CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of molybdenum. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized by health effect. These data are discussed in terms of route of exposure (inhalation, oral, and dermal) and three exposure periods: acute (≤14 days), intermediate (15–364 days), and chronic (≥365 days).

As discussed in Appendix B, a literature search was conducted to identify relevant studies examining health effect endpoints. Figure 2-1 provides an overview of the database of studies in humans or experimental animals included in this chapter of the profile. These studies evaluate the potential health effects associated with inhalation, oral, or dermal exposure to molybdenum, but may not be inclusive of the entire body of literature. A systematic review of the scientific evidence of the health effects associated with exposure to molybdenum was also conducted; the results of this review are presented in Appendix C.

Human and animal inhalation studies are presented in Table 2-1 and Figure 2-2; animal oral studies are presented in Table 2-2 and Figure 2-3; and animal dermal studies are presented in Table 2-3.

Levels of significant exposure (LSEs) for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an endpoint should be

classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these endpoints. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health. Levels of exposure associated with cancer (Cancer Effect Levels, CELs) of molybdenum are indicated in Table 2-1 and Figure 2-2.

A User's Guide has been provided at the end of this profile (see Appendix D]). This guide should aid in the interpretation of the tables and figures for LSEs and MRLs.

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 (NAS 2001; Sardesai 1993). 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 (Wahl et al. 2010). Within the last 10 years, a fourth enzyme, mitochondrial amidoxime reducing component (mARC), has been identified in mammals (Wahl et al. 2010). Clear signs of molybdenum deficiency have not been found in healthy humans (NAS 2001). 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 molybdoenzymes is manifested in central nervous system effects (Bayram et al. 2013). 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 (Bayram et al. 2013). The nutritional requirements for molybdenum are based on maintaining molybdenum balance; the Institute of Medicine has established the following age-specific Recommended Dietary Allowances (RDAs) (NAS 2001):

- 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
- 50 μg/day in pregnant and lactating women

As illustrated in Figure 2-1, a number of human and laboratory animal studies have evaluated the toxicity of molybdenum following inhalation, oral, or dermal exposure; this toxicological profile on molybdenum does not include discussion of the health effects of molybdenum nanoparticles, which could have different toxicological and toxicokinetic properties than larger molybdenum particles. Of the 92 identified toxicity publications, 84% evaluated health outcomes in laboratory animals; most (74%) were conducted by the oral route of exposure. Inhalation studies primarily focused on the respiratory tract, although intermediate- and chronic-duration studies examined a wide range of endpoints in rats and mice exposed to molybdenum trioxide. Although a large number of laboratory oral exposure studies have been identified, most had a limited scope (examined one or two potential targets). However, a small number of studies evaluated a wide range of endpoints. The most studied endpoints following oral exposure were potential hematological, musculoskeletal, and reproductive outcomes. No human dermal exposure studies were identified; the animal studies primarily focused on dermal and immunological endpoints.

A number of factors can influence the toxicity of molybdenum including the animal species; previous dietary history; relative amounts of dietary molybdenum, copper, and sulfur; and the form of molybdenum. The oral toxicity of molybdenum has been well-established in ruminants, particularly cows and sheep. The toxicity is likely due to an interaction between molybdate and sulfide in the rumen, resulting in the formation of thiomolybdates (Gould and Kendall 2011). 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. The available data suggest that the findings in ruminants do not appear to be relevant to humans or monogastric animals (NAS 2001). Thus, ruminant data will not be further discussed in the toxicological profile.

Studies in rats provide evidence that copper status, particularly the copper content of the diet, can influence the toxicokinetics and toxicity of molybdenum; see Section 3.4 for a more detailed discussion of the interaction between molybdenum and copper. Administration of 150 or 500 mg/kg molybdenum in

the diet for up to 6 weeks to rats fed a copper-deficient or copper-adequate diet resulted in profound differences in the distribution of copper and molybdenum in the plasma, liver, and kidneys (Nederbragt 1980, 1982). For example, at a molybdenum dietary concentration of 150 mg/kg, molybdenum levels in the liver and kidneys were 3.5 and 9 times higher than pre-exposure levels, respectively, in the copper-adequate rats as compared to 6 and 4 times higher, respectively, in the copper-deficient rats. Additionally, the relative increases in copper levels in the liver and kidneys associated with molybdenum exposure were greater in the rats fed the copper-deficient diet, as compared to those fed the copper-adequate diet. Exposure to elevated levels of dietary molybdenum in animals maintained on basal diets with inadequate copper levels resulted in marked toxicity (for example, Brinkman and Miller 1961; Johnson et al. 1969; Sasmal et al. 1968). Similar effects were not observed when animals were fed similar molybdenum levels and maintained on a copper-adequate diet (for example, Mills et al. 1958; Murray et al. 2014a; Peredo et al. 2013). In the United States, the average copper intake is 1.0–1.6 mg/day and the copper RDA is 0.9 mg/day (NAS 2001). Thus, 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. Studies in which the laboratory animals were fed a basal diet with inadequate copper levels are clearly identified in the text, are discussed separately from studies in which there were adequate dietary copper levels, and are not included in the LSE table or figure. The current recommended dietary copper concentrations of 5, 6, and 3 ppm have been established for rats, mice, and rabbits, respectively (NAS 1977, 1995); for rats and mice, a copper dietary level of 8 ppm has been established to support gestation and lactation (NAS 1995).

Ammonium tetrathiomolybdate is an experimental chelating agent used to decrease excess copper levels in individuals with Wilson's disease, a genetic disease that limits copper excretion resulting in an accumulation of toxic levels of copper in the liver, brain, and eyes. Administration of tetrathiomolybdate compounds, as compared to other molybdate compounds, results in more dramatic shifts in copper levels in rats fed copper-adequate diets (Mills et al. 1981a), and the toxicity may differ from other molybdenum compounds. Significant increases in serum and kidney copper levels, decreases in liver copper levels, and increases in serum, liver, and kidney molybdenum levels were found in rats exposed to ammonium tetrathiomolybdate as compared to rats receiving the same molybdenum dose as sodium molybdate (Mills et al. 1981a); these results suggest that the tetrathiomolybdate impaired utilization of dietary copper, utilization of stored copper, or both. A study in rats demonstrated that administration of supplemental copper could reverse the adverse effects observed following administration via gavage of 12 mg molybdenum/kg/day as ammonium tetrathiomolybdate (Lyubimov et al. 2004). This study suggests that ammonium tetrathiomolybdate may interfere with copper homeostasis. No studies evaluating whether

copper supplementation would reverse the toxicity of other molybdenum compounds were identified. Because tetrathiomolybdate compounds may not be representative of other molybdenum compounds, studies involving exposure to tetrathiomolybdate compounds are not included in the LSE table and figure, but are discussed in the text.

The human and animal studies suggest several sensitive targets of molybdenum toxicity:

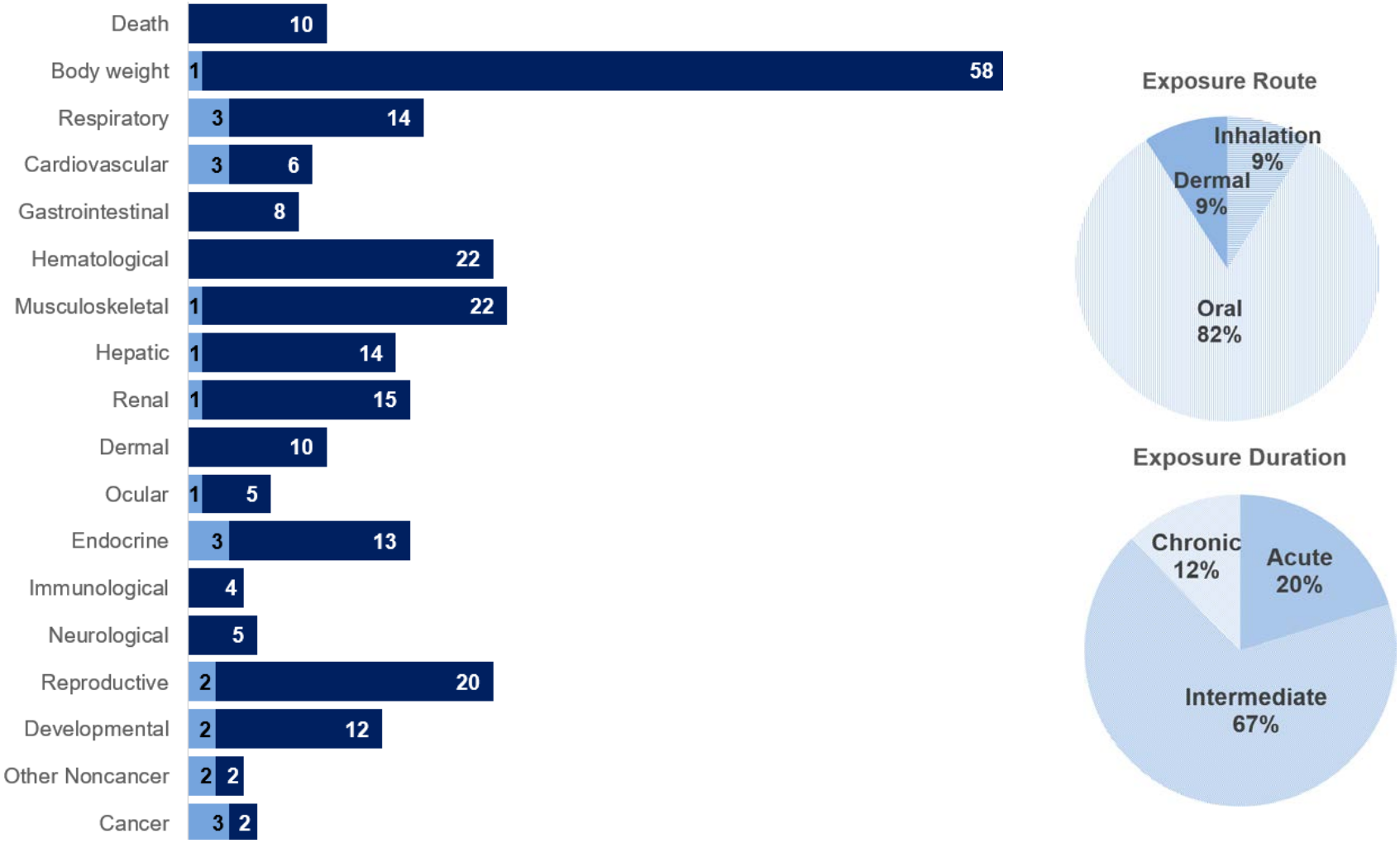
- **Respiratory Endpoints:** Respiratory effects are a presumed health effect for humans based on inadequate evidence in molybdenum oxide workers and a high level of evidence in rats and mice chronically exposed to airborne molybdenum trioxide.

- **Renal Endpoints:** Renal effects are a presumed health effect for humans based on no data in humans and a high level of evidence in laboratory animals. The observed effects include histological alterations in the kidneys and alterations in renal function.

- **Other Endpoints:** Although there is some evidence that molybdenum exposure may result in hepatic, reproductive, or developmental effects, the data are not considered adequate to classify whether molybdenum is a hepatic or developmental hazard to humans.
  - **Hepatic Effects:** There is inadequate evidence of increased risk of liver disease in humans. There is high evidence that inhalation or oral exposure to molybdenum compounds will result in histological alterations in rats, mice, or rabbits. There is moderate evidence in rats that exposure may result in alterations in serum clinical chemistry parameters and/or lipid levels in laboratory animals.
  - **Reproductive Effects:** There is low evidence of male reproductive effects in cross-sectional studies that do not establish causality. Two high-quality animal studies have not found evidence of reproductive effects in rats. Several lower-quality studies have reported male and female reproductive effects; other studies have not reported any reproductive alterations.
  - **Developmental Effects:** There is low evidence of developmental effects in epidemiological studies that do not establish causality. There are mixed results in laboratory animal studies, with most studies not finding evidence of developmental toxicity.

Figure 2-1. Overview of the Number of Studies Examining Molybdenum Health Effects

Most studies examined the potential body weight, hematological, musculoskeletal, and reproductive effects of molybdenum
Fewer studies evaluated health effects in **humans** than **animals** (counts represent studies examining endpoint)



*Includes studies discussed in Chapter 2. A total of 91 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

Table 2-1. Levels of Significant Exposure to Molybdenum – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg Mo/m^3)	Less serious LOAEL (mg Mo/m^3)	Serious LOAEL (mg Mo/m^3)	Effects
ACUTE EXPOSURE									
1	Rat (Sprague-Dawley) 5 M, 5 F	4 hours	0, 1,200	CS, BW, FI, WI, OW, HP	Bd wt		1,200		Weight loss or no body weight gain during first 2–3 post-exposure days; thereafter, weight gain was similar to controls
					Resp	1,200			
Ammonium dimolybdate Jackson et al. 1991a									
2	Rat (Sprague-Dawley) 5 M, 5 F	4 hours	0, 3,890	CS, BW, FI, WI, OW, HP	Bd wt		3,890		Weight loss during first 2–3 post-exposure days; thereafter, weight gain was similar to controls
					Resp	3,890			
Molybdenum trioxide Jackson et al. 1991b									
3	Rat (Sprague-Dawley) 5 M, 5 F	4 hours	0, 899	CS, BW, FI, WI, OW, HP	Bd wt		899		Weight loss during first 2–3 post-exposure days; thereafter, weight gain was similar to controls
					Resp	899			
Sodium molybdate Jackson et al. 1991c									
4	Rat (Sprague-Dawley) 5 M, 5 F	4 hours	0, 2,613	CS, BW, FI, WI, OW, HP	Bd wt		2,613		14% decrease in body weight gain on post-exposure day 3
					Resp	2,613			
Molybdenum trioxide Jackson et al. 1991d									
5	Rat (CD) 3 M, 3 F	4 hours	3,360	CS, GN, HP	Resp	3,360			
Molybdenum trioxide Leuschner 2010									

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6	Rat (Fischer-344) 5 M, 5 F	6 hours/day 5 days/week 14 days	0, 2, 6.7, 20, 67, 200	CS, BW, HP	Bd wt		67	200	Decreased body weight gain in males at 67 mg/m^3 (10%) and females exposed to 200 mg/m^3 (13%); weight loss in males at 200 mg/m^3 (terminal weight 5% less than initial weight)
					Resp	200			
Molybdenum trioxide NTP 1997									
7	Mouse (B6C3F1) 5 M, 5 F	6 hours/day 5 days/week 14 days	0, 2, 6.7, 20, 67, 200	CS, BW, HP	Bd wt			200	Body weight loss in males and decrease in body weight gain in females
					Resp	200			
Molybdenum trioxide NTP 1997									
INTERMEDIATE EXPOSURE									
8	Rat (Fischer-344) 10 M, 10 F	6.5 hours/day 5 days/week 13 weeks	0, 0.67, 2, 6.7, 20, 67	CS, BW, OW, HP, RX	Bd wt	67			
					Resp	67			
					Cardio	67			
					Gastro	67			
					Hemato	67			
					Musc/skel	67			
					Hepatic	67			
					Renal	67			
					Endocr	67			
					Repro	67 M			
Molybdenum trioxide NTP 1997									
9	Mouse (B6C3F1) 10 M, 10 F	6.5 hours/day 5 days/week 13 weeks	0, 0.67, 2, 6.7, 20, 67	CS, BW, OW, HP, RX	Bd wt	67			
					Resp	67			
					Cardio	67			
					Gastro	67			

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					Hemato	67			
					Musc/skel	67			
					Hepatic	67			
					Renal	67			
					Endocr	67			
					Repro	67 M			
Molybdenum trioxide NTP 1997									
CHRONIC EXPOSURE									
10	Human 25 M	Occupational	0, 9.47	BI, OF	Resp	9.47			
					Other noncancer		9.47		Increased serum uric acid levels
Molybdate Walravens et al. 1979									
11	Rat (Fischer-344) 50 M, 50 F	6 hours/day 5 days/week 105 weeks	0, 6.7, 20, 67	CS, BW, HP	Bd wt	67			
					Resp		6.7[b]		Hyaline degeneration of nasal respiratory and olfactory epithelium (females only), squamous metaplasia of the epiglottis, and chronic lung inflammation (only significant at 20 and 67 mg/m^3 concentrations); $BMCL_{HEC}$ of 0.071 mg/m^3
					Cardio	67			
					Gastro	67			
					Musc/skel	67			
					Hepatic	67			
					Renal	67			
					Endocr	67			
Molybdenum trioxide NTP 1997									

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Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/m^3)	Parameters monitored	Endpoint	NOAEL (mg Mo/m^3)	Less serious LOAEL (mg Mo/m^3)	Serious LOAEL (mg Mo/m^3)	Effects
12	Mouse (B6C3F1) 50 M, 50 F	6 hours/day 5 days/week 105 weeks	0, 6.7, 20, 67	CS, BW, HP	Bd wt	67			
					Resp		6.7		Squamous metaplasia of the epiglottis, histiocytic cellular infiltration in the lungs, and alveolar epithelial metaplasia were observed at ≥6.7 mg/m^3; nasal suppurative inflammation in males at 20 or 67 mg/m^3 and hyaline degeneration of nasal respiratory and olfactory epithelium (females only) at 67 mg/m^3
					Cardio	67			
					Gastro	67			
					Musc/skel	67			
					Hepatic	67			
					Renal	67			
					Endocr	67			
					Cancer			6.7	Alveolar/bronchiolar carcinoma in males at ≥6.7 mg/m^3 and increased incidence of alveolar/bronchiolar adenoma in females at ≥20 mg/m^3; an increase in alveolar/ bronchiolar adenoma or carcinoma in male mice exposed to 6.7 or 20 mg/m^3

Molybdenum trioxide
NTP 1997

[a]The number corresponds to entries in Figure 2-2; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-2. Where such differences exist, only the levels of effect for the most sensitive gender are presented.
[b]Used to derive a chronic-duration oral MRL for molybdenum trioxide of 0.002 mg molybdenum/m^3 based on a $BMCL_{10}$ human equivalent concentration (HEC) of 0.071 mg molybdenum/m^3 and an uncertainty factor of 30.

Bd wt or BW = body weight; BI = biochemical changes; BMCL = 95% lower confidence limit on the benchmark concentration; Cardio = cardiovascular; CS = clinical signs; Endocr = endocrine; F = female(s); FI = food intake; Gastro = gastrointestinal; GN = gross necropsy; Hemato = hematological; HP = histopathology; LOAEL = lowest-observed-adverse-effect level; M = male(s); MRL = minimal risk level; Musc/skel = muscular skeletal; NOAEL = no-observed-adverse-effect level; OF = organ function; OW = organ weight; Repro = reproductive; Resp = respiratory; RX = reproductive effects; WI = water intake

Figure 2-2. Levels of Significant Exposure to Molybdenum – Inhalation

Acute (≤14 days)

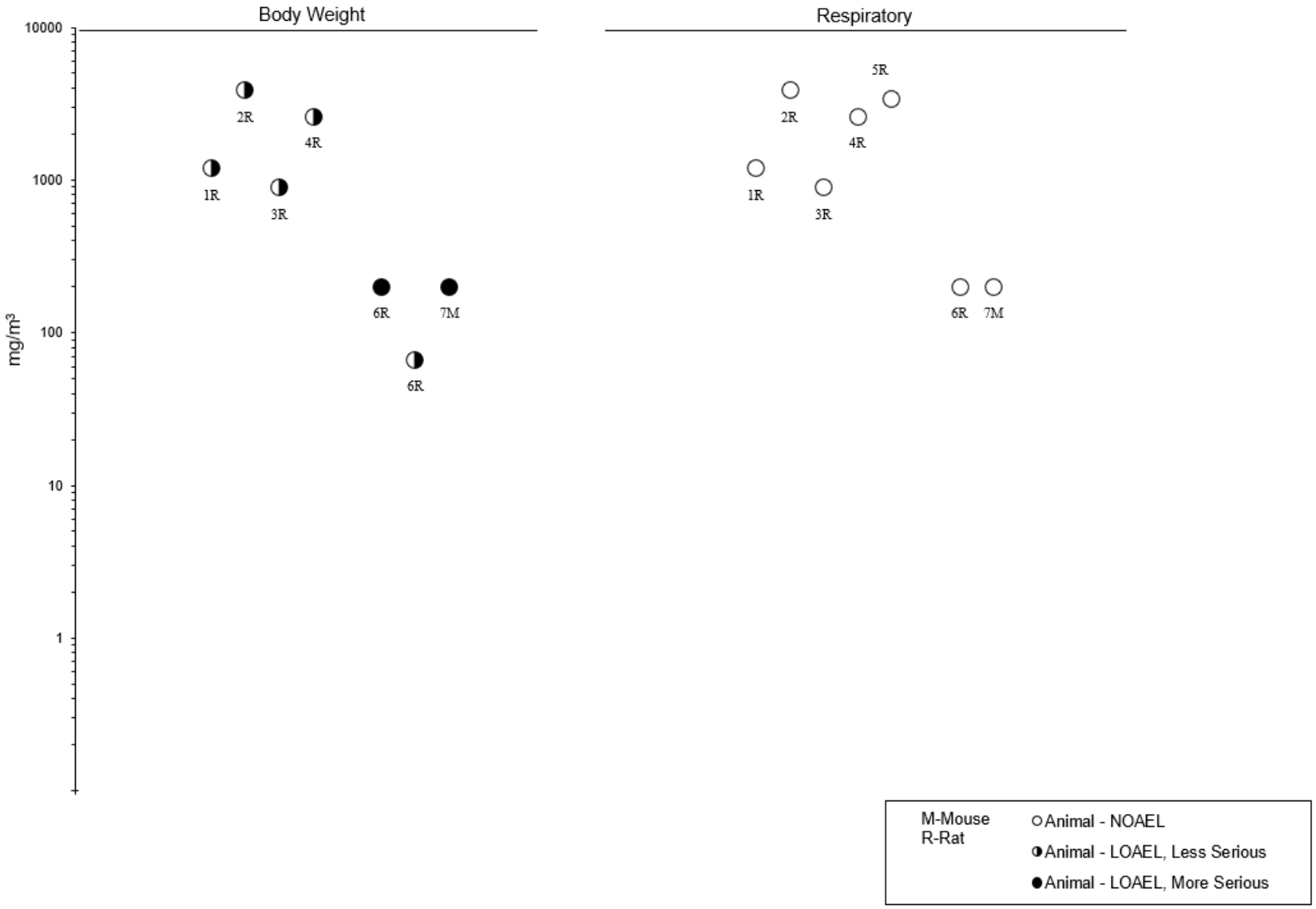

Figure 2-2. Levels of Significant Exposure to Molybdenum – Inhalation

Intermediate (15-364 days)

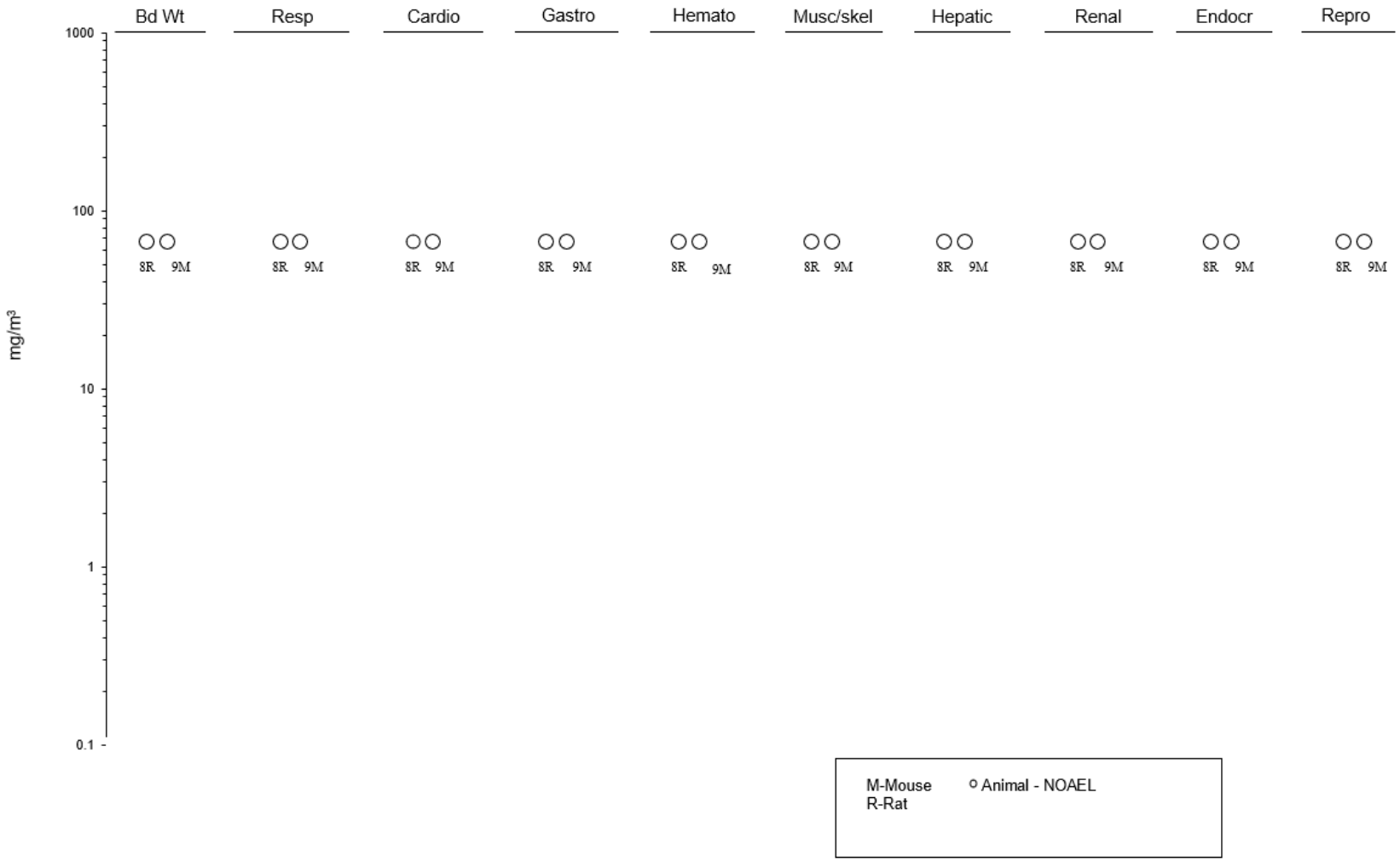

Figure 2-2. Levels of Significant Exposure to Molybdenum – Inhalation

Chronic (≥365 days)

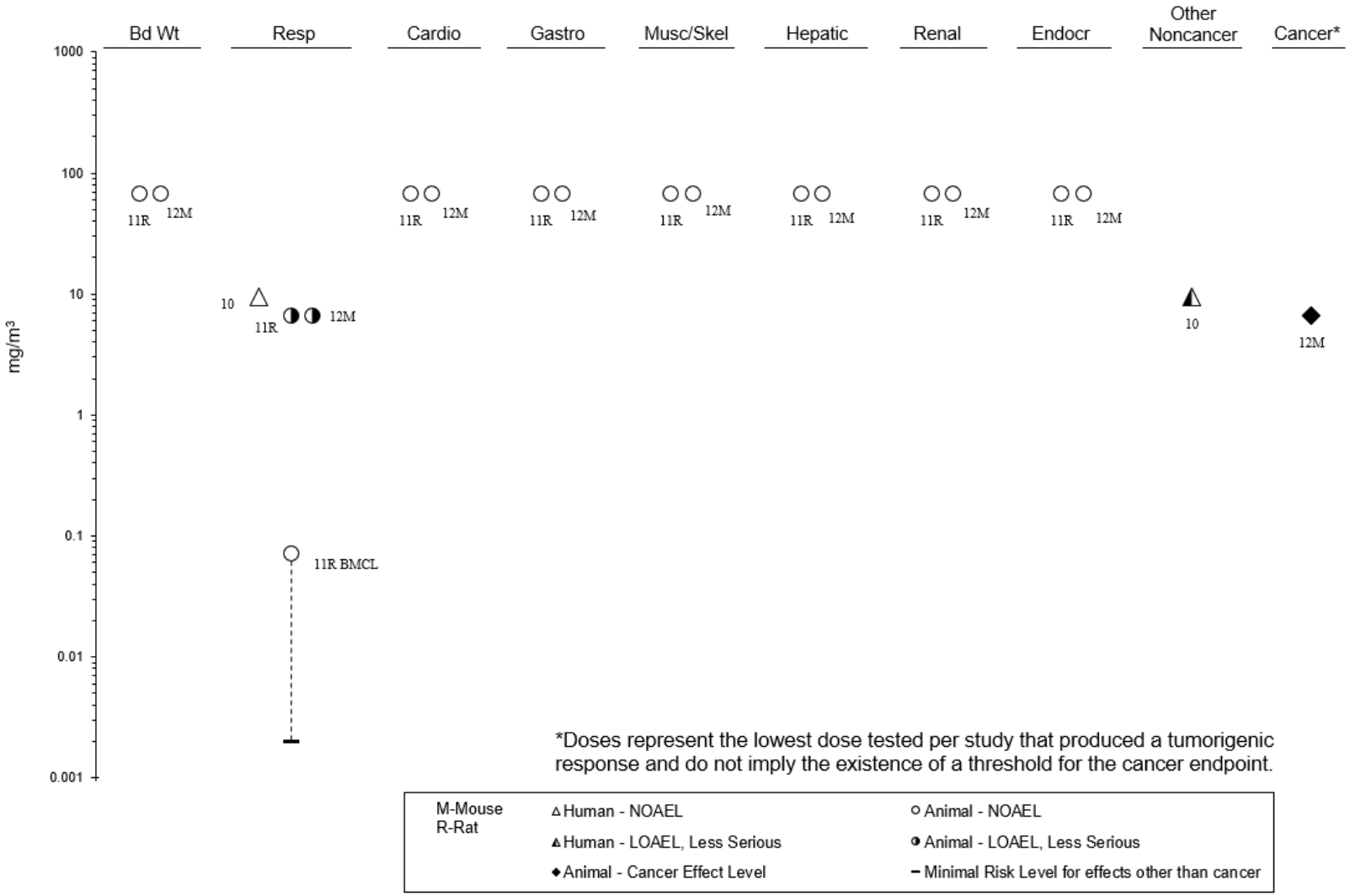

Table 2-2. Levels of Significant Exposure to Molybdenum – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg Mo/kg/day)	Less serious LOAEL (mg Mo/kg/day)	Serious LOAEL (mg Mo/kg/day)	Effects
ACUTE EXPOSURE									
1	Human 4 M	10 days (F)	0.00237, 0.00771, 0.022	UR	Other noncancer	0.022			No alterations in urinary uric acid levels
Ammonium molybdate Deosthale and Gopalan 1974									
2	Rat (Sprague-Dawley) 5 M, 5 F	Once (GO)	1,900, 2,400, 3,000	LE, CS, BW, GN	Death			2,291	LD_{50}
					Gastro	2,400	3,000		Thickening of the glandular stomach
Ammonium dimolybdate Baldrick and Healing 1990e									
3	Rat (Sprague-Dawley) 5 M, 5 F	Once (GO)	2,000, 2,500 (males only), 3,200, 4,000 (females only), 5,000	LE, CS, BW, GN	Death			2,566 F, 1,802 M	LD_{50}
Molybdenum trioxide Baldrick and Healing 1990f									
4	Rat (Sprague-Dawley) 5 M, 5 F	Once (GO)	1,500, 2,300, 3,000	LE, CS, BW, GN	Death			2,079 F, 1,912 M	LD_{50}
Sodium molybdate Baldrick and Healing 1990g									
5	Rat (Sprague-Dawley) 22 M	PNDs 4–17 (G)	0, 50	BW, HP	Bd wt	50			
					Musc/skel		50		Increased buccal and sulcal enamel lesions following pre-eruptive exposure to molybdenum and administration of a caries promoting diet
Sodium molybdate Hunt and Navia 1975									

Table 2-2. Levels of Significant Exposure to Molybdenum – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg Mo/kg/day)	Less serious LOAEL (mg Mo/kg/day)	Serious LOAEL (mg Mo/kg/day)	Effects
6	Mouse (ICR) 25 F	14 days (W)	0, 1.3, 2.6, 5.3, 11	HP	Repro	2.6	5.3		Increase in the rate of abnormal MII oocytes and decrease in ovarian weights at 11 mg/kg/day; ovarian hyperemia at 5.3 and 11 mg/kg/day (incidence not reported)
Sodium molybdate Zhang et al. 2013									
7	Mouse (ICR) 10 M	14 days (W)	0, 3, 6, 12, 25, 49	RX	Repro	12	25		Decreases in relative epididymides weight, sperm concentration, and sperm motility and increase in rate of sperm abnormalities
Sodium molybdate Zhai et al. 2013									
8	Rabbit (New Zealand) 5 M	14 days (F)	0, 0.58	BW, HP	Bd wt	0.58			
					Hepatic	0.58			
					Renal	0.58			
Ammonium heptamolybdate Bersenyi et al. 2008									
INTERMEDIATE EXPOSURE									
9	Rat (Sprague-Dawley) 7 M	8 weeks (GW)	0, 40, 80	BW, OW, UR	Bd wt	40	80		Decrease in body weight gain; terminal body weight was 26% lower than in controls
					Renal	40	80		Increases in diuresis and creatinuria, decreases in creatinine clearance, increases in urinary kallikrein (distal tubule enzyme) levels, and increases in relative and absolute kidney weights
Ammonium heptamolybdate Bompart et al. 1990									

Table 2-2. Levels of Significant Exposure to Molybdenum – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg Mo/kg/day)	Less serious LOAEL (mg Mo/kg/day)	Serious LOAEL (mg Mo/kg/day)	Effects
10	Rat (Sprague-Dawley) 6 F	8 weeks (W)	0, 0.76, 1.5, 7.6, 15	BW, WI, RX	Repro	0.76	1.5		Prolonged estrus phase (6–12 hours) of the estrous cycle at ≥1.5 mg/kg/day; no effects on fertility
Sodium molybdate Fungwe et al. 1990									
11	Rat (Sprague-Dawley) 3–6 M, 2–3 F	6 weeks (F)	0, 70	BW, HE	Hemato	70			
Sodium molybdate Gray and Daniel 1954									
12	Rat (Long-Evans) 4 M, 4 F	At least 8 weeks (F)	0, 7	BW, HE	Bd wt	7			
					Hemato	7			
					Repro	7			
					Develop	7			
Sodium molybdate Jeter and Davis 1954									
13	Rat (Wistar) 4 M	5 weeks (F)	0, 74	BW, BI	Bd wt		74		36% decrease in body weight gain
Sodium molybdate Mills et al. 1958									
14	Rat (Sprague-Dawley) 10 M, 10 F	90 days (F)	0, 5, 17, 60	CS, BW, BC, HE, FI, GN, HP, OW	Bd wt	17 M	60 M		15.2% lower terminal body weight in males
					Resp	60			
					Cardio	60			
					Gastro	60			
					Hemato	60			
					Hepatic	60			
					Renal	17 F[b]	60 F		Slight diffuse hyperplasia in the renal proximal tubules were observed in 2/10 female rats

Table 2-2. Levels of Significant Exposure to Molybdenum – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg Mo/kg/day)	Less serious LOAEL (mg Mo/kg/day)	Serious LOAEL (mg Mo/kg/day)	Effects
					Ocular	60			
					Endocr	60			
					Repro	60 F 60 M			
					Other noncancer	60			
Sodium molybdate Murray et al. 2014a									
15	Rat (Sprague-Dawley) 25 F	GDs 6–20 (F)	0, 3, 10, 20, 40	DX	Develop	40			
Sodium molybdate Murray et al. 2014b									
16	Rat (Sprague-Dawley) 24 M, 24 F	2 generations 10 weeks prior to mating, 10–17 days mating period, and gestation and lactation periods (W)	0, 5, 17, 40	CS, BW, OW, HP, RX, DX	Bd wt	40			
					Resp	40			
					Renal	40			
					Endocr	40			
					Repro	40			
					Develop	40			
Sodium molybdate Murray et al. 2019									
17	Rat (Sprague-Dawley) 24 M, 24 F	2 generations 10 weeks prior to mating, 10–17 days mating period, and gestation and lactation periods (F)	0, 40	CS, BW, OW, HP, RX, DX	Bd wt		40 F		Decreased maternal weight gain (22%) on GDs 0–7
					Resp	40			
					Renal	40			
					Endocr	40			
					Repro	40			
					Develop	40			

Table 2-2. Levels of Significant Exposure to Molybdenum – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg Mo/kg/day)	Less serious LOAEL (mg Mo/kg/day)	Serious LOAEL (mg Mo/kg/day)	Effects
Sodium molybdate Murray et al. 2019									
18	Rat (Druckery) 10 M	5 days/week 60 days (GW)	0, 4.7, 14, 24	BW	Bd wt	24			
					Repro	4.7	14		Decreases in sperm count and sperm motility and increases in sperm abnormalities at ≥14 mg/kg/day; degeneration of seminiferous tubules in the testes at 24 mg/kg/day; it is unclear whether this was also observed at 14 mg/kg/day
Sodium molybdate Pandey and Singh 2002									
19	Rat (Druckery) 20 M	5 days/week 60 days (GW)	0, 14	DX, RX	Repro			14	Decrease in fertility (60% versus 80% in controls) and increased pre-implantation losses
					Develop			14	Increased post-implantation losses, increased resorptions, decreased number of live fetuses, and decreases in fetal weight and crown-rump length
Sodium molybdate Pandey and Singh 2002									
20	Rat (Wistar) 6 M	9 weeks (W)	0, 100	BW, BI, OW	Bd wt	100			
					Cardio	100			
					Other noncancer	100			No alterations in blood triglyceride, glucose, or insulin levels
Sodium molybdate Peredo et al. 2013									

Table 2-2. Levels of Significant Exposure to Molybdenum – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg Mo/kg/day)	Less serious LOAEL (mg Mo/kg/day)	Serious LOAEL (mg Mo/kg/day)	Effects
21	Rat (Wistar) 10 M or 5 M, 5 F	4–5 weeks (F)	0, 110	BW, BI	Bd wt		110 M		46–48% decrease in body weight gain
Sodium molybdate Van Reem and Williams 1956									
22	Rat (Wistar) 8 NR	6 weeks (F)	0, 85	BW, BI	Bd wt	85			
Sodium molybdate Williams and Van Reem 1956									
23	Rat (Wistar) 8 NR	6 weeks (F)	0, 90, 144, 185	BW, BI	Bd wt		90		Decreases in body weight gain of 22, 44, and 60% in the 90, 144, and 185 mg/kg/day groups
Sodium molybdate Williams and Van Reem 1956									
24	Rat (Sprague-Dawley) 10 F	8 weeks (W)	0, 0.015, 0.076, 0.15, 0.30, 0.76, 1.5	BW, BI, OW	Bd wt	1.5			
Sodium molybdate Yang and Yang 1989									
25	Mouse (Kunming) 20 M	100 days (W)	0, 100	BW, BC, HP, RX	Bd wt	100			
					Repro		100		Decreased sperm density and motility; testicular atrophy (no incidence data reported)
Molybdenum Wang et al. 2016									

Table 2-2. Levels of Significant Exposure to Molybdenum – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg Mo/kg/day)	Less serious LOAEL (mg Mo/kg/day)	Serious LOAEL (mg Mo/kg/day)	Effects
26	Rabbit (Dutch) 2–5 M, F	30–84 days (F)	0, 7.1, 25, 54, 120, 240	CS, LE, BW, HE	Death			120	4/5 and 2/2 died at 120 and 240 mg/kg/day; average survival was 44 and 30 days, respectively
					Bd wt	25		120	Weight loss at 120 and 240 mg/kg/day
					Hemato	25	54		Anemia in 2/5, 5/5, and 4/5 rabbits at 54, 120, and 240 mg/kg/day
					Musc/skel	25		54	Front leg abnormality described as weakness progressing to inability to “maintain weight and legs spread outward”
					Dermal	25	54		Alopecia
Sodium molybdate Arrington and Davis 1953									
CHRONIC EXPOSURE									
27	Human 262 M, F	NR (F)	0.21	BC	Other noncancer		0.21		Increased incidence of symptoms of gout and an increased blood uric acid levels
Molybdenum Koval’sky et al. 1961									

[a]The number corresponds to entries in Figure 2-3; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-3. Where such differences exist, only the levels of effect for the most sensitive gender are presented.
[b]Used to derive an intermediate-duration oral MRL of 0.06 mg/kg/day based on a NOAEL of 17 mg molybdenum/kg/day, a total uncertainty factor of 100, and a modifying factor of 3.

BC = biochemistry; Bd wt or BW = body weight; BI = biochemical changes; Cardio = cardiovascular; CS = clinical signs; Develop = developmental; DX = developmental effects; Endocr = endocrine; (F) = feed; F = female(s); FI = food intake; (GO) = gavage in oil; (GW) = gavage in water; Gastro = gastrointestinal; GD = gestation day; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathology; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); MRL = minimal risk level; Musc/skel = muscular/skeletal; NOAEL = no-observed-adverse-effect level; NR = not reported; OW = organ weight; PND = postnatal day; Repro = reproductive; Resp = respiratory; RX = reproductive effects; UR = urinalysis; (W) = water; WI = water intake

Figure 2-3. Levels of Significant Exposure to Molybdenum – Oral

Acute (≤14 days)

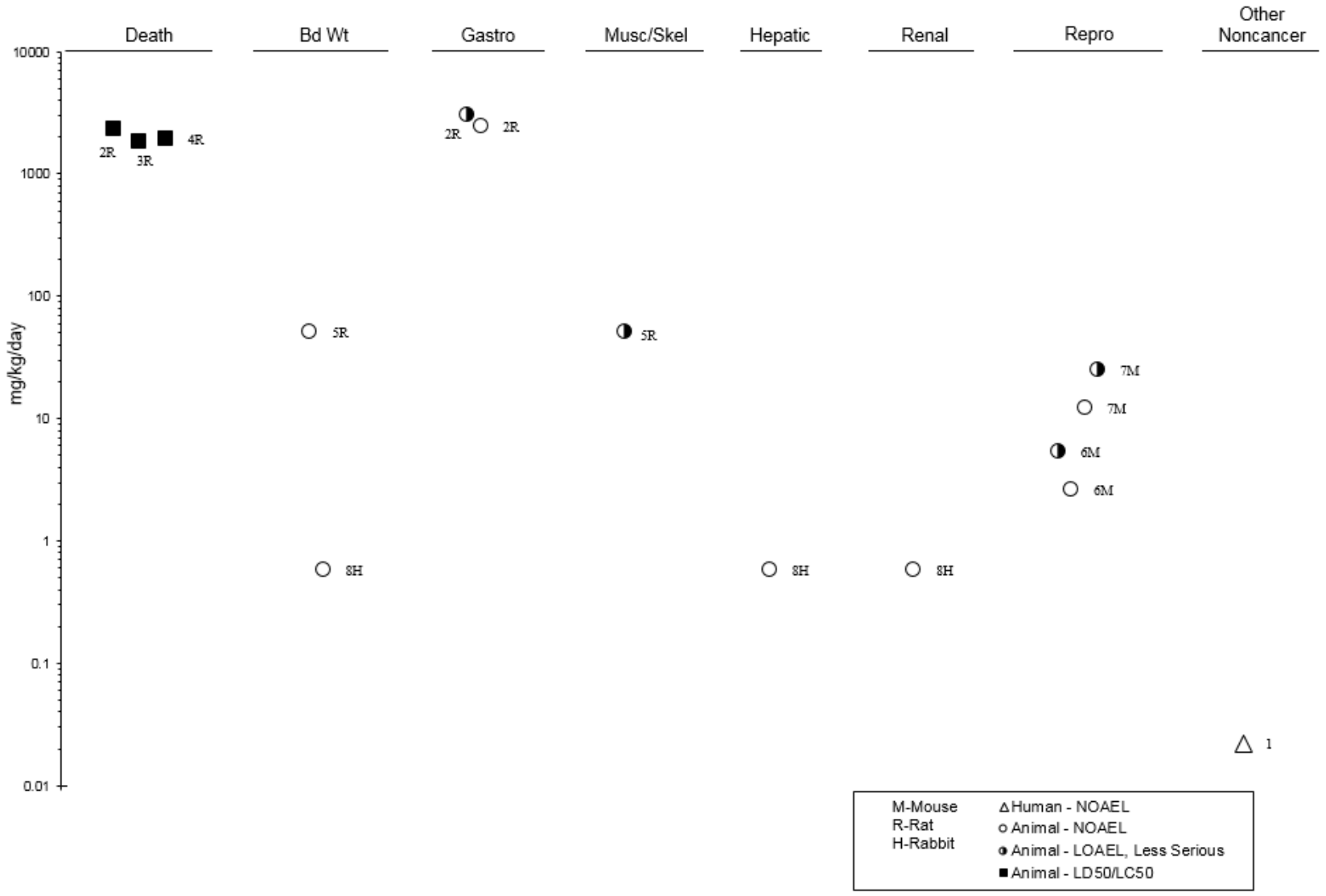

Figure 2-3. Levels of Significant Exposure to Molybdenum – Oral

Intermediate (15-364 days)

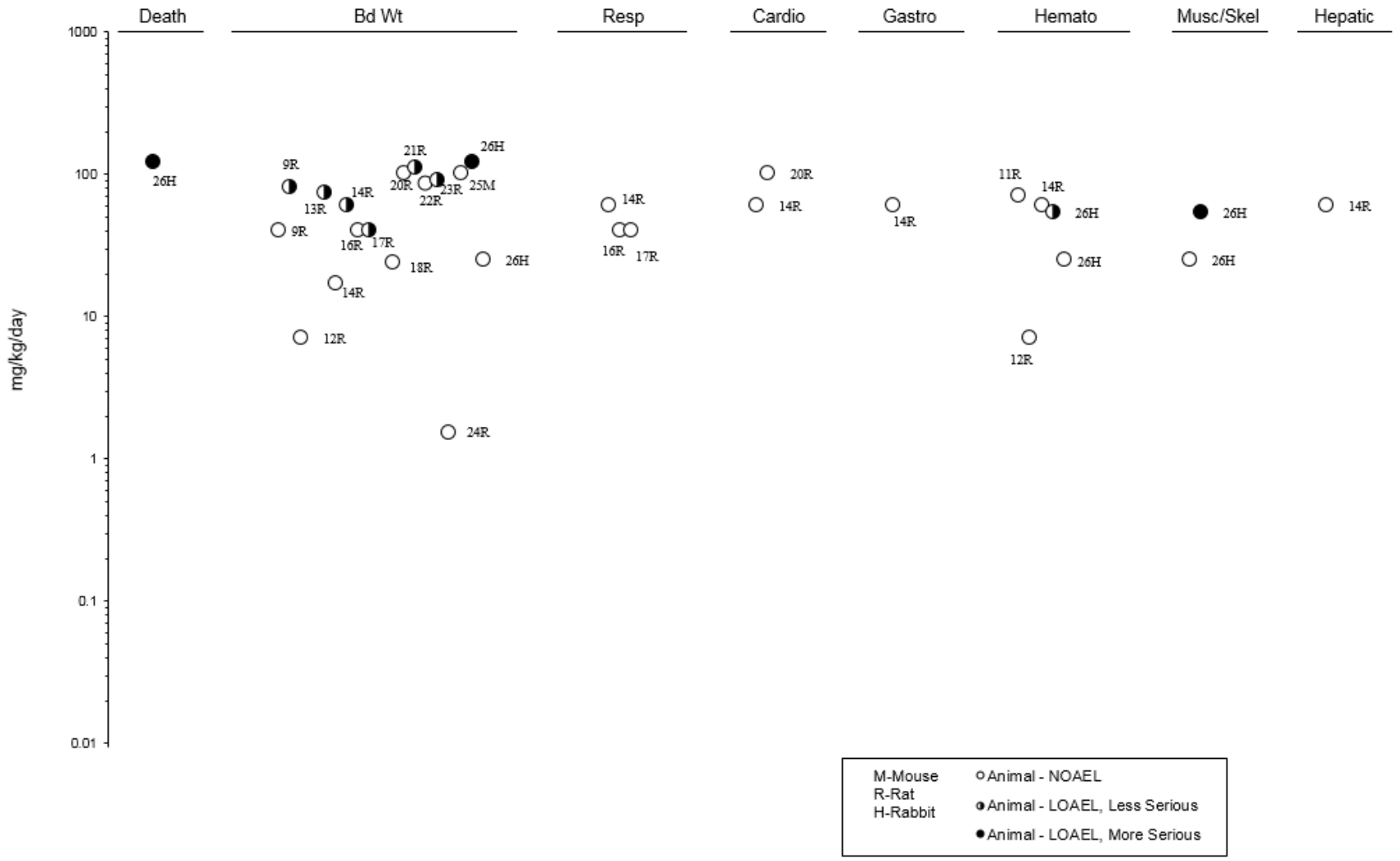

Figure 2-3. Levels of Significant Exposure to Molybdenum – Oral

Intermediate (15-364 days)

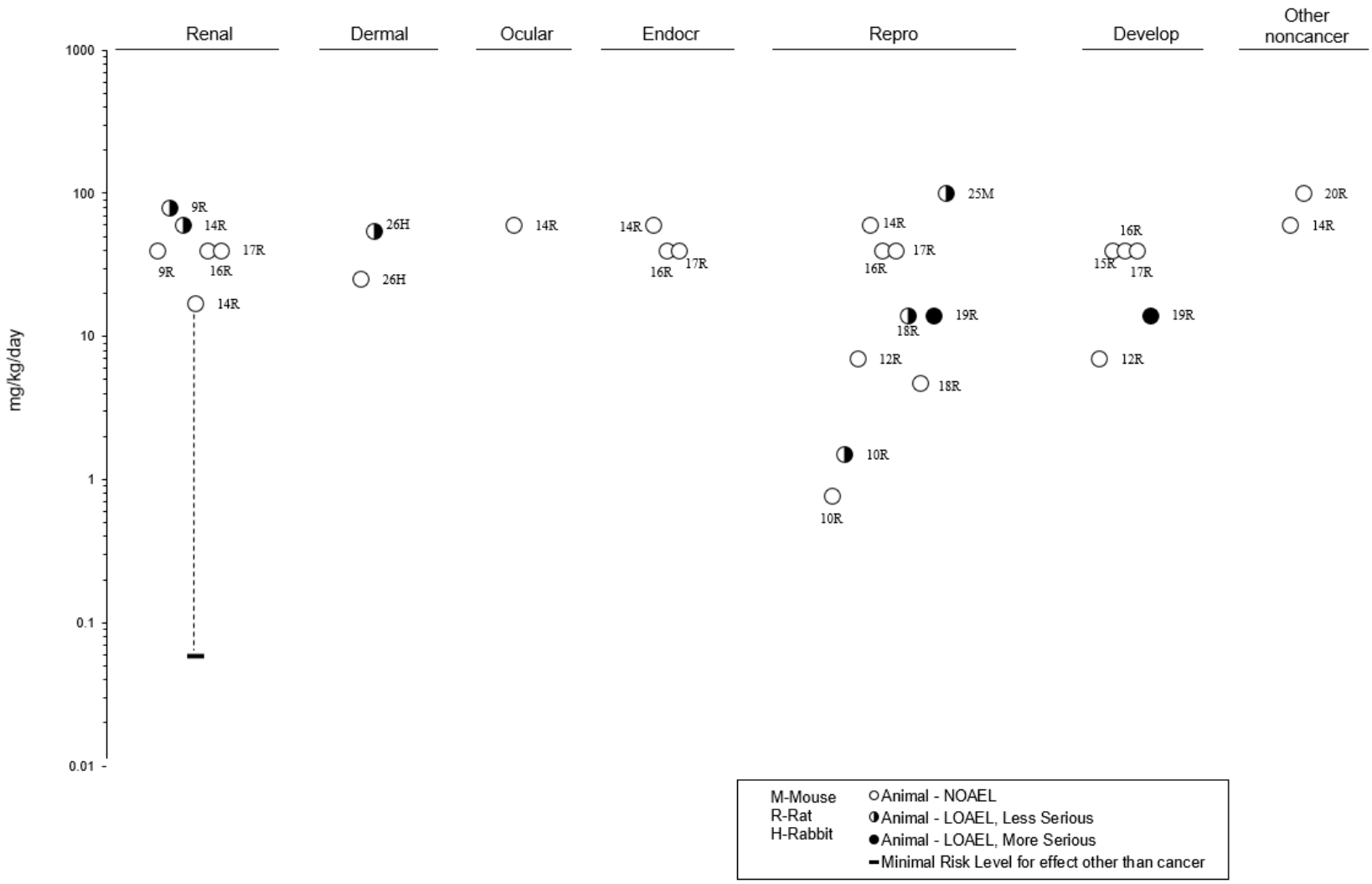

Figure 2-3. Levels of Significant Exposure to Molybdenum – Oral

Chronic (≥365 days)

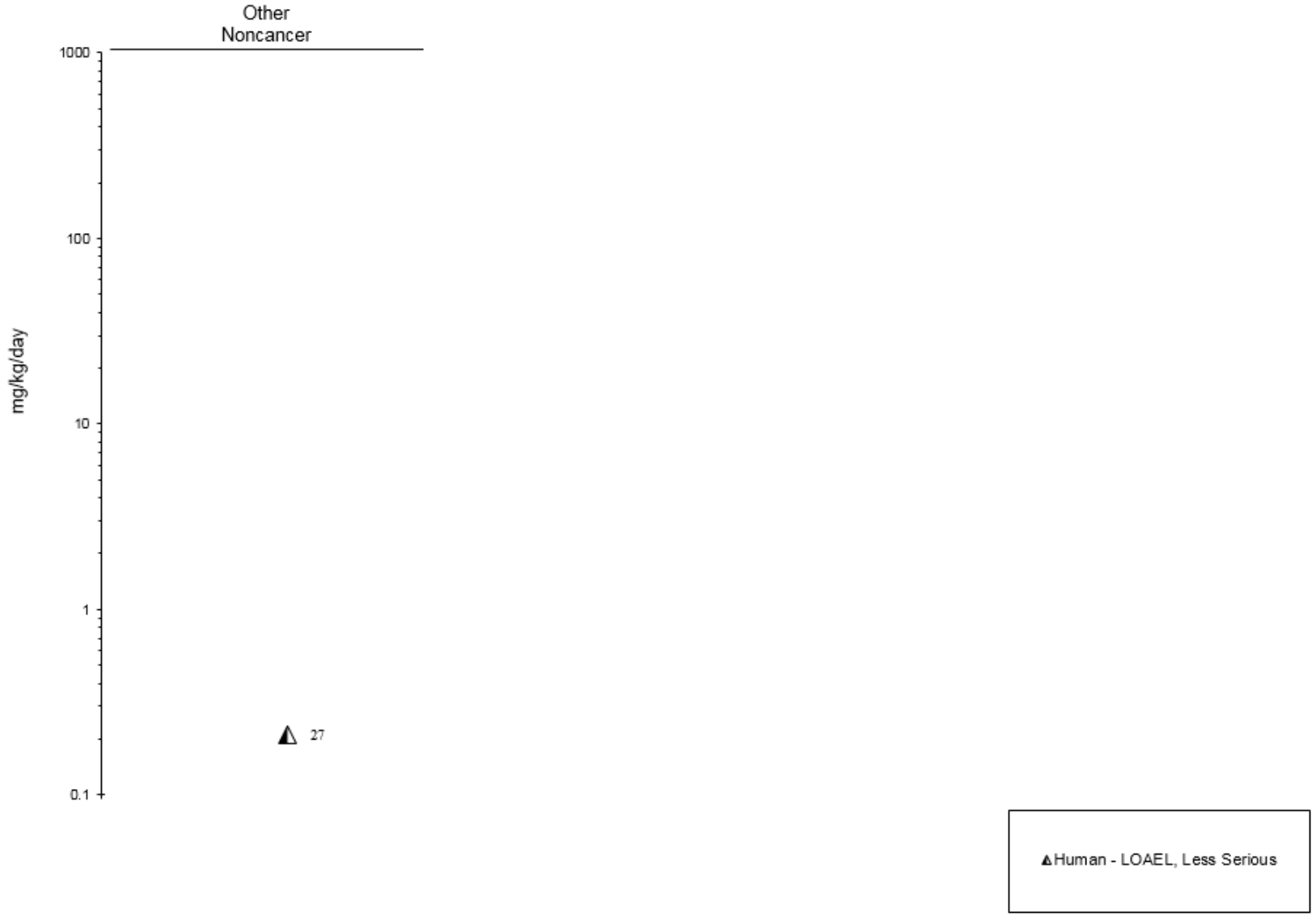

Table 2-3. Levels of Significant Exposure to Molybdenum – Dermal

Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg Mo/kg/day)	Less serious LOAEL (mg Mo/kg/day)	Serious LOAEL (mg Mo/kg/day)	Effects
ACUTE EXPOSURE								
Guinea pig (Dunkin/Hartley) 20 F	Twice	90%	CS, BW, IX	Immuno	90			
Ammonium dimolybdate Allan 1996a								
Guinea pig (Dunkin/Hartley) 20 F	Twice	70%	CS, BW, IX	Immuno	70			
Molybdenum trioxide Allan 1996c								
Guinea pig (Dunkin/Hartley) 20 F	Twice	70%	CS, BW, IX	Immuno	70			
Sodium molybdate Allan 1996d								
Guinea pig (Dunkin/Hartley) 20 F	Twice	70%	CS, BW, IX	Immuno	70			
Molybdenum trioxide Allan 1996b								
Rat (CD) 5 M, 5 F	24 hours	0, 1,200 mg/kg	CS, BW, GN	Dermal	1,200			
Ammonium dimolybdate Baldrick and Healing 1990a								
Rat (CD) 5 M, 5 F	24 hours	0, 1,300 mg/kg	CS, BW, GN	Dermal	1,300			
Molybdenum trioxide Baldrick and Healing 1990b								
Rat (CD) 5 M, 5 F	24 hours	0, 930 mg/kg	CS, BW, GN	Dermal	930			
Sodium molybdate Baldrick and Healing 1990c								

Table 2-3. Levels of Significant Exposure to Molybdenum – Dermal

Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg Mo/kg/day)	Less serious LOAEL (mg Mo/kg/day)	Serious LOAEL (mg Mo/kg/day)	Effects
Rat (CD) 5 M, 5 F	24 hours	0, 1,300 mg/kg	CS, BW, GN	Dermal	1,300			
Molybdenum trioxide **Baldrick and Healing 1990d**								
Rabbit (New Zealand) 6 M	Once	0, 56 mg	CS	Ocular		56		Mild conjunctival inflammation
Ammonium dimolybdate **Liggett and McRae 1990a**								
Rabbit (New Zealand) 6 M	Once	0, 67 mg	CS	Ocular		67		Mild conjunctival inflammation
Molybdenum trioxide **Liggett and McRae 1990b**								
Rabbit (New Zealand) 6 M	Once	0, 46 mg	CS	Ocular		46		Mild conjunctival inflammation
Sodium molybdate **Liggett and McRae 1990c**								
Rabbit (New Zealand) 6 M	Once	0, 67	CS	Ocular		67		Conjunctival inflammation
Molybdenum trioxide **Liggett and McRae 1990d**								
Rabbit (New Zealand) 6 F	4 hours	280 mg	CS	Dermal	280			
Ammonium dimolybdate **Liggett and McRae 1990e**								
Rabbit (New Zealand) 6 F	4 hours	340 mg	CS	Dermal	340			
Molybdenum trioxide **Liggett and McRae 1990f**								

Table 2-3. Levels of Significant Exposure to Molybdenum – Dermal

Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg Mo/kg/day)	Less serious LOAEL (mg Mo/kg/day)	Serious LOAEL (mg Mo/kg/day)	Effects
Rabbit (New Zealand) 6 F	4 hours	230 mg	CS	Dermal	230			
Sodium molybdate Liggett and McRae 1990g								

BW = body weight; CS = clinical signs; F = female(s); GN = gross necropsy; IX = immune function; LOAEL = lowest-observed-adverse-effect level; M = male(s); NOAEL = no-observed-adverse-effect level

2.2 DEATH

The lethality of molybdenum compounds has been investigated in several inhalation and oral exposure studies in laboratory animals. In inhalation studies, no deaths were reported in rats or mice exposed to ≤200 mg molybdenum/m^3 for 14 days (NTP 1997) or ≤67 mg molybdenum/m^3 for 90 days or 2 years (NTP 1997).

Oral LD_{50} values have been estimated in rats exposed to several molybdenum compounds. The estimated LD_{50} values were 2,291 mg molybdenum/kg for ammonium dimolybdate (Baldrick and Healing 1990e), 1,802 and 2,566 mg molybdenum/kg for pure molybdenum trioxide for males and females, respectively (Baldrick and Healing 1990f), and 1,912 and 2,079 mg molybdenum/kg for sodium molybdate for males and females, respectively (Baldrick and Healing 1990g). A study of technical-grade molybdenum trioxide did not report deaths occurring in rats administered a single dose of 3,400 mg molybdenum/kg (Baldrick and Healing 1990h).

Several oral studies have reported deaths in rabbits repeatedly exposed to molybdenum. Mortality rates of 42–100% were observed in rabbits exposed to 59–120 mg molybdenum/kg/day for intermediate durations (Arrington and Davis 1953; Robinson et al. 1969; Valli et al. 1969; Widjajakusuma et al. 1973). Although the causes of death were not reported, anorexia, body weight loss, and anemia were observed in most of the studies at the lethal concentrations, suggesting that the deaths may be related to a functional copper deficiency. The copper content of the diet was adequate in the Arrington and Davis (1953) study and was not reported in the Widjajakusuma et al. (1973), Robinson et al. (1969), and Valli et al. (1969) studies. No deaths have been reported in rat studies (e.g., Lyubimov et al. 2004; Murray et al. 2014a, 2014; Pandey and Singh 2002).

2.3 BODY WEIGHT

There are limited epidemiological data evaluating possible associations between molybdenum and body weight. A cross-sectional study of National Health and Nutrition Examination Survey (NHANES) participants did not find an association between urinary molybdenum levels and the risk of being overweight (Mendy et al. 2012).

Several inhalation exposure studies have reported body weight effects in laboratory animals. Single 4-hour exposures to 1,200 mg molybdenum/m^3 as ammonium dimolybdate (Jackson et al. 1991a),

3,890 mg molybdenum/m^3 as molybdenum trioxide (Jackson et al. 1991b), 2,613 mg molybdenum/m^3 as molybdenum trioxide (Jackson et al. 1991d), or 899 mg molybdenum/m^3 as sodium molybdate (Jackson et al. 1991c) resulted in decreases in body weight gain or weight loss during the first 2–3 days post-exposure; thereafter, the body weight gain was similar to controls. Decreases in body weight gain and weight loss were observed in rats and mice exposed via inhalation to molybdenum trioxide for 14 days (NTP 1997). Terminal body weights were 10% lower in male rats exposed to 67 mg molybdenum/m^3 compared to controls, and weight loss was observed in male rats and mice exposed to 200 mg molybdenum/m^3. In female rats and mice exposed to 200 mg molybdenum/m^3, the terminal body weights were 13 and 10%, respectively, lower than the control groups. No significant alterations in body weight gain were observed in rats or mice exposed to airborne molybdenum trioxide concentrations as high as 67 mg molybdenum/m^3 for 13 weeks or 2 years (NTP 1997).

A large number of animal studies reported alterations in body weight following acute- or intermediate-duration oral exposure to molybdenum. Large differences in terminal body weights between controls and molybdenum-exposed groups and weight loss have been reported in many studies in which the basal diet did not provide adequate levels of copper (Brinkman and Miller 1961; Fell et al. 1979; Johnson and Miller 1961; Ostrom et al. 1961; Sasmal et al. 1968; Van Reen 1959). In one study, exposure to 500 mg molybdenum/kg/day as sodium molybdate resulted in weight loss in rats (Sasmal et al. 1968); no alterations in weight loss were observed at 50 or 100 mg molybdenum/kg/day. The weight loss began early in the study; the animals weighed about 35% less than at the start of the study after 1 week of exposure. In another study by this group (Sasmal et al. 1968), exposure to 50 mg molybdenum/kg/day as ammonium molybdate resulted in weight loss. Although the study suggests differences between the two molybdenum compounds, the very low copper content of the diet (no additional copper was added to the purified diet) precludes extrapolating these data to other conditions. In another study comparing molybdenum compounds, a 10-day dietary exposure to 0.6 mg molybdenum/kg/day as ammonium tetrathiomolybdate resulted in a 10% decrease in body weight in rats; however, no alterations in body weight gain were observed in rats exposed to 0.6 mg molybdenum/kg/day as ammonium heptamolybdate under the same exposure conditions (Parry et al. 1993). The copper content of the diet was 3 ppm, which is lower than the recommendation of 5 ppm in the diet (NAS 1995).

Decreases in body weight gain have been observed in studies in which the basal diet provided a nutritionally adequate level of copper (Arrington and Davis 1953; Bompart et al. 1990; Jeter and Davis 1954; Johnson et al. 1969; Lyubimov et al. 2004; Mills et al. 1958; Murray et al. 2014a; Van Reen and Williams 1956). Significant decreases in body weight gain were observed at 60–110 mg

molybdenum/kg/day as sodium molybdate or ammonium heptamolybdate in intermediate-duration studies (Bompart et al. 1990; Mills et al. 1958; Murray et al. 2014a; Van Reen and Williams 1956; Williams and Van Reen 1956). The magnitude of the decrease in body weight gain appeared to be related to the dose, with approximately 15% decreases observed at 60 mg molybdenum/kg/day and 48% decreases observed at 110 mg molybdenum/kg/day. Administration of ammonium tetrathiomolybdate resulted in a LOAEL of 4.4 mg molybdenum/kg/day for decreases in body weight gain (Lyubimov et al. 2004); the interaction between the ammonium tetrathiomolybdate and copper may have resulted in copper insufficiency and contributed to the body weight effect. Decreases in food intake have also been reported in dietary exposure studies (Murray et al. 2014a; Williams and Van Reen 1956) and a gavage study (Lyubimov et al. 2004). Williams and Van Reen (1956) found that when the control group food intake was matched to the molybdenum group, body weight was not adversely affected after 5 weeks of exposure to 85 mg molybdenum/kg/day as sodium molybdate. However, when the control group had *ad libitum* access to food, exposure to 90 mg molybdenum/kg/day as sodium molybdate resulted in a 22% decrease in body weight gain. In contrast, Murray et al. (2014a) found a decrease in food conversion efficiency suggesting that factors other than the reduction in feed intake resulted in the decreased body weight gain. Similarly, in a study by Johnson and Miller (1961) in which the basal diet contained 3.2 ppm copper, large differences (50–60% less) in food intake were observed between the control group and the group exposed to 20 ppm molybdenum/kg/day as sodium molybdate. However, when the control intake was matched to the molybdenum group's intake, significant decreases in body weight gain were still observed.

2.4 RESPIRATORY

Limited data are available on the toxicity of molybdenum to the respiratory tract of humans. A cohort study of workers exposed to molybdenum trioxide and other oxides at a molybdenite roasting plant reported normal lung function test results in 20/25 workers (Walravens et al. 1979). Some alterations in lung function (forced expiratory volume in 1 second, FEV_1) were observed in the remaining five workers; the decrease in FEV_1 was characterized as mild in three of the workers and "more marked" in two workers, which may be indicative of mild obstructive lung disease. The study did not provide lung function data for a reference group. The estimated 8-hour time-weighted average (TWA) molybdenum concentration in total dust was 9.46 mg molybdenum/m^3; the molybdenum content of the respirable dust ranged from 1.02 to 4.49 mg molybdenum/m^3. Another cohort study of workers exposed to fine and ultrafine molybdenum trioxide dust reported dyspnea and cough in symptomatic workers (Ott et al. 2004). Radiographic abnormalities were noted in the lungs of most of the symptomatic workers and in half of the asymptomatic workers, although none of the radiographs showed evidence of interstitial lung disease.

Significant differences in lung function (increased predicted FEV_1 and forced vital capacity) were also observed in the workers, as compared to a control group. In symptomatic workers, alterations in bronchioalveolar lavage cytology suggestive of subclinical alveolitis were noted. This study (Ott et al. 2004) has several limitations including the lack of monitoring data, minimal information on the control group, which does not appear to be comprised of workers at this facility, and differences in the mean and ranges of ages of the different groups (40.0 years [range of 24–58 years], 30.5 years [22–45 years], and 30.0 years [14–72 years] in the symptomatic workers, asymptomatic workers, and controls, respectively), which were not adjusted for in the statistical analyses.

The potential respiratory toxicity of molybdenum has been investigated in laboratory animals exposed to airborne molybdenum trioxide for acute, intermediate, and chronic durations and in intermediate-duration oral studies in rats. No histological alterations were observed in the lungs of rats exposed for 4 hours to 1,200 mg molybdenum/m^3 as ammonium dimolybdate (Jackson et al. 1991a), 2,613–3,890 mg molybdenum/m^3 as molybdenum trioxide (Jackson et al. 1991b, 1991d; Leuschner 2010), or 899 mg molybdenum/m^3 as sodium molybdate (Jackson et al. 1991c). In inhalation studies conducted by the National Toxicology Program (NTP 1997), no histological alterations were observed in the nasal cavity of rats and mice exposed to 200 mg molybdenum/m^3 as molybdenum trioxide for 14 days (NTP 1997); no other regions of the respiratory tract were examined. Similarly, no histological alterations were observed in the respiratory tract of rats or mice exposed to ≤67 mg molybdenum/m^3 as molybdenum trioxide for 13 weeks (NTP 1997). In contrast, chronic exposure resulted in lesions in the nose, larynx, and lungs in rats and mice exposed to molybdenum trioxide for 2 years (NTP 1997). In the nose, hyaline degeneration of the respiratory and olfactory epitheliums was observed in rats exposed to ≥6.7 mg molybdenum/m^3 and in mice exposed to 67 mg molybdenum/m^3; other nasal lesions observed in mice included suppurative inflammation at ≥20 mg molybdenum/m^3 and olfactory epithelial atrophy at 67 mg molybdenum/m^3. Squamous metaplasia of the epiglottis was observed in rats and mice exposed to ≥6.7 mg molybdenum/m^3. In the lungs, chronic inflammation was observed in rats exposed to ≥20 mg molybdenum/m^3, and alveolar epithelial metaplasia and histiocytic cellular infiltration were observed at ≥6.7 mg molybdenum/m^3.

Two laboratory animal studies examined the respiratory tract following oral exposure to molybdenum. No lesions were observed in the lungs of rats exposed to ≤60 mg molybdenum/kg/day as sodium molybdate in the diet for 90 days (Murray et al. 2014a) or ≤40 mg molybdenum/kg/day as sodium molybdate in the drinking water or diet for 147–158 days (Murray et al. 2019).

2.5 CARDIOVASCULAR

Using the dataset from the NHANES cross-sectional study (2009–2012), Shiue and Hristova (2014) found an association between urinary molybdenum levels and high blood pressure among adults after adjusting for potential confounders (adjusted odds ratio [OR] of 1.45; 95% confidence interval [CI] of 1.04–2.02). The investigators estimated that molybdenum accounted for 6.3% of the variance in the population risk and significant associations were also found for other metals including cesium, lead, platinum, antimony, arsenic, and tungsten and industrial pollutants including phthalates, bisphenol A, and parabens. In a cross-sectional study examining the possible association between municipal water constituents and cardiovascular mortality in residents of 94 large cities in the United States, Schroeder and Kraemer (1974) found a weak negative correlation between arteriosclerotic heart disease deaths and molybdenum levels among white males, but not white females or nonwhite males or females. The mean concentration of molybdenum in the municipal water samples was 1.25 µg/L (0.00003 mg molybdenum/kg/day, assuming a water intake of 2 L/day and body weight of 70 kg) with a range of 0–16 µg/L. These studies appear to provide conflicting results, with one study suggesting a beneficial effect of increased molybdenum (Schroeder and Kraemer 1974) and the other a detrimental effect (Shiue and Hristova 2014). However, a number of etiological factors contribute to the overall risk of both diseases and the contribution of molybdenum to the overall risk was low in both studies.

In the only laboratory animal study evaluating blood pressure, Peredo et al. (2013) reported a slight decrease (approximately 4%) in systolic blood pressure in rats exposed to 100 mg molybdenum/kg/day as sodium molybdate in drinking water for 9 weeks; this slight decrease in blood pressure was not considered biologically relevant. No histological alterations were observed in the hearts of rats or mice exposed to airborne molybdenum trioxide concentrations as high as 67 mg molybdenum/m^3 for 13 weeks or 2 years (NTP 1997) or in rats ingesting ≤60 mg molybdenum/kg/day as sodium molybdate in the diet for 90 days (Murray et al. 2014a).

2.6 GASTROINTESTINAL

Intermediate- or chronic-duration inhalation exposure to ≤67 mg molybdenum/m^3 as molybdenum trioxide did not result in histological alterations in the gastrointestinal tract (NTP 1997).

A single-dose oral lethality study reported thickening of the glandular stomach in rats receiving a gavage dose of 3,000 mg molybdenum/kg as ammonium dimolybdate (Baldrick and Healing 1990e). No

histological alterations were observed in the gastrointestinal tract of rats exposed to ≤60 mg molybdenum/kg/day as sodium molybdate in the diet for 90 days (Murray et al. 2014a). In contrast, Fell et al. (1979) reported soft feces and diarrhea and a number of histological alterations in the gastrointestinal tract of rats exposed for up to 21 days to 0.5 mg molybdenum/kg/day as ammonium tetrathiomolybdate in the diet (diet provided an inadequate amount of copper). The alterations included shortening of the gastric pits with a reduction in the amount of mucin in the stomach, an increase in the crypt to villus ratio in the small intestine due to a lengthening of the crypts, edema of the lamina propria in the ileum, and submucosal edema of the cecum resulting in a thickening of the cecum but no effect on the brush border. However, the investigators did not provide incidence data, which limits the assessment of these alterations.

2.7 HEMATOLOGICAL

No significant alterations in hematological parameters were observed in rats or mice following inhalation exposure to molybdenum trioxide at concentrations as high as 67 mg molybdenum/m^3 for 13 weeks (NTP 1997).

In general, the hematological system does not appear to be a target of molybdenum oral toxicity when the basal diet contains adequate levels of copper. In rats exposed to sodium molybdate or ammonium heptamolybdate, the highest NOAEL values for hematological alterations ranged from 3.35 to 150 mg molybdenum/kg/day for intermediate-duration exposure (Brinkman and Miller 1961; Franke and Moxon 1937; Gray and Daniel 1954; Hunt and Navia 1973; Jeter and Davis 1954; Johnson et al. 1969; Murray et al. 2014a). One study reported decreases in erythrocyte counts, hemoglobin, and hematocrit in rats exposed to 4.4 mg molybdenum/kg/day as ammonium tetrathiomolybdate administered via gavage for 59–61 days (Lyubimov et al. 2004). Although the basal diet contained the National Research Council's (NRC's) recommended amount of copper (NAS 1995), hematological effects were not observed in rats exposed to the same molybdenum dose receiving a diet containing additional copper (110 ppm), suggesting that the hematological effects may have been secondary to a molybdenum-induced copper deficiency (anemia is a sign of copper deficiency). In young rabbits, exposure to 54 mg molybdenum/kg/day as sodium molybdate in the diet resulted in anemia (Arrington and Davis 1953). Even though the reported copper concentration in the diet exceeded the more recently recommended standard of 3 ppm (NAS 1977), administration of additional copper resulted in increases in hemoglobin levels. In a similar study using mature rabbits, anemia was observed in one of two rabbits exposed to 30 mg molybdenum/kg/day as sodium molybdate in the diet (Arrington and Davis 1953). Decreases in

hemoglobin levels and packed cell volume were also observed in two other rabbit studies (Valli et al. 1969; Widjajakusuma et al. 1973) in which rabbits were exposed to 77 or 59 mg molybdenum/kg/day in the diet for approximately 4 weeks. Mortality was observed in both studies and neither study reported the copper levels of the basal diet; Valli et al. (1969) did note that the rabbits were fed a diet with a low copper content. In pigs, no hematological alterations were observed following dietary exposure to 20–100 ppm molybdenum as sodium molybdate or ammonium heptamolybdate in the diet for at least 8 weeks (Gipp et al. 1967; Kline et al. 1973); the studies did not provide sufficient information to allow for an estimation of the molybdenum dose.

2.8 MUSCULOSKELETAL

No histological alterations were observed in the bones of rats or mice exposed via inhalation to 6.7–67 mg molybdenum/m^3 as molybdenum trioxide for 13 weeks or 2 years (NTP 1997). Chronic molybdenum inhalation exposure also did not affect femoral bone density or curvature in groups of 10 rats exposed to concentrations as high as 67 mg molybdenum/m^3 (NTP 1997).

A number of oral exposure studies in laboratory animals have examined the effect of molybdenum on bone growth and strength and on the promotion of dental caries. Musculoskeletal effects were observed in two studies in which the diet contained at least the recommended level of copper. In a study by Johnson et al. (1969) in which rats were exposed to 150 mg molybdenum/kg/day as sodium molybdate in the diet for 6 weeks (the basal diet contained copper levels that were 3 times higher than the recommended amount), decreases in femur breaking strength (22% less than controls) and tail ring rupture strength (32% less than controls) were observed. Young rabbits exposed to ≥54 mg molybdenum/kg/day as sodium molybdate for 30–84 days exhibited a front limb abnormality characterized by weakness progressing to an inability to "maintain weight and legs spread outward" (Arrington and Davis 1953). This was not observed in mature rabbits exposed to ≤120 mg molybdenum/kg/day as sodium molybdate for at least 54 days (Arrington and Davis 1953). The investigators noted that in three of the seven affected animals, one or both feet bent inward at the carpus joint, the articular surface of the radius was exposed, and the tendon slipped out of normal position. It should also be noted that increases in mortality were also observed in the young rabbits exposed to 54 mg molybdenum/kg/day, and in two of the rabbits with limb abnormalities, administration of additionally copper did not reverse the skeletal effect, although there was improvement of other effects including anemia and body weight gain.

In an acute-duration study, femurs were significantly shorter in rats exposed to 0.6 mg molybdenum/kg/day as ammonium heptamolybdate or ammonium tetrathiomolybdate for 13 days (Parry et al. 1993). No alterations in the width of the growth plate or the bone composition (dry matter content, ash content, or percentage of calcium or phosphorus) were found. Similar findings were found in a 26-day study conducted by Parry et al. (1993); significant decreases in femur length were noted in rats exposed to 0.6 mg molybdenum/kg/day as ammonium heptamolybdate or ammonium tetrathiomolybdate in the diet. Although no direct comparisons were made between the two molybdenum groups, the magnitude of the decrease in femur length, as compared to the controls, was greater in the tetrathiomolybdate group. Increases in growth plate width were also observed in the rats exposed to ammonium tetrathiomolybdate, but not in rats exposed to ammonium heptamolybdate. In both experiments, the rats were fed a basal diet with inadequate copper levels (60% of the recommended concentration); in the ammonium tetrathiomolybdate study, plasma and liver copper levels indicated that the animals were extremely copper deficient. Spence et al. (1980) examined the development of widening of the epiphyseal growth plate over time in rats exposed to 1 mg molybdenum/kg/day as ammonium tetrathiomolybdate in the diet for 2–21 days. The study found cartilaginous dysplasia at the epiphyseal growth plate with impaired or arrested endochondral ossification, increases in periosteal osteogenesis and production of large amounts of disorganized bone, resorption of most trabecular bone, hemorrhaging within and tearing of tendons and ligaments, rotation and slipping of the distal epiphysis in the femur without fracture, and impaired fibrogenesis at ligamentous attachments to bone. Thickening and widening of the epiphyseal growth plate were observed in the distal femur and proximal and in the epiphyses of the humeral head, distal radius, and ulna; these effects were observed within the first 2 weeks of the study. Other morphological alterations in the bone were observed after 7 days of exposure; these included loss of alignment of hypertrophic cells at the periphery of the epiphyseal cartilage and localized increases in cell numbers. In rats allowed to recover for 39 days following the 21-day exposure period, osteogenesis and fibrogenesis returned to normal, and remodeling and growth returned (although some abnormal cartilage and bone were present). As with the Parry et al. (1993) study, the rats in the Spence et al. (1980) study were fed a basal diet containing an inadequate amount of copper (60% of the recommended level). Fejery et al. (1983) found an increase in femur breaking strength in rats exposed to 0.17 or 1.7 mg molybdenum/kg/day (copper content of the diet was not reported), which was considered a beneficial effect; at 17 mg molybdenum/kg/day, breaking strength was similar to controls. However, if the rats were maintained on a protein-deficient diet, decreases in breaking strength were observed at 1.7 and 17 mg molybdenum/kg/day. In rabbits exposed to a lethal concentration of sodium molybdate (77 mg molybdenum/kg/day) in the diet for 4 weeks, fractures of the humeral bone epiphyses were observed in 50% of the animals (Valli et al. 1969). Other effects included

longitudinal widening of the epiphyseal cartilage, marked reduction in trabecular bone, irregularly arranged spicules, and irregular metaphyseal calcification. In addition, the investigators noted that there was marked muscular degeneration in the pelvic limbs in 25% of the rabbits. The copper content of the basal diet was not reported in this study, although the investigators noted that the diet had a low copper content.

Alterations in tooth enamel and caries formation have also been observed in laboratory animals exposed to molybdenum. In rat pups administered 50 mg molybdenum/kg/day as sodium molybdate via gavage on postnatal days (PNDs) 4–17 (prior to tooth eruption) and fed a caries-promoting diet on PNDs 18–35, a 25% increase in buccal enamel lesion and 85 and 12.5% increases in lesions penetrating to the buccal and sulcal dentine-enamel junctions, respectively, were observed in the mandibular molars (Hunt and Navia 1975). Fejery et al. (1983) reported biphasic alterations in incisor tooth enamel microhardness in rats exposed to sodium molybdate in drinking water for 6 weeks (the copper content of the basal diet was not reported). At 1.7 mg molybdenum/kg/day, there were increases in microhardness (6–7% increases in surface and deep enamel microhardness), which was considered a beneficial effect. However, at 17 mg molybdenum/kg/day, tooth surface and deep enamel microhardness was decreased by 14.5 and 7.5%, respectively. The study also examined the possible effect of a low protein diet (3% in the low-protein groups compared to 18% in the protein-adequate groups) and found that the beneficial effect of 1.7 mg molybdenum/kg/day did not occur in the rats in the low-protein diet; a 4–5% reduction in microhardness was found at 1.7 mg/kg/day. Van Reen et al. (1962) did not find increases in dental caries in weanling NMRI-D rats (a caries susceptible strain) exposed to 8 mg molybdenum/kg/day as sodium molybdate for 5 weeks (the basal diet provided adequate copper levels).

2.9 HEPATIC

There are limited data on the hepatotoxicity of molybdenum in humans. Using the NHANES 2007–2008 cross-sectional study data, Mendy et al. (2012) found a significant association between urinary molybdenum levels and the risk of having a self-reported liver condition (OR 3.09; 95% CI 1.24–7.73). The geometric mean urinary molybdenum level of the population was 43.8 μg molybdenum/g creatinine (95% CI 42.61–45.19); the investigators did not report the urinary concentration associated with the increased risk of liver conditions. This study does not establish causality between molybdenum exposure and liver damage, and significant associations were also found between uranium and cesium levels and liver conditions.

The liver does not appear to be a sensitive target of molybdenum toxicity in laboratory animals, although some studies have reported biochemical alterations. No significant alterations in serum clinical chemistry parameters or liver weights were observed in rats or mice exposed to airborne molybdenum trioxide concentrations as high as 67 mg molybdenum/m^3 for 13 weeks (NTP 1997). No significant alterations in the incidence of hepatic lesions were observed following 13 weeks or 2 years of exposure (NTP 1997).

No histological alterations were observed in livers of rabbits exposed to 1.2 mg molybdenum/kg/day as ammonium heptamolybdate in the diet for 14 days (Bersenyi et al. 2008), rabbits exposed to 0.58 mg molybdenum/kg/day from carrots grown in ammonium heptamolybdate rich soil, or rats exposed to 60 mg molybdenum/kg/day in the diet for 90 days (Murray et al. 2014a); these are the only studies that included histological examination of the liver. The Bersenyi et al. (2008) female rabbit study did not find alterations in serum alanine or aspartate aminotransferases levels, γ-glutamyl transferase, alkaline phosphatase, or cholesterol levels; however, a 60% increase in serum triglyceride levels was found at 1.2 mg molybdenum/kg/day. In contrast, the Murray et al. (2014a) study examined similar serum clinical chemistry parameters (including triglyceride levels) and did not find any significant alterations.

A series of studies conducted by Rana and associates have also reported some liver alterations in rats exposed to 300–490 mg molybdenum/kg/day as ammonium molybdate. The reported alterations included increases in total lipid levels (Rana et al. 1980; Rana and Kumar 1980b, 1980c), decreases in "total carbohydrate" levels (Rana and Kumar 1980c), decreases in glycogen content (Rana et al. 1985), and increases in serum alanine aminotransferase and aspartate aminotransferase activities (Rana and Chauhan 2000). The addition of 100 mg/kg body weight/day copper to the basal diet (approximately 5 ppm) appeared to reverse the effects of molybdenum on hepatic lipid and carbohydrate levels (Rana and Kumar 1980c). There was low confidence in these studies due to the poor reporting of the study design (including route of oral administration, whether the dose was reported in terms of molybdenum or ammonium molybdate, and copper content of the diet), the lack of histological examination of the liver, and the reported body weight losses (Rana et al. 1980; Rana and Chauhan 2000).

2.10 RENAL

Intermediate- or chronic-duration inhalation exposure to molybdenum trioxide (highest concentration tested was 67 mg molybdenum/m^3) did not result in histological alterations in the kidney of rats or mice (NTP 1997).

The available data from laboratory animal studies suggest that the kidney may be a target of molybdenum toxicity following oral exposure. In the only available acute-duration study, no histological alterations were observed in the kidneys of female rabbits exposed to 1.2 mg molybdenum/kg/day as ammonium heptamolybdate in the diet for 14 days (Bersenyi et al. 2008) or male rabbits exposed to 0.58 mg molybdenum/kg/day from carrots grown in ammonium heptamolybdate-rich soil for 14 days (Bersenyi et al. 2008). Murray et al. (2014a) reported a slight diffuse hyperplasia in the renal proximal tubules in 2/10 female rats exposed to 60 mg molybdenum/kg/day as sodium molybdate in the diet for 90 days; no renal lesions were observed in females exposed to 60 mg molybdenum/kg/day for 90 days and allowed to recover for 60 days. No alterations were observed in the male rats. Although the incidence was low, the investigators considered it to be treatment-related because it is an uncommon finding in female rats of this age. In a subsequent 2-generation study by this group, no histological alterations were observed in male or female rats exposed to 40 mg molybdenum/kg/day as sodium molybdate in drinking water or diet for 147–158 days (Murray et al. 2019). Degenerative changes in the kidneys were noted in male rats exposed to 240 mg molybdenum/kg/day as ammonium molybdate (Bandyopadhyay et al. 1981). It should be noted that the food intake in the molybdenum group was paired to another group of rats fed a low-protein diet and exposed to molybdenum; the basal diet likely provided adequate copper levels. No other studies included histological examination of the kidneys.

Several studies reported alterations in serum and urinary parameters that could be suggestive of altered renal function. Diuresis and creatinuria and a decrease in creatinine clearance were observed in rats administered via gavage 80 mg molybdenum/kg/day as ammonium heptamolybdate for 8 weeks (Bompart et al. 1990). The study did not find significant alterations in urinary protein or glucose levels. Studies by Rana and associates have reported increases in total lipid levels in the kidneys (Rana et al. 1980; Rana and Kumar 1980c), decreases in “total carbohydrate” levels in the kidney (Rana and Kumar 1980c), increases in serum urea and urinary albumin levels (Rana and Kumar 1983), and increases in urine specific gravity (Rana and Kumar 1983) in rats exposed to high doses of ammonium molybdate (300–490 mg molybdenum/kg/day). The addition of copper (approximately 5 ppm) to the basal diet appeared to reverse the increased lipid and decreased carbohydrate levels (Rana and Kumar 1980c). As noted in the hepatic effects section, there is low confidence in these studies and the results should be interpreted cautiously.

2.11 DERMAL

Information on the dermal toxicity of molybdenum comes from a small number of oral exposure studies reporting skin and hair effects and acute-exposure dermal studies. In an oral exposure study of weanling rabbits (Arrington and Davis 1953), alopecia and slight dermatosis were observed in four of five rabbits exposed to 54 mg molybdenum/kg/day as sodium molybdate in the diet for 84 days; no dermal effects were observed at 25 mg molybdenum/kg/day. In another study by this group, alopecia and slight dermatosis were observed in one of two mature rabbits exposed to 30 mg molybdenum/kg/day as sodium molybdate. Anemia was also observed at these doses. In the study of weanling rabbits, administration of additional copper resulted in a return to a normal hair coat, suggesting that copper insufficiency, possibly molybdenum induced, was a contributing factor to the dermal toxicity. Johnson et al. (1969) reported decreases (25% lower than controls) in skin rupture strength in rats exposed to 150 mg molybdenum/kg/day as sodium molybdate in the diet for 6 weeks.

No dermal effects were observed in rats following a 24-hour dermal application of 280 or 1,200 mg molybdenum/kg as ammonium dimolybdate (Baldrick and Healing 1990a; Liggett and McRae 1990e), 340 or 1,300 mg molybdenum/kg as pure molybdenum trioxide (Baldrick and Healing 1990b; Liggett and McRae 1990f), 230 or 930 mg molybdenum/kg as sodium molybdate (Baldrick and Healing 1990c; Liggett and McRae 1990g), or 1,333 mg molybdenum/kg as technical-grade molybdenum trioxide (Baldrick and Healing 1990d).

2.12 OCULAR

No ocular lesions were observed in rats exposed to 60 mg molybdenum/kg/day as sodium molybdate in the diet for 90 days (Murray et al. 2014a); no other oral or inhalation studies examined ocular endpoints.

Instillation of 56 mg molybdenum/kg as ammonium dimolybdate (Liggett and McRae 1990a), 67 mg molybdenum/kg as pure molybdenum trioxide (Liggett and McRae 1990b), 67 mg molybdenum/kg as technical grade molybdenum trioxide (Liggett and McRae 1990d), or 46 mg molybdenum/kg as sodium molybdate (Liggett and McRae 1990c) resulted in conjunctival inflammation in rabbits.

2.13 ENDOCRINE

The possible association between molybdenum and thyroid effects was investigated in adults (subjects did not report having thyroid disease, thyroid cancer, or taking thyroid medication on a medical questionnaire completed at the blood sampling) using the NHANES 2007–2008 cross-sectional study data set (Yorita Christensen 2013). Associations between decreased levels of triiodothyronine (free and total) and thyroxine (free) and higher urinary molybdenum levels were found. Although the study found associations, these data are inadequate for establishing causality. Another study of NHANES participants did not find an association between urinary molybdenum levels and thyroid problems (Mendy et al. 2012). A cross-sectional study of men at a fertility clinic found a significant inverse relationship between blood molybdenum levels and prolactin levels (Meeker et al. 2009). The men were categorized into three groups based on blood molybdenum levels (<70th, 70th–85th, and >85th percentile); the association was found in the men with blood molybdenum levels >85th percentile, as compared to men with levels <70th percentile. The study did not find a significant association with thyroid stimulating hormone and blood molybdenum levels.

Inhalation studies did not find histological alterations in the adrenal, pituitary, pancreas, parathyroid, or thyroid glands in rats and mice exposed to ≤67 mg molybdenum/m^3 as molybdenum trioxide for 13 weeks or 2 years (NTP 1997).

In oral exposure laboratory animal studies, increases in serum cortisol, prolactin, and follicle stimulating hormone levels were found in male rats administered 240 mg molybdenum/kg/day as ammonium molybdate for 4 weeks (Bandyopadhyay et al. 1981); as noted in the renal effects section, food intake was matched to a low-protein molybdenum group. No increases in the incidence of histological alterations in the adrenal glands, pituitary gland, or thyroid were observed in rats exposed to 60 mg molybdenum/kg/day as sodium molybdate in the diet for 90 days (Murray et al. 2014a) or up to 40 mg molybdenum/kg/day as sodium molybdate in drinking water or diet for 147–158 days (Murray et al. 2019). Several thyroid effects were reported in rabbits exposed to 59 mg molybdenum/kg/day as sodium molybdate in the diet for 25–31 days (Widjajakusuma et al. 1973). The investigators did not report the copper content of the diet; it is likely to be low based on the severe decreases in body weight, hematological parameters, and increased mortality. The effects included decreases in thyroxine secretion rates; decreases in follicle size (height and diameter); atrophy of the follicular epithelium, colloids, and stroma; and degenerative alterations in the follicular epithelium and interfollicular connective tissue. With the exception of the degenerative changes, similar, but less prominent, thyroid effects were also

observed in pair-fed controls, suggesting that the decreases in food intake and body weight contributed to the thyroid toxicity.

2.14 IMMUNOLOGICAL

There are limited data on the immunotoxicity of molybdenum in humans. Studies of patients with stainless steel stents (which contain nickel, chromate, and molybdenum) or in patients prior to hip or knee replacements found a low rate of positive results in patch tests with molybdenum (Koster et al. 2000; Menezes et al. 2004; Zeng et al. 2014). In patients with stainless steel stents, 3% had a positive delayed-type contact hypersensitivity reaction to molybdenum chloride (Koster et al. 2000). In the other studies, exposure to an unspecified molybdenum compound did not result in any positive hypersensitivity results (Menezes et al. 2004; Zeng et al. 2014).

No studies have examined immune function following inhalation exposure to molybdenum. Intermediate- and chronic-duration studies in rats and mice did not report histological alterations in the thymus or spleen at molybdenum trioxide levels as high as 67 mg molybdenum/m^3 (NTP 1997). No studies were located regarding immune effects in laboratory animals following oral exposure to molybdenum.

Guinea pigs showed contact sensitization to a topical challenge with molybdenum pentachloride after induction via intradermal injection with 0.03% molybdenum and topical exposure to 5.2% molybdenum and an epicutaneous challenge with ≥0.35% molybdenum as molybdenum pentachloride (Boman et al. 1979). Similarly, guinea pigs were sensitized to 3.2% molybdenum as sodium molybdate following intradermal (3.2% molybdenum) or topical (8% molybdenum) induction (Boman et al. 1979). In contrast, other studies of skin sensitization in guinea pigs were negative for ammonium dimolybdate (Allan 1996a), pure and technical-grade molybdenum trioxide (Allan 1996b, 1996c), and sodium molybdate (Allan 1996d); these studies tested higher molybdenum concentrations (70–90% molybdenum) than the Boman et al. (1979) study.

2.15 NEUROLOGICAL

Information on the potential neurotoxicity of molybdenum comes from inhalation and oral exposure studies in laboratory animals evaluating brain histology or monitoring for overt signs of neurotoxicity. None of these studies included function testing. No overt signs of neurotoxicity were observed in

laboratory animal studies (e.g., Murray et al. 2014a; NTP 1997). No histological alterations were observed in the brain of rats and mice exposed via inhalation to ≤67 mg molybdenum/m^3 as molybdenum trioxide for 13 weeks or 2 years (NTP 1997) or rats exposed to ≤60 mg molybdenum/kg/day as sodium molybdate in the diet for 90 days (Murray et al. 2014a). In contrast, Helaly et al. (2018) reported dense inflammation and neurocyte degeneration in the cerebral cortex and hippocampus of rats receiving gavage doses of 30 mg molybdenum/kg/day as molybdenum dihydrate for 30 days; however, the study did not include incidence data.

2.16 REPRODUCTIVE

There are limited data on reproductive effects of molybdenum in humans. The available studies have evaluated correlations between ambient molybdate exposure and reproductive health measures, including semen quality (Meeker et al. 2008) and sex hormone levels (Meeker et al. 2010). A cross-sectional study by Meeker et al. (2008) reported an inverse association between higher molybdenum blood levels (>85th percentile, based on molybdenum levels in blood) and sperm concentration (adjusted OR 3.48; 95% CI 1.12–10.8) after adjustment for potential confounders and other metal exposures. No associations were found for sperm morphology (adjusted OR 2.61; 95% CI 0.97–7.0) or sperm motility (adjusted OR 2.24; 95% CI 0.77–6.49). In another cross-sectional study, Meeker et al. (2010) reported an inverse correlation between higher molybdenum blood levels (≥70th percentile) and testosterone and free androgen index (molar ratio of total testosterone sex hormone-binding globulin) levels. The men in these studies, who were recruited from Michigan infertility clinics and were not all considered to be infertile (i.e., their partners may have been infertile), were only exposed to molybdenum from their surroundings. An inverse association between a biomarker of molybdenum exposure (urinary levels) and serum testosterone levels was also observed in a cross-sectional study of males participating in NHANES (Lewis and Meeker 2015). The study found a 3.82% decrease in serum testosterone levels when urinary molybdenum levels doubled (after adjustment for age, body mass index [BMI], income, race, and smoking). Although these studies found associations, they do not establish causality and the alterations in reproductive parameters may be due to multiple factors rather than only to molybdenum exposure.

Studies in laboratory animals have evaluated potential alterations in male reproductive tissues, female reproductive tissue, and fertility following inhalation (no evaluation of fertility) or oral exposure. No studies have evaluated reproductive toxicity following dermal exposure.

Several studies have evaluated the reproductive toxicity in male laboratory animals. No alterations in sperm count or motility or histological alterations of male reproductive tissues were observed in rats or mice exposed via inhalation to molybdenum trioxide concentrations as high as 67 mg molybdenum/m^3 (NTP 1997). Murray et al. (2014a) did not find any alterations in spermatid, sperm counts, sperm motility, or sperm morphology in rats exposed to 60 mg molybdenum/kg/day as sodium molybdate in the diet for 90 days. Although the study found no alterations in the percentage of motile sperm, a slight, but statistically significant, decrease in the percentage of progressively motile sperm was observed at 60 mg molybdenum/kg/day (59.0% compared to 69.4% in controls). The investigators noted that the decrease was likely attributable to the control group having a value that approached the upper end of the range for historical controls (mean of 59.8±16.2%). No alterations in sperm parameters were observed in male rats exposed to ≤40 mg molybdenum/kg/day as sodium molybdate in drinking water in a 2-generation study (Murray et al. 2019). In parental-generation males exposed to 40 mg molybdenum/kg/day as sodium molybdate in the diet, an increase in the number of sperm with no head was found (Murray et al. 2019). However, the investigators did not consider this to be treatment-related since it was largely due to one male rat, was not observed in the F1 males, and the values were within the range of historical controls.

In contrast to these findings, other studies have reported male reproductive effects. Decreases in sperm motility and concentration and increases in sperm morphological changes were observed in rats administered via gavage 14 mg molybdenum/kg/day as sodium molybdate for 60 days (Pandey and Singh 2002), and in mice exposed to 25 mg molybdenum/kg/day as sodium molybdate in the drinking water for 14 days (Zhai et al. 2013). These studies also found decreases in epididymides, seminal vesicles, and/or prostate gland weights (Pandey and Singh 2002; Zhai et al. 2013). The Zhai et al. (2013) study also found increases in sperm motility and concentration and decreases in the occurrence of sperm morphological alterations in rats exposed to lower molybdenum doses (6 mg molybdenum/kg/day as sodium molybdate). A study in rabbits reported reductions in the number of germ cells and mature spermatocytes in the testes (Bersenyi et al. 2008); the investigators also noted a large number of syncytial giant cells and degenerated cells in the seminiferous tubules. Interpretation of these results are limited since incidence data or statistical analyses were not reported. Degeneration of the seminiferous tubules was found in rats at 7 mg molybdenum/kg/day as sodium molybdate, which was administered in the diet from weaning through sexual maturity (Jeter and Davis 1954); although this study provided an adequate amount of copper, there was evidence of copper deficiency (achromotrichia) at ≥7 mg molybdenum/kg/day. Degeneration of the seminiferous tubules was also reported by Pandey and Singh (2002) for intermediate-duration (60 days) exposures in rats administered molybdenum at doses up to 24 mg molybdenum/kg/day (sodium molybdate); however, the dose(s) producing the effects are unclear

and incidence data were not reported. The Pandey and Singh (2002) and Zhai et al. (2013) studies did not report the copper content of the basal diet, although both studies used commercial diets. Lyubimov et al. (2004) reported delayed spermiation, increased sperm and seminal fluid concentration, and increased sloughing of epididymal tail epithelial cells at 4.4 mg molybdenum/kg/day as ammonium tetrathiomolybdate. Although the basal diet in the Lyubimov et al. (2004) study provided 11 ppm of copper, which is above the National Academy of Sciences (NAS 1995) recommended amount for rats (5 ppm), dietary copper supplementation (110 ppm) prevented testicular toxicity. It is likely that the tetrathiomolybdate interfered with the absorption of dietary copper, resulting in a secondary effect of copper insufficiency.

As with the male reproductive effects, conflicting results have been reported for female reproductive effects. Murray et al. (2014a) did not find any alterations in vaginal cytology or estrus cycle in female rats exposed to ≤60 mg molybdenum/kg/day as sodium molybdate in the diet for 90 days or in a 2-generation study in which rats were exposed to ≤40 mg molybdenum/kg/day as sodium molybdate in the drinking water or the diet (Murray et al. 2019). No histological alterations were observed in female reproductive tissues in rats or mice following inhalation exposure to ≤67 mg molybdenum/m^3 for 13 weeks or 2 years (NTP 1997), in rats exposed to ≤60 mg molybdenum/kg/day as sodium molybdate in the diet for 90 days (Murray et al. 2014a), or in rabbits exposed to 1.2 mg molybdenum/kg/day as ammonium heptamolybdate in the diet for 14 day (Bersenyi et al. 2008). Zhang et al. (2013) reported an increase in the rate of MII oocyte morphological abnormalities and decreases in relative ovarian weights were observed in mice exposed to 11 mg molybdenum/kg/day as sodium molybdate in drinking water for 14 days. The investigators also reported ovarian hyperemia in mice exposed to 5.3 and 11 mg molybdenum/kg/day; however, the incidence and statistical significance were not reported. Irregularities in the estrous cycle were reported in rats administered 1.5 mg molybdenum/kg/day in the drinking water from weaning through sexual maturity (Fungwe et al. 1990).

Several intermediate-duration oral studies evaluated fertility. No alterations in fertility were observed in female rats exposed to ≤15 mg molybdenum/kg/day as sodium molybdate in drinking water (Fungwe et al. 1990), in a 2-generation study in rats exposed to ≤40 mg molybdenum/kg/day as sodium molybdate in drinking water or diet (Murray et al. 2019), or in male and female rats exposed to 7 mg molybdenum/kg/day as sodium molybdate in the diet when a high copper diet was administered (Jeter and Davis 1954). In contrast, Pandey and Singh (2002) reported decreases in fertility in males exposed to 14 mg molybdenum/kg/day as sodium molybdate and mated to unexposed females. Another study conducted by Jeter and Davis (1954) in which rats were exposed to 7 mg molybdenum/kg/day from

weaning to maturity also found impaired male fertility; in this study, there is some indication that the diet did not provide an adequate level of copper.

2.17 DEVELOPMENTAL

Information on the potential developmental toxicity of molybdenum is limited to two epidemiological studies and oral exposure studies in laboratory animals. Vazquez-Salas et al. (2014) found an association between third-trimester maternal urinary molybdenum levels (mean level of 54.0 µg/g creatinine) and infant psychomotor development indices, including gross and fine motor coordination, during the first 30 months of life in a cross-sectional study of women in Mexico participating in a prospective study of neurodevelopment in children. A doubling of creatinine corrected urinary molybdenum levels resulted in significant decreases in psychomotor development index scores. No association was found between maternal urinary molybdenum levels during pregnancy (mean levels ranged from 45.6 to 54.6 µg/g creatinine during the first, second, and third trimesters) and newborn body weight or infant mental development indices (sensory ability, memory, learning, problem solving, and verbal ability). Shirai et al. (2010) found no association between maternal urinary molybdenum levels and newborn body weight, length, or head circumference in a cross-sectional study of women in Japan with mean urinary molybdenum levels of 79.0 µg/g creatinine. As noted elsewhere in this document, these observational epidemiology studies do not establish causality between molybdenum and developmental effects, and other factors are likely to have contributed to the risk.

No developmental effects were reported in three studies of rats exposed to molybdenum in the presence of adequate copper concentrations in the basal diet (Jeter and Davis 1954; Murray et al. 2014b, 2019). In a 2-generation study, no alterations in pup survival, sex ratios, pup body weight, or developmental landmarks were observed in the F1 or F2 offspring of rats exposed to up to 40 mg molybdenum/kg/day as sodium molybdate in the drinking water or diet (Murray et al. 2019). In a single-generation study, Murray et al. (2014b) reported no effects on litter size, embryofetal survival, sex ratio, fetal body weight, or fetal malformations and variations in rats exposed to 40 mg molybdenum/kg/day as sodium molybdate in the diet on gestation days (GDs) 6–20. No alterations in birth weights were observed in the offspring of male and female rats exposed to 7 mg molybdenum/kg/day as sodium molybdate for at least 14 weeks (Jeter and Davis 1954). In contrast to these findings, one study found decreases in the number of live fetuses, fetal crown-rump length, and fetal body weight in the offspring of male rats administered 14 mg molybdenum/kg as sodium molybdate via gavage for 60 days prior to mating to untreated females

(Pandey and Singh 2002). The copper content of the commercial diet was not reported but was assumed to be adequate.

Developmental effects have also been reported in studies in which the copper content of the diets was lower than the NAS-recommended standard of 8 ppm for pregnant rats (NAS 1995). Fungwe et al. (1990) reported increases in fetal resorptions and decreases in litter weights in female rats exposed to 1.3 mg molybdenum/kg/day as sodium molybdate in the drinking water for 8 weeks prior to mating through GD 21; the copper content in the basal diet was 6.3 ppm. Decreased maternal body weight gain was also observed at doses resulting in developmental toxicity. Decreased weaning weights were observed in the offspring of rats exposed to ≥2 mg molybdenum/kg/day as sodium molybdate; the copper content of the diet was 5 ppm (Jeter and Davis 1954). Lyubimov et al. (2004) found no effects on litter size or fetal survival in rats administered molybdenum daily via gavage at 4.4 mg molybdenum/kg/day as ammonium tetrathiomolybdate for 59–61 days (for 29 days prior to mating, during mating, and thereafter until sacrifice) in males or for 22–35 days (for 15 days prior to mating, during mating, and during GDs 0–6) in females. Two studies only available as abstracts provide additional information on the potential developmental toxicity of molybdenum. Lyubimov et al. (2002) found no developmental effects in rats exposed to 6 mg/kg/day as tetrathiomolybdate on GDs 6–17. Exposure on GDs 7–20 resulted in an increase in carpal/tarsal flexure in the offspring of dams exposed to 20 mg/kg/day ammonium tetrathiomolybdate (Lyubimov et al. 2003). Although neither study provided information on the copper content of the diet, it is assumed to be adequate based on Lyubimov et al. (2004).

2.18 OTHER NONCANCER

Several studies have evaluated the possible associations between molybdenum and uric acid levels. Slight, but significant increases in serum uric acid levels were observed in molybdenite roasting facility workers exposed to a TWA concentration of 9.47 mg molybdenum/m^3 as molybdenum trioxide and other oxides (Walravens et al. 1979). The serum uric acid levels were 5.90 mg/dL in the exposed workers and 5.01 mg/dL in the controls; these levels are within the normal range. No significant associations between serum molybdenum levels and serum uric acid levels were found, and none of the workers reported gout-like symptoms.

Koval'skiy et al. (1961) reported a significant increase in blood uric acid levels and symptoms of gout in a cross-sectional study of residents living in an area of Armenia with high levels of molybdenum in the soil and food, as compared to residents living outside of this area. The mean uric acid levels in a subset

of the examined population (n=52) was 6.2 mg/dL, as compared to levels in five control subjects who had a mean level of 3.8 mg/dL; the mean uric acid levels were 8.1 mg/dL among the subjects with gout symptoms and 5.3 mg/dL among the exposed subjects without symptoms. The investigators reported that copper intakes (5–10 mg/day) were lower in the high molybdenum area as compared to copper intake for residents outside of this area (10–15 mg/day). It was also noted that gout-like symptoms have not been observed in other high molybdenum areas that have higher copper intakes (Koval'skiy et al. 1961). Interpretation of the result of this study is limited by the small control group, as compared to the exposed group; lack of information on the selection of controls, particularly if they were matched to the exposed group; and lack of information on diet and alcohol exposure, which could influence uric acid levels. Additionally, NAS (2001) noted potential analytical problems with the serum and urine copper measurements. Based on the levels of molybdenum in the foodstuff, the investigators estimated a daily dose of 10–15 mg (0.14–0.21 mg/kg/day assuming a 70-kg body weight). Deosthale and Gopalan (1974) did not find significant increases in urinary uric acid levels in four subjects exposed to a low molybdenum diet for 10 days followed by a high molybdenum diet with an ammonium molybdate supplement for 7 days (TWA molybdenum intake was 0.014 mg molybdenum/kg/day), as compared to uric acid levels when the subjects were fed a low molybdenum diet. 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). 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. Another study (EPA 1979) noted that serum uric acid levels were within the normal range in students with an estimated molybdenum intake of 500 μg/day (0.007 mg/kg/day) (EPA 1979). A third study found significant increases in uric acid levels in residents with low molybdenum (20 μg/L; 0.0006 mg/kg/day) levels in the water and in residents with high molybdenum levels (150–200 μg/L; 0.004–0.006 mg/kg/day) in the drinking water; as compared to residents with drinking water levels of 0–50 μg/L (0–0.001 mg/kg/day). The inconsistencies in the results could be explained by the lack of control of several variables including age, sex, alcohol intake, dietary habits, and altitude.

Murray et al. (2014s) found a statistically significant decrease in serum uric acid levels in female rats exposed to ≥5 mg molybdenum/kg/day as sodium molybdate in the diet for 90 days; no alterations were observed in male rats exposed to up to 60 mg molybdenum/kg/day. Other statistically significant alterations in serum clinical chemistry parameters noted in the Murray et al. (2014a) study include decreases in total protein and calcium at 60 mg molybdenum/kg/day in males and decreases in serum creatinine at ≥5 mg molybdenum/kg/day in females. The investigators noted that the changes in serum

clinical chemistry (including uric acid levels) were not considered treatment-related because the alterations were of small magnitude, not dose-related, due to outliers in the controls, and/or consistent with normal variability. Quantitative data for the serum clinical chemistry parameters were not provided in the published paper.

Possible associations between molybdenum and diabetes and related outcomes have also been investigated in a limited number of epidemiological and laboratory animal studies. In a cross-sectional study of 9,447 NHANES participants, Menke et al. (2016) found an association between urinary molybdenum levels and diabetes. The ORs and 95% CIs for subjects with urinary molybdenum levels in the second, third, and fourth quartiles, as compared to the first quartile were 1.46 (1.09–1.97), 1.89 (1.35–2.66), and 1.76 (1.24–2.50), respectively. Associations were also found for Homeostatic Model Assessment (HOMA) insulin resistance levels for all subjects and in subjects without diabetes.

Two studies in rats did not find significant alterations in serum glucose levels following intermediate-duration exposure to 60 or 100 mg molybdenum/kg/day (Murray et al. 2014a; Peredo et al. 2013); additionally, serum insulin levels were not altered by exposure to 100 mg molybdenum/kg/day (Peredo et al. 2013). Prakash (1989) reported decreases in glycogen levels in the hindlimb muscles of rats administered 490 mg molybdenum/kg/day as ammonium molybdate via gavage for 30 days. The significance of this effect is difficult to determine since the study did not provide information on body weight gain.

2.19 CANCER

The potential carcinogenicity of molybdenum compounds has been evaluated in an occupational exposure study and in a rat and mouse inhalation study. In a case-control study examining the potential association between lung cancer and exposure to 16 potential carcinogens, Droste et al. (1999) did not find a significant increase in lung cancer among workers who self-reported exposure to molybdenum. However, an increased risk of lung cancer was found in workers who self-reported working in industries that could involve exposure to molybdenum (OR 2.1; 95% CI 1.2–3.7); the job most often related to molybdenum exposure was processing of stainless steel in the manufacture of metal goods, which could also involve exposure to other carcinogens including chromium, nickel, and arsenic. Limitations of this study, including self-reported exposure and the potential exposure to other lung carcinogens, preclude its use in assessing the potential carcinogenicity of molybdenum.

In the 2-year NTP rat study (NTP 1997), an increase in the combined incidence of alveolar/bronchiolar adenoma or carcinoma was observed in male rats exposed to 67 mg molybdenum/m^3 as molybdenum trioxide; however, the incidence was within the range of historical controls and NTP considered this to be equivocal evidence of carcinogenic activity of molybdenum trioxide. No other concentration-related increases in neoplastic lesions were observed in the rats. In mice, there were significant increases in the incidences of alveolar/bronchiolar carcinoma in males at ≥6.7 mg molybdenum/m^3, alveolar/bronchiolar adenoma or carcinoma in males at 6.7 and 20 mg molybdenum/m^3, alveolar/bronchiolar adenoma in females at 20 and 67 mg molybdenum/m^3, and alveolar/bronchiolar adenoma or carcinoma in females at 67 mg molybdenum/m^3 (NTP 1997). The incidences of alveolar/bronchiolar adenoma and carcinoma were highest in the 6.7 mg molybdenum/m^3 groups and lowest in the 67 mg molybdenum/m^3 groups. NTP (1997) concluded that the male and female mouse data provided some evidence of carcinogenic activity of molybdenum trioxide.

The Department of Health and Human Services (NTP 2016) and EPA have not evaluated the carcinogenic potential of molybdenum. IARC has categorized molybdenum trioxide as possibly carcinogenic to human (Group 2B).

2.20 GENOTOXICITY

No studies were available regarding genotoxic effects of molybdenum compounds in humans following environmental or occupational exposure to these compounds. The genotoxicity of molybdenum compounds has been studied mostly in *in vitro* assays utilizing prokaryotic organisms and in mammalian cells. Limited information is available regarding the *in vivo* genotoxicity of molybdenum.

As shown in Table 2-4, sodium molybdate induced a modest, but statistically significant, increase in micronucleated bone marrow cells (polychromatic erythrocytes [PCEs]) from male C57BL/6J mice following two intraperitoneal injections of 200 or 400 mg/kg sodium molybdate on 2 consecutive days (Titenko-Holland et al. 1998). The increase in micronucleated cells per 1,000 PCE or in micronuclei per 1,000 PCE were about half of those produced by colchicine, the positive control. The same group of investigators reported that sodium molybdate induced a positive response in the dominant lethal assay in mice. In these experiments, male C57BL/6J mice were treated with 200 or 400 mg/kg sodium molybdate and were mated with non-treated female C3H/J mice at various times after dosing. Sodium molybdate did not significantly affect pregnancy rate, but induced a significant dose-related increase in post-implantation loss.

Table 2-4. Genotoxicity of Molybdenum Compounds *In Vivo*

Species	Compound	Endpoint	Results	Reference
Mouse (male C57BL/6J)	Sodium molybdate	Micronuclei in bone marrow cells	(+)	Titenko-Holland et al. 1998
Mouse (male C57BL/6J)	Sodium molybdate	Dominant lethal assay	(+)	Titenko-Holland et al. 1998
Drosophila melanogaster wing spot test	Molybdenum chloride	Gene mutation	+	Ogawa et al. 1994

+ = positive result; (+) = weakly positive result

Assessment of the activity of molybdenum chloride in the *Drosophila melanogaster* wing spot test showed that the compound induced spots with one or two mutant hairs (small spots) (Ogawa et al. 1994). Almost all of the spots detected were mutant clones expressing the *mwh* phenotype which, according to the investigators, suggested a nonlethal genetic change such as gene mutation or mitotic recombination occurring at a late developmental stage, or a semi-lethal change such as partial aneuploidy for a chromosomal region containing the *mwh* locus.

Table 2-5 summarizes studies of genotoxic effects of molybdenum compounds in *in vitro* systems. Results of gene mutation and DNA tests performed in prokaryotic organisms, almost all conducted without metabolic activation, were mixed, but negative results outnumbered positive results. It is worth noting the positive results reported for potassium molybdate and ammonium molybdate in the DNA repair assay (Nishioka 1975).

Table 2-5. Genotoxicity of Molybdenum Compounds *In Vitro*

			Results		
Species (test system)	Compound	Endpoint	With activation	Without activation	Reference
Prokaryotic organisms:					
Salmonella typhimurium, TA98, TA100, TA1535, TA1537, 1538	Ammonium molybdate	Gene mutation	No data	–	Arlauskas et al. 1985
S. typhimurium, TA97, TA98, TA100, TA 1535, TA1537	Molybdenum trioxide	Gene mutation	–	–	NTP 1997; Zeiger et al. 1992
S. *typhimurium*, TA98, TA100, TA1535, TA1537	Molybdenum trioxide	Gene mutation	–	–	Jones 2004

Table 2-5. Genotoxicity of Molybdenum Compounds *In Vitro*

Species (test system)	Compound	Endpoint	Results		Reference
			With activation	Without activation	
S. *typhimurium*, TA98, TA100, TA1535, TA1537, TA102	Sodium molybdate	Gene mutation	–	–	Beevers 2009
S. *typhimurium*, TA98, TA100, TA1535, TA1537, TA102	Sodium molybdate	Gene mutation	–	–	Burzlaff et al. 2017
S. *typhimurium*, TA98, TA100, TA1535, TA1537, TA102	Sodium molybdate	Gene mutation	–	–	Burzlaff et al. 2017
Saccharomyces cerevisiae D3	Sodium molybdate	Gene conversion and mutation	No data	–	Singh 1983
Escherichia coli, WP2uvrA$^-$	Ammonium molybdate	Reverse gene mutation	No data	–	Arlauskas et al. 1985
E. coli, WP2uvrA	Molybdenum trioxide	Gene mutation	–	–	Jones 2004
E. coli, 2 WP2 strains	Ammonium heptamolybdate	Reverse gene mutation	No data	+	Nishioka 1975
E. coli, CM571	Ammonium heptamolybdate	Reverse gene mutation	No data	–	Nishioka 1975
E. coli PQ37	Molybdenum chloride	DNA damage	No data	–	Olivier and Marzin 1987
E. coli WP2$_s$(ƛ)	Sodium molybdate	DNA damage	No data	(+)	Rossman et al. 1984
E. coli WP2$_s$(ƛ)	Sodium molybdate	DNA damage	No data	(+)	Rossman et al. 1991
Bacillus subtilis, H17 and M45	Molybdic acid	DNA repair assay	No data	–	Kanematsu et al. 1980
B. subtilis H17 and M45	Molybdenum disulfide	DNA repair assay	No data	–	Kanematsu et al. 1980
B. subtilis H17 and M45	Molybdenum pentachloride	DNA repair assay	No data	–	Nishioka 1975
B. subtilis H17 and M45	Potassium molybdate	DNA repair assay	No data	(+)	Nishioka 1975
B. subtilis H17 and M45	Ammonium heptamolybdate	DNA repair assay	No data	+	Nishioka 1975
Photobacterium fischeri	Sodium molybdate	Direct mutation	No data	–	Ulitzur and Barak 1988

Table 2-5. Genotoxicity of Molybdenum Compounds *In Vitro*

Species (test system)	Compound	Endpoint	Results		Reference
			With activation	Without activation	
Mammalian cells:					
Mouse lymphoma (L5178Y) cells	Sodium molybdate	Gene mutation	–	–	Lloyd 2009
Mouse lymphoma L5178Y tk (+/-) cells	Sodium molybdate dihydrate	Gene mutation	–	–	Burzlaff et al. 2017
Human peripheral lymphocytes	Sodium molybdate	Micronucleus assay	No data	(+)	Titenko-Holland et al. 1998
Human peripheral lymphocytes	Sodium molybdate	Micronucleus assay	–	–	Taylor 2009
Human peripheral blood lymphocytes	Sodium molybdate dihydrate	Micronucleus assay	–	–	Burzlaff et al. 2017
Human peripheral lymphocytes	Ammonium molybdate	Micronucleus assay	No data	+	Titenko-Holland et al. 1998
Human peripheral lymphocytes	Molybdenum Trioxide	Micronucleus assay	–	–	Fox 2005
Syrian hamster embryo (SHE) cells	Molybdenum trioxide	Micronucleus assay	No data	+	Gibson et al. 1997
Chinese hamster ovary (CHO) cells	Molybdenum trioxide	Chromosomal aberrations	–	–	NTP 1997
CHO cells	Molybdenum trioxide	Sister chromatid exchanges	–	–	NTP 1997

+ = positive result; (+) = weakly positive result; – = negative result; ± = equivocal result

The few studies that tested molybdenum compounds in mammalian cells provided mixed results (Table 2-4). For molybdenum trioxide, NTP (1997) reported negative results for chromosomal aberrations; Fox (2005) and Gibson et al. (1997) reported negative and positive results, respectively, for micronuclei formation, with both studies evaluating overlapping dose ranges. Titenko-Holland et al. (1998) reported positive results for micronuclei formation in human peripheral lymphocytes incubated with sodium or ammonium molybdate. However, cell viability was affected by treatment, and blood was collected from only two donors; therefore, the results from this study should be interpreted with caution. More recent studies with human peripheral lymphocytes did not find increases in micronuclei formation for molybdenum trioxide (Fox 2005) or sodium molybdate (Burzlaff et al. 2017; Taylor 2009).

In summary, the limited information regarding effects *in vivo* of molybdenum compounds is insufficient to infer possible outcomes of exposure in human populations. *In vitro* studies in prokaryotic organisms mostly found no alterations in gene mutations and mixed results for DNA damage and repair. *In vitro* studies in mammalian cells primarily found no alterations in the occurrence of clastogenic effects.

2.21 MECHANISMS OF ACTION

The mechanism of molybdenum toxicity has not been well-established. There are some indications that the mode of action may involve altered copper utilization; however, it is likely that other mechanisms, including direct molybdenum alterations, are involved. Support of the mode of action involving impaired copper utilization comes from toxicology studies demonstrating more severe effects when animals are maintained on a copper-deficient diet; molybdenum induced increases in copper levels in the plasma, liver, and kidneys; and apparent reversal of adverse effects following administration of high doses of copper. A number of the effects observed in animals orally exposed to molybdenum, particularly decreases in body weight and anemia (Arrington and Davis 1953; Brinkman and Miller 1961; Franke and Moxon 1937; Gray and Daniel 1954; Johnson et al. 1969), are similar to those observed in copper-deficient animals. Administration of high levels of copper results in a fairly rapid improvement or prevents the effect from occurring (Arrington and Davis 1953; Lyubimov et al. 2004). In rats fed a copper-adequate diet, exposure to high levels of molybdenum in the diet resulted in significant increases in plasma copper levels (Nederbragt 1980, 1982), most of which were in a “tightly bound form” that did not appear to be associated with ceruloplasmin (major copper-carrying protein in the blood), as evidenced by the lack of an increase in ceruloplasmin levels (Nederbragt 1980). Significant increases in liver and kidney copper levels were also observed in rats exposed to molybdenum in the diet and maintained on a copper-adequate diet.

In ruminants, which appear to be very sensitive to molybdenum toxicity, it is believed that molybdenum reacts with sulfate generated in the rumen to form thiomolybdates; copper can bind to these thiomolybdates, which impairs its absorption. There is also some indication that cupric thiomolybdates can form in the blood if dietary copper levels are inadequate (Telfer et al. 2004). The copper in these cupric thiomolybdates is unavailable to ceruloplasmin and other copper-containing proteins, resulting in a functional copper deficiency (Vyskocil and Viau 1999). In monogastric animals exposed to sodium molybdate, administration of sulfate decreases the toxicity of molybdenum (Miller et al. 1956; Van Reen 1959). However, when rats were fed diets containing molybdate and sulfide, there was a substantial increase in plasma molybdenum and copper levels and liver molybdenum levels and a decrease in

ceruloplasmin activity. In the plasma, there was a shift in the fraction of copper associated with albumin and ceruloplasmin (Mills et al. 1981a). Similar findings were observed in rats administered tetrathiomolybdates, but not in rats exposed to molybdates in the absence of sulfide (Mills et al. 1981a). In rats, exposure to tetrathiomolybdates resulted in effects similar to those observed in ruminants including signs of copper deficiency, such as loss of pigmentation in hair and a similar distribution of copper between the plasma proteins (Mills et al. 1981b). However, these interactions between tetrathiomolybdate and copper only occurred when both were present in the gastrointestinal tract (Mills et al. 1981b). It is not known if the interactions between copper and molybdenum only occur at higher molybdenum doses. As discussed by Brewer et al. (2000), tetrathiomolybdate can form a tripartite complex with copper and protein, which can prevent copper absorption through the gastrointestinal tract. When tetrathiomolybdate is not administered with food, it can complex with copper and serum albumin, which prevents cellular uptake of copper. Due to these mechanisms, tetrathiomolybdate is used to treat individuals with Wilson's disease, which is a metabolic defect that limits the excretion of copper. Other molybdenum compounds may also interfere with copper balance in humans. Significant increases in serum and urine copper levels were observed in men exposed to 0.022 mg molybdenum/kg/day (the source of molybdenum was high molybdenum sorghum supplemented with ammonium molybdate) for 10 days, as compared to exposure to 0.00771 mg molybdenum/kg/day for 10 days (Deosthale and Gopalan 1974). However, there was no difference in fecal excretion of copper, suggesting that copper absorption was not affected. In contrast, another study (Turnlund and Keys 2000) did not find any significant alterations in serum copper levels in humans exposed to molybdenum levels of 22–1,490 μg/day (0.0003–0.02 mg/kg/day) for 24 days (subjects were fed diets containing naturally high or low levels of molybdenum).

A number of studies have reported that molybdenum induces oxidative stress. An *in vitro* study in mouse fibroblasts and liver cancer cells found that trivalent molybdenum induced oxidative stress as indicated by increases in reactive oxygen species generation and increases in malondialdehyde concentration (Terpilowska and Siwicki 2019). This possible mechanism of action is supported by several *in vivo* studies. A general population study found an association between urinary molybdenum levels and ratio of oxidized glutathione to reduced glutathione in the general population suggestive of a relationship between molybdenum and oxidative stress (Domingo-Relloso et al. 2019). Zhai et al. (2013) showed that the levels of two enzymatic antioxidants (superoxide dismutase and glutathione peroxidase) in the testes of mice paralleled the molybdenum-induced sperm effects. Increases in antioxidant levels and improvements in sperm parameters were observed at lower molybdenum doses. However, at higher molybdenum doses, there were significant decreases in antioxidant levels and significant decreases in

sperm motility and concentration and an increase in the rate of sperm abnormalities. Zhang et al. (2013) reported a similar finding for superoxide dismutase and glutathione peroxidase levels in the ovaries of mice and the rate of MII oocyte abnormalities. Molybdenum-induced hepatocyte apoptosis was observed in goats orally exposed to ammonium molybdate for 50 days (Zhuang et al. 2016). Molybdenum exposure resulted in down-regulation of superoxide dismutase and catalase expression in liver cells and an up-regulation of malondialdehyde, nitric oxide, and total nitric oxide synthase expression. The investigators suggested that the observed effect may be due to a disruption of the mitochondrial antioxidant defense system resulting in apoptosis via activation of the mitochondrial signaling pathways.