CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

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 (NLM 2020a). It does not occur naturally in the pure metallic form, but principally as oxide or sulfide compounds (Barceloux 1999; EPA 1979). 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, ferrimolybdite, and ilsemannite. In this toxicological profile, "molybdenum" is used to refer to the element (molybdenum metal) and generically for substances or compounds containing molybdenum. The most common forms used in commerce and found in the environment are molybdenum trioxide and molybdate salts (sodium molybdate or ammonium molybdate). Industrial applications of molybdenum nanoparticles have also been identified; however, molybdenum nanoparticle exposure is not discussed in this toxicological profile because their physical-chemical properties differ from that of larger molybdenum particles and the toxicological and toxicokinetic properties of nanoparticles can vastly differ from those of larger particles.

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 (EPA 1979; Stiefel 2011).

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/m^3 (EPA 1979). 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 $\mu g/m^3$. It has been reported that concentrations of molybdenum in surface waters are generally <1.0 µg/L (USGS 2006) and drinking water (USGS 2011) and groundwaters contain about 1.0 µg/L (USGS 2011). Near mining activities, surface water molybdenum concentrations can be orders of magnitude higher (Frasacoli and Hudson-Edwards 2018). Concentrations as high as 1,400 µg/L have been detected in drinking waters in areas impacted by mining and milling operations (USGS 2011), far exceeding the U.S. Environmental Protection Agency (EPA) health-based screening level of 40 µg/L (EPA 2018a). 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 (EPA 1979).

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 (Barceloux 1999). Drinking water coming from sources close to areas with high molybdenum contamination from industrial effluents may contain a higher concentration of molybdenum.

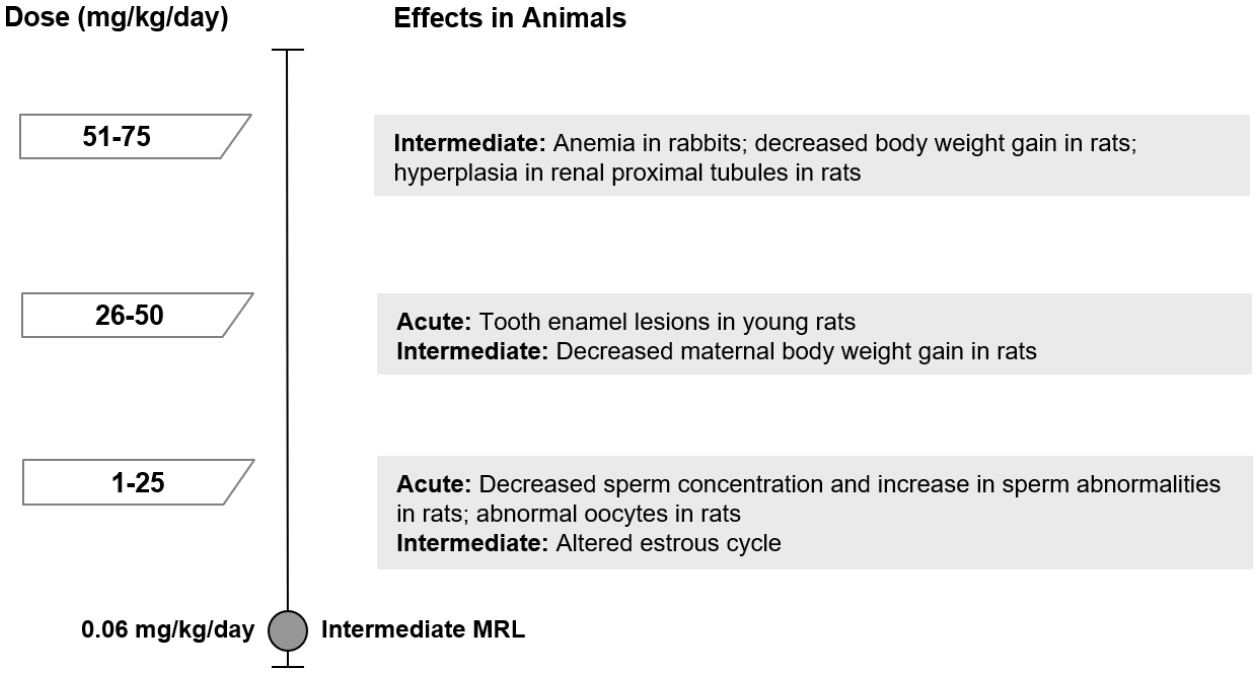
1.2 SUMMARY OF HEALTH EFFECTS

Molybdenum is an essential nutrient; the nutritional requirement for adults is 45 µg/day (0.64 µg/kg/day) (NAS 2001). Exposure to excess levels has been associated with adverse health outcomes. The most sensitive effects appear to be respiratory effects following inhalation exposure to molybdenum trioxide, and decreases in body weight, kidney damage, decreases in sperm count, and anemia following oral exposure (see Figure 1-1). A systematic review of the available human and laboratory animal health effects database resulted in the following hazard identification conclusions:

- Respiratory effects are a presumed health effect for humans for molybdenum oxides.
- Renal effects are a presumed health effect for humans.
- The data were inadequate to conclude whether hepatic, uric acid level, reproductive, or developmental effects will occur in humans.

Respiratory Effects. Decreases in lung function, dyspnea, and cough were reported in a study of workers exposed to fine or ultrafine molybdenum trioxide dust (Ott et al. 2004). Another study of workers at a molybdenite roasting facility exposed to molybdenum trioxide and other oxides did not have alterations in lung function (Walravens et al. 1979). 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 (NTP 1997). However, no effects were observed following a 13-week exposure to similar concentrations (NTP 1997).

Figure 1-1. Health Effects Found in Animals Following Oral Exposure to Molybdenum



Hepatic Effects. 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 (Rana and Chauhan 2000; Rana and Kumar 1980b, 1980c; Rana et al. 1980, 1985). No hepatic effects have been observed at lower (≤60 mg/kg/day) doses (Bersenyi et al. 2008; Murray et al. 2014a).

Renal Effects. Several studies have reported renal effects in rats exposed to ≥60 mg/kg/day (Bompart et al. 1990; Murray et al. 2014a; Rana and Kumar 1980c, 1983; Rana et al. 1980). The effects included hyperplasia of the renal proximal tubules, degeneration, increases in total lipid levels in the kidney, and diuresis and creatinuria.

Reproductive Effects. Cross-sectional epidemiological studies have reported significant associations between blood molybdenum levels and sperm concentration and morphology (Meeker et al. 2008) or testosterone levels (Lewis and Meeker 2015; Meeker et al. 2010). No significant alterations in sperm parameters or estrous cycling were observed in a 90-day rat study (Murray et al. 2014a) or in a 2-generation reproductive toxicity study (Murray et al. 2019). Studies providing limited information on molybdenum doses and/or the copper content of the diet have reported reproductive effects. Decreases in sperm motility and concentration and increases in sperm morphological changes have been observed in

rats exposed to approximately 25 mg molybdenum/kg/day as sodium molybdate (Pandey and Singh 2002; Zhai et al. 2013). Degeneration of the seminiferous tubules was also observed at similar molybdenum doses (Jeter and Davis 1954). 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 (Fungwe et al. 1990; Jeter and Davis 1954; Zhang et al. 2013).

Developmental Effects. 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 (Pandey and Singh 2002). Interpretation of the results of this study is limited by the lack of information on the copper content of the diet and the lack of developmental effects reported in two high-quality studies in which rats were exposed to doses as high as 40 mg molybdenum/kg/day as sodium molybdate (Murray et al. 2014b, 2019).

Uric Acid Levels. A study of workers at a molybdenite roasting facility exposed to molybdenum trioxide and other oxides reported an increase in serum uric acid levels (Walravens et al. 1979). An increased occurrence of gout-like symptoms and increased blood uric acid levels were also observed in residents living in an area of high molybdenum levels in the soil (Koval'skiy et al. 1961); no alterations in urinary uric acid levels were found in a 10-day experimental study in men (Deosthale and Gopalan 1974).

Cancer Effects. No increases in the risk of lung cancer were reported in workers who self-reported exposure to molybdenum (Droste et al. 1999). An increase in alveolar/bronchiolar adenomas or carcinomas was observed in mice exposed to molybdenum trioxide for 2 years (NTP 1997); in rats chronically exposed to airborne molybdenum trioxide, the incidence of alveolar/bronchiolar adenoma/ carcinoma was within the range of historical controls (NTP 1997). The potential carcinogenicity of molybdenum in humans has not been evaluated by the Department of Health and Human Services or the EPA. The International Agency for Research on Cancer (IARC 2018) categorized molybdenum trioxide as possibly carcinogenic to humans (Group 2B).

1.3 MINIMAL RISK LEVELS (MRLs)

As summarized in Table 1-1, an inhalation MRL has been derived for chronic-duration exposure to molybdenum trioxide and an oral MRL has been derived for intermediate-duration exposure to molybdenum. As presented in Figure 1-2, available data have identified the kidney as a sensitive target of

molybdenum toxicity following oral exposure. The available data were not considered adequate for derivation of acute- or intermediate-duration inhalation MRLs or acute- or chronic-duration oral MRLs.

Table 1-1. Minimal Risk Levels (MRLs) for Molybdenum[a]

Exposure duration	MRL	Critical effect	Point of departure	Uncertainty and modifying factors	Reference
Inhalation exposure (mg molybdenum/m^3)					
Acute	Insufficient data for derivation of an MRL				
Intermediate	Insufficient data for derivation of an MRL				
Chronic (molybdenum trioxide)	0.002	Squamous metaplasia of the epiglottis in female rats	0.071 ($BMCL_{HEC}$)	UF: 30	NTP 1997
Oral exposure (mg/kg/day)					
Acute	Insufficient data for derivation of an MRL				
Intermediate	0.06	Renal proximal tubule hyperplasia	17 (NOAEL)	UF: 100 MF: 3	Murray et al. 2014a
Chronic	Insufficient data for derivation of an MRL				

[a]See Appendix A for additional information.

BMCL = benchmark concentration lower confidence limit; HEC = human equivalent concentration; MF = modifying factor; NOAEL = no-observed-adverse-effect level; UF = uncertainty factor

Figure 1-2. Summary of Sensitive Targets of Molybdenum – Oral

The kidney is the most sensitive target of molybdenum oral exposure.
Numbers in circles are the lowest LOAELs for all health effects in animals.
No reliable dose response data were available for humans.