The MRL of 0.06 mg molybdenum/kg/day is equivalent to 4.8 mg of molybdenum/day for an 80 kg person. Thus, for exposures to exceed 80% of 4.8 mg of molybdenum/day, it would need to exceed 3.84 mg of molybdenum/day. The average daily dietary exposure to molybdenum for the U.S. general population appears to be approximately 100 µg/day (0.1 mg/day) based on the NAS (2001) estimates. The average daily exposure to molybdenum from drinking water for the U.S. general population appears to be no more than 12 µg/day (based on a conservative estimate of the average daily concentration of molybdenum in drinking water of 5 µg/L and consumption of 2.4 L/day of drinking water). Thus, a conservative estimate of the average daily exposure to molybdenum from food and drinking water combined for the general public is about 112 µg/day (or 0.112 mg/day), which is only 2.3% of the 4.8 mg/day MRL.

Alternatively, the high end of the ranges may be used to make this comparison of exposures from multiple sources to the MRL. ATSDR noted the high end of the range for daily dietary exposure was the estimate of 240 µg/day by Tsongas et al. (1980). In EPA's recent UCMR drinking water monitoring data, only 40 (0.8%) of the 4,922 public water systems (PWS) tested had at least one measurable level above 40 µg/L. If a person consumed 2.4 L/day of drinking water containing 40 µg/L of molybdenum, the daily exposure to molybdenum from the drinking water would be 96 µg/day. Using the high end of the range of dietary exposure of 240 µg/day and the high end of the range for drinking water exposure of 96 µg/day, the combined exposure from both sources would be 336 µg/day (or 0.336 mg/day) of molybdenum. This highly conservative estimate of daily exposure to 0.336 mg/day molybdenum from both food and drinking water is still only 7% of the MRL (4.8 mg/day).

As noted previously, the highest concentration of molybdenum in drinking water found by USGS was 1,400 µg/L in areas impacted by mining and milling operations.[53] A person drinking 2.4 L/day of water containing 1,400 µg/L of molybdenum would be exposed to 3,360 µg/day (3.36 mg/day) of molybdenum, which is 70% of the MRL (4.8 mg/day).

In summary, the average daily exposure to molybdenum from food and drinking water combined represents only about 2.3% of the MRL. Even the high-end estimates of exposure to molybdenum from food and drinking water combined would not exceed 80% of the MRL.

Because exposures from multiple sources are not at levels near (i.e., over 80%), at or in excess of the MRL, the answer to Step 9 is "no" and the Exposure Decision Tree moves to Step 11.

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[52] ATSDR (2020) Toxicological Profile for Molybdenum [Toxicological Profile for Molybdenum (cdc.gov)]
[53] USGS. 2011. Trace elements and radon in groundwater across the United States, 1992-2003. Scientific investigations report 2011-5059. U.S. Geological Survey.

Step 11. Is there more than one regulatory action (i.e., criteria, standard, guidance) relevant for the chemical in question?

No. There is no regulatory action for molybdenum in foods. FDA does not regulate molybdenum in foods. The NAS Food and Nutrition Board provides Recommended Dietary Allowances (RDA) that are focused on defining how much of the essential element molybdenum is required to meet the nutritional requirements of nearly all healthy individuals. The NAS Food and Nutrition Board (FNB) is not a regulatory agency, and it does not regulate molybdenum in foods. The only relevant regulatory action for molybdenum in the current context would be a Colorado water supply standard.

Since the answer to Step 11 is no, the Exposure Decision Tree moves to Step 12, the subtraction approach.

Step 12. Use subtraction of appropriate intake levels from sources other than source of concern, including 80% ceiling/20% floor.

Step 12 requires the use of the subtraction method for establishing the RSC. It states: "Use subtraction of appropriate intake levels from sources other than source of concern, including 80% ceiling/20% floor. In other words, the RSC cannot be greater than 80% or less than 20%.

The RSC is determined by subtracting the dietary contribution of molybdenum intake from the total allowed intake of molybdenum in order to determine the percentage of intake allowed in drinking water (i.e., the RSC). There are two variable factors in this calculation: (1) the estimated dietary intake of molybdenum and (2) the total allowed daily intake of molybdenum. For molybdenum, the RSC is determined below using two different sets of assumptions, and in both cases, the RSC is determined to be 80%.

Determination of the RSC assuming the total allowed daily intake of Mo is the current ATSDR MRL and using the estimated average dietary intake of Mo of 100 µg/day based on NAS (2001)

The two determinations of the RSC assume that the total allowed daily intake of Mo is the current ATSDR Minimal Risk Level (MRL) of 0.06 mg Mo/kg bw/day. Based on EPA's default body weight of 80 kg, the MRL represents a daily dose of 4.8 mg Mo/day (0.06 mg Mo/kg bw/day x 80 kg = 4.8 mg Mo/day). Thus, for the two sets of calculations, the total allowed daily intake of Mo is assumed to be 4.8 mg Mo/day based on the ATSDR MRL.

The best estimate of the average dietary intake of molybdenum in the U.S. is the estimate provided by the National Academy of Sciences (2001). The estimated average dietary intake of molybdenum for the general population is approximately 100 µg/day (or 0.1 mg/day) based on the NAS estimates of 109 and 76 µg/day for men and women, respectively. Subtracting 0.1 mg/day from the ATSDR MRL of 4.8 mg/day yields 4.7 mg/day available for water. This calculates to an RSC of 98% (4.7 ÷ 4.8 = 0.98). But due to the 80% ceiling for RSCs, only 3.84 mg/day (4.8 mg Mo/day x 0.80 = 3.84 mg/day) is available for apportionment for drinking water. Thus, using these assumptions, **the RSC for molybdenum is 80%.**

Assuming that a person drinks 2.4 L/day of water (EPA's default assumption) and assuming that the maximum amount of molybdenum allowed in drinking water is 3.84 mg/L due to the 80% RSC, the maximum allowable concentration of molybdenum in drinking is calculated to be 1.6 mg/L or 1600 µg/L (3.84 mg/L ÷ 2.4 L/day = 1.6 mg/L). The RSC of 80% for water would leave an RSC of 20% for food, and 20% of 4.8 mg/day would apportion 0.96 mg/day or 960 µg/day for food. Daily dietary exposure to Mo would never come close to exceeding 960 µg/day, even taking into account any potential contribution of food preparation (e.g., washing, cooking) or any additional exposure from a vegetarian or vegan diet.

Determination of the RSC assuming the total allowed daily intake of Mo is the current ATSDR MRL and using the estimated average dietary intake of Mo of 240 µg/day based on the highest estimate (Tsongas et al., 1980)

The most conservative estimate of the average dietary intake of molybdenum in the U.S. is the estimate by Tsongas et al. (1980) of 240 µg/day. As noted earlier, there are many methodological limitations of this estimate. However, the highest estimate of 240 µg/day for the average dietary intake of molybdenum in the U.S. could be used out of an abundance of caution. Subtracting 240 µg/day (i.e., 0.24 mg/day) of molybdenum from the point of departure (POD) of 4.8 mg/day (the ATSDR MRL) yields 4.56 mg/day available for water. This calculates to an RSC of 95% (4.56 ÷ 4.8 = 0.95). But, once again, due to the 80% ceiling, only 3.84 mg/L could be available for apportionment for drinking water. Thus, as in the previous example, **the RSC for molybdenum is 80%**. And, as before, the maximum allowable concentration in the drinking water is 1600 mg/L.

In summary, the RSC for Mo is always 80% whether the NAS (2001) or the Tsongas et al. (1980) estimates of average dietary consumption of Mo are used. Dietary consumption of Mo is a small fraction of the total allowed daily intake of Mo, and the calculated RSC is above 80% in both examples. But, because of the 80% ceiling, the RSC is 80% in both cases.

Conclusion

The current evaluation shows EPA's current Exposure Decisions Tree for establishing an RSC supports the use of the subtraction method for molybdenum and the establishment of an 80% RSC for molybdenum in drinking water. EPA Region 8 came to the same conclusion in 2017 in "EPA's Rebuttal Comments on the Proposed Revisions to Regulation 31 and 33 (Molybdenum)."[54] EPA Region 8 stated:

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

> "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."

EPA Region 8 used the subtraction method to establish an RSC for molybdenum in drinking water. Both EPA Region 8 and the current evaluation used the conservative "high-end exposure to molybdenum from food" estimate of 240 mcg/day in its calculation of the RSC.[55] To calculate the RSC, EPA Region 8 used the yet-to-be-published 2-generation reproductive toxicity study by Murray et al. (2019) to establish a Reference Dose for molybdenum.[56] Both EPA Region 8 and the current report came to the same conclusion: the RSC of 0.8 (i.e., 80%) is justified using EPA's Exposure Decision Tree methodology because dietary intake remains only a small percentage of the total allowable daily intake of molybdenum.

[55] Id.
[56] Id.