2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO MOLYBDENUM IN THE UNITED STATES

Molybdenum (Mo) is a naturally occurring trace element that can be found extensively in nature. Molybdenum is a metal that exists as a dark-gray or black powder with a metallic luster or as a silvery-white mass. It does not occur naturally in the pure metallic form, but principally as oxide or sulfide compounds. Therefore, almost all exposure is to a molybdenum compound rather than the actual metal. Important naturally occurring molybdenum compounds are the minerals molybdenite, powellite, wulfenite, ferrimolybdate, and ilsemannite.

Biologically, molybdenum plays an important role as a micronutrient in plants and animals, including humans. It is used widely in industry for metallurgical applications; some of these applications include high temperature furnaces, as a support wire for tungsten filaments in incandescent light bulbs, and as a component of steel used in solar panels and wind turbines.

Molybdenum is more abundant in areas of natural mineral deposits and can be found in all environmental media. Higher concentrations in air, water, and soil can be found near industrial operations due to contamination. Molybdenum concentrations in ambient air have been reported to range from below detection limits to 0.03 mg/m³. Concentrations of molybdenum in ambient air of urban areas, 0.01–0.03 µg/m³, are higher than those found in rural areas, 0.001–0.0032 µg/m³. It has been reported that concentrations of molybdenum in surface waters are generally <1.0 µg/L and drinking water and groundwaters contain about 1.0 µg/L. Near industrial sources, surface water molybdenum concentrations can reach 200–400 µg/L and groundwater concentrations can reach 25,000 µg/L. Concentrations as high as 1,400 µg/L have been detected in drinking waters in areas impacted by mining and milling operations, far exceeding the U.S. Geological Survey (USGS) health-based screening level of 40 µg/L. Globally, most soils contain molybdenum at concentrations between 0.6 and 3.5 ppm, although total concentrations in soils can vary widely depending on geological composition or industrial contamination. The average concentration of soils is generally 1–2 ppm. 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.

The exposure to molybdenum to the general population is almost entirely 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. Drinking water coming from sources close to areas with high molybdenum contamination from industrial effluents may contain a higher concentration of molybdenum. The primary source of dietary molybdenum intake among children in the United States is milk. Exposure to molybdenum in an industrial setting such as mining can be significant.

2.2 SUMMARY OF HEALTH EFFECTS

Molybdenum, as a component of pterin-based cofactor, is an essential element. Historically, three molybdenum cofactor-containing enzymes have been identified: sulfite oxidase, xanthine oxidase, and aldehyde oxidase. These enzymes are involved in the degradation of sulfur-containing amino acids and sulfatides, purine degradation pathway catalyzing the oxidation of hypoxanthine to xanthine and of xanthine to uric acid, and oxidation of aromatic and nonaromatic heterocycles and aldehydes to carboxylic acids. Within the last 10 years, a fourth enzyme, mitochondrial amidoxime reducing component (mARC), has been identified in mammals. Clear signs of molybdenum deficiency have not been found in healthy humans. However, a deficiency in molybdenum cofactor has been observed in individuals with a severe metabolic defect. The lack of molybdenum cofactor and subsequent deficiencies in molybdenoenzymes is manifested in central nervous system effects. The effects that typically occur shortly after birth include intractable seizures and feeding difficulties; the patients develop severe psychomotor retardation due to progressive cerebral atrophy and ventricular dilatation. The nutritional requirements for molybdenum are based on maintaining molybdenum balance; the Institute of Medicine has established the following age-specific RDAs:

- 17 μg/day for 1–3 year olds,
- 22 μg/day for 4–8 year olds,
- 34 μg/day for 9–13 year olds,
- 43 μg/day for 14–18 year olds,
- 45 μg/day (0.64 μg/kg/day) for adults, and
- 50 μg/day in pregnant and lactating women.

A small number of studies have investigated the toxicity of molybdenum following inhalation exposure. Decreases in lung function, dyspnea, and cough were reported in workers exposed to fine or ultrafine molybdenum trioxide dust. Another study of workers at a molybdenite roasting facility exposed to molybdenum trioxide and other oxides did not have alterations in lung function. However, this study did
find an increase in serum uric acid levels. In studies of rats and mice exposed to molybdenum trioxide for 2 years, hyaline degeneration of the nasal epithelium, squamous metaplasia of the epiglottis, and chronic inflammation (rats only) were observed. However, no effects were observed following a 13-week exposure to similar concentrations. No other alterations were observed in the intermediate- or chronic-duration studies.

The oral toxicity of molybdenum has been well-established in ruminants, particularly cows and sheep. The toxicity is likely due to an interaction between molybdenum and sulfate in the rumen, resulting in the formation of thiomolybdates. In the absence of adequate copper in the rumen, the thiomolybdate is absorbed through the rumen or small intestine and can bind to copper-containing compounds such as ceruloplasmin and cytochrome oxidase, resulting in symptoms resembling copper deficiency (a condition often referred to as molybdenosis). The observed effects can include decreases in weight gain, alterations in hair/wool texture and pigmentation, delayed puberty, and reduced conception rates. Molybdenum also interacts with copper in monogastric animals; however, the mode of interaction differs between the species. Exposure to molybdenum results in decreases in blood and liver copper levels in ruminants, which is in contrast to the higher relative levels of liver and kidney copper in rats fed a copper-deficient diet, as compared to those fed a copper-adequate diet. Exposure to a molybdenum excess and copper-deficient diet also resulted in higher relative levels of liver molybdenum and lower relative levels of kidney molybdenum. Exposure of rats to thiomolybdate compounds can result in effects that mimic copper deficiency. These data suggest that the findings in ruminants do not appear to be relevant to humans or monogastric animals. Additionally, studies in which laboratory animals were fed a copper-deficient diet may not be relevant to evaluating the risk of molybdenum toxicity to the general population with adequate copper intake. A human study showed that a 24-day exposure to high molybdenum levels in the diet (1,490 μg/day, approximately 21 mg/kg/day) did not result in any significant alterations in copper metabolism. In the United States, the average copper intake is 1.0–1.6 mg/day and the copper recommended dietary allowance is 0.9 mg/day.

A small number of studies have evaluated the toxicity of molybdenum in humans following oral exposure. An increased occurrence of gout and increased blood uric acid levels were observed in residents living in an area of high molybdenum levels in the soil; no alterations in urinary uric acid levels were found in a 10-day experimental study in men. Several studies have used the National Health and Nutrition Examination Survey (NHANES) dataset to evaluate potential associations between urinary molybdenum levels and several diseases; statistically significant associations were found for the occurrence of high blood pressure, self-reported liver conditions, and decreased triiodothyronine or...
thyroxine. Although the studies did not specifically evaluate copper intake, it is likely to be adequate based on a NAS finding that copper intake in the United States is greater than or equal to the dietary requirement. Other population studies have found significant associations between blood molybdenum levels and sperm concentration and morphology or testosterone levels and between urinary molybdenum levels and the psychomotor index in infants. 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.

A number of studies have examined the oral toxicity in laboratory animals. Studies in which the basal diet provided an adequate amount of copper have identified a number of end points including hepatic effects, renal effects, reproductive effects, and possibly developmental effects. Based on the available animal data, the reproductive effects appear to be the most sensitive targets. Consistent with the findings in an epidemiology study, decreases in sperm motility and concentration and increases in sperm morphological changes have been observed in rats exposed to ≥4.4 mg molybdenum/kg/day as ammonium tetrathiomolybdate or sodium molybdate. Degeneration of the seminiferous tubules was also observed at similar molybdenum doses. Effects have also been observed in the female reproductive system (oocyte morphological alterations, abnormal rate of ovulation, and irregularities in the estrous cycle) at ≥1.5 mg molybdenum/kg/day in rats. Mixed results have been observed in animal developmental toxicity studies. Decreases in the number of live fetuses and fetal growth were observed in rats administered 14 mg molybdenum/kg as sodium molybdate; however, no developmental effects were observed in rats at 4.4 or 38 mg/kg/day as ammonium tetrathiomolybdate or sodium molybdate, respectively. Several studies have reported renal effects in rats exposed to ≥60 mg/kg/day. The effects included hyperplasia of the renal proximal tubules, degeneration, increases in total lipid levels in the kidney, and diuresis and creatinuria. The liver effects, which consisted of decreases in glycogen content, increases in aminotransferase activities, and increases in lipid content, have been observed at higher doses (≥300 mg/kg/day) that are often associated with body weight losses. No hepatic effects have been observed at lower (≤60 mg/kg/day) doses.

### 2.3 MINIMAL RISK LEVELS (MRLs)

As summarized in Table 2-1, an inhalation MRL has been derived for chronic-duration exposure to molybdenum and oral MRLs have been derived for acute- and intermediate-duration exposure to molybdenum. The chronic-duration inhalation MRL is based on squamous metaplasia of the epiglottis in female mice exposed to molybdenum trioxide 6 hours/day, 5 days/week for 2 years (NTP 1997). Acute-
and intermediate-duration inhalation MRLs were not derived because the available studies did not identify adverse effects in rats or mice exposed for 14 days or 13 weeks (NTP 1997); the acute-duration study did identify a no-observed-adverse-effect level (NOAEL) and lowest-observed-adverse-effect levels (LOAELs) for decreases in body weight gain, but this was not considered a primary effect. The acute- and intermediate-duration oral MRLs for molybdenum were based on reproductive effects in female mice and rats, respectively. The data were considered inadequate for derivation of a chronic-duration oral MRL for molybdenum. Refer to Section 3.6.2 and Appendix A for detailed information regarding MRL derivation for molybdenum.
### Table 2-1. Minimal Risk Levels (MRLs) for Molybdenum$^a$

<table>
<thead>
<tr>
<th>Exposure duration</th>
<th>MRL</th>
<th>Critical effect</th>
<th>Point of departure</th>
<th>Uncertainty factor</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inhalation exposure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>Insufficient data for derivation of an MRL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>Insufficient data for derivation of an MRL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic</td>
<td>0.0004 mg Mo/m$^3$</td>
<td>Squamous metaplasia in female mice exposed to ≥6.7 mg Mo/m$^3$</td>
<td>BMCL_HEC of 0.012 mg Mo/m$^3$</td>
<td>30</td>
<td>NTP 1997</td>
</tr>
<tr>
<td><strong>Oral exposure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>0.05 Mg Mo/kg/day</td>
<td>Increase rate of abnormal MI oocytes in mice</td>
<td>NOAEL of 5.3 mg Mo/kg/day</td>
<td>100</td>
<td>Zhang et al. 2013</td>
</tr>
<tr>
<td>Intermediate</td>
<td>0.008 mg Mo/kg/day</td>
<td>Increased estrous cycle length in rats</td>
<td>NOAEL of 0.76 mg Mo/kg/day</td>
<td>100</td>
<td>Fungwe et al. 1990</td>
</tr>
<tr>
<td>Chronic</td>
<td>Insufficient data for derivation of an MRL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$The respective exposure durations for acute, intermediate, and chronic MRLs are ≤14 days, 15–364 days, and ≥1 year.

BMCL = benchmark concentration lower confidence limit; HEC = human equivalent concentration; NOAEL = no-observed-adverse-effect level