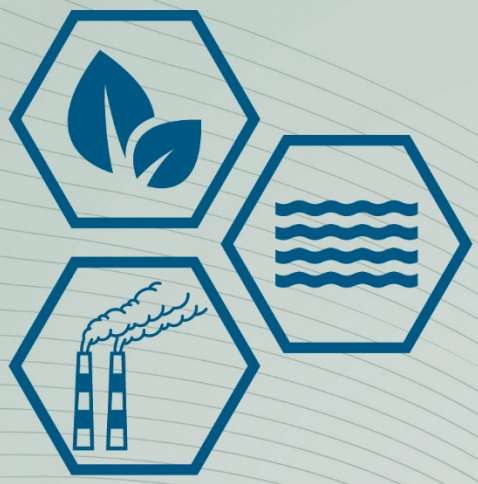

Toxicological Profile for Molybdenum

May 2020

U.S. Department of Health and Human Services
Agency for Toxic Substances and Disease Registry

CS274127-A

DISCLAIMER

Use of trade names is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry, the Public Health Service, or the U.S. Department of Health and Human Services.

FOREWORD

This toxicological profile is prepared in accordance with guidelines* developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a relevance to public health discussion which would allow a public health professional to make a real-time determination of whether the presence of a particular substance in the environment poses a potential threat to human health. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to the protection of public health are identified by ATSDR.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance due to associated acute, intermediate, and chronic exposures;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, intermediate, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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*Legislative Background

The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i)(1) directs the Administrator of ATSDR to "…effectuate and implement the health related authorities" of the statute. This includes the preparation of toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL) and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the NPL, in an effort to "…establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

VERSION HISTORY

Date	Description
May 2020	Final toxicological profile released
April 2017	Draft for public comment toxicological profile released

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ATSDR scientists review peer reviewers' comments and determine whether changes will be made to the profile based on comments. The peer reviewers' comments and responses to these comments are part of the administrative record for this compound.

The listing of peer reviewers should not be understood to imply their approval of the profile's final content. The responsibility for the content of this profile lies with ATSDR.

CONTENTS

LIST OF FIGURES

LIST OF TABLES

CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

Molybdenum (Mo) is a naturally occurring trace element that can be found extensively in nature. Molybdenum is a metal that exists as a dark-gray or black powder with a metallic luster or as a silvery-white mass (NLM 2020a). It does not occur naturally in the pure metallic form, but principally as oxide or sulfide compounds (Barceloux 1999; EPA 1979). Therefore, almost all exposure is to a molybdenum compound rather than the actual metal. Important naturally occurring molybdenum compounds are the minerals molybdenite, powellite, wulfenite, ferrimolybdite, and ilsemannite. In this toxicological profile, "molybdenum" is used to refer to the element (molybdenum metal) and generically for substances or compounds containing molybdenum. The most common forms used in commerce and found in the environment are molybdenum trioxide and molybdate salts (sodium molybdate or ammonium molybdate). Industrial applications of molybdenum nanoparticles have also been identified; however, molybdenum nanoparticle exposure is not discussed in this toxicological profile because their physical-chemical properties differ from that of larger molybdenum particles and the toxicological and toxicokinetic properties of nanoparticles can vastly differ from those of larger particles.

Biologically, molybdenum plays an important role as a micronutrient in plants and animals, including humans. It is used widely in industry for metallurgical applications; some of these applications include high temperature furnaces, as a support wire for tungsten filaments in incandescent light bulbs, and as a component of steel used in solar panels and wind turbines (EPA 1979; Stiefel 2011).

Molybdenum is more abundant in areas of natural mineral deposits and can be found in all environmental media. Higher concentrations in air, water, and soil can be found near industrial operations due to contamination. Molybdenum concentrations in ambient air have been reported to range from below detection limits to 0.03 mg/m^3 (EPA 1979). Concentrations of molybdenum in ambient air of urban areas, 0.01–0.03 $\mu g/m^3$, are higher than those found in rural areas, 0.001–0.0032 $\mu g/m^3$. It has been reported that concentrations of molybdenum in surface waters are generally <1.0 µg/L (USGS 2006) and drinking water (USGS 2011) and groundwaters contain about 1.0 µg/L (USGS 2011). Near mining activities, surface water molybdenum concentrations can be orders of magnitude higher (Frasacoli and Hudson-Edwards 2018). Concentrations as high as 1,400 µg/L have been detected in drinking waters in areas impacted by mining and milling operations (USGS 2011), far exceeding the U.S. Environmental Protection Agency (EPA) health-based screening level of 40 µg/L (EPA 2018a). Globally, most soils

contain molybdenum at concentrations between 0.6 and 3.5 ppm, although total concentrations in soils can vary widely depending on geological composition or industrial contamination. The average concentration of soils is generally 1–2 ppm. In the United States, it has been reported that the median concentration of molybdenum in soils is 1.2–1.3 ppm, with a range of 0.1–40 ppm (EPA 1979).

The exposure to molybdenum to the general population is almost entirely through food. Foods derived from above-ground plants, such as legumes, leafy vegetables, and cauliflower, generally have a relatively higher concentration of molybdenum in comparison to food from tubers or animals. Beans, cereal grains, leafy vegetables, legumes, liver, and milk are reported as the richest sources of molybdenum in the average diet (Barceloux 1999). Drinking water coming from sources close to areas with high molybdenum contamination from industrial effluents may contain a higher concentration of molybdenum.

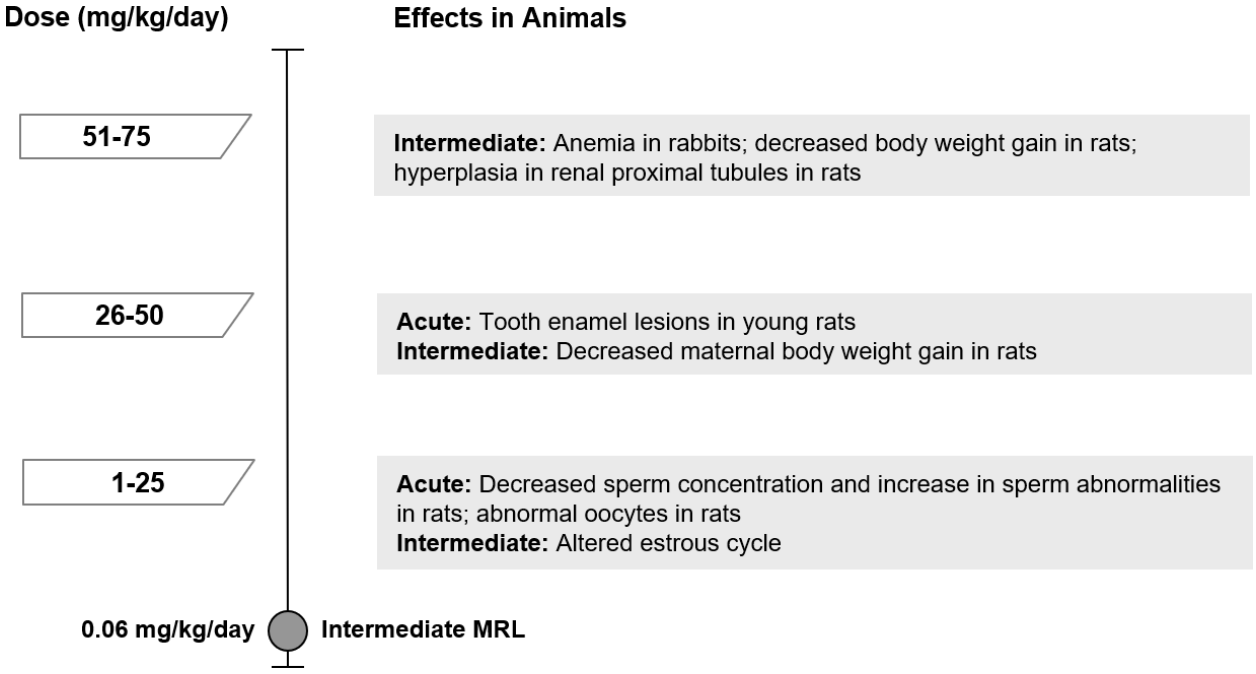
1.2 SUMMARY OF HEALTH EFFECTS

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

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

Respiratory Effects. Decreases in lung function, dyspnea, and cough were reported in a study of workers exposed to fine or ultrafine molybdenum trioxide dust (Ott et al. 2004). Another study of workers at a molybdenite roasting facility exposed to molybdenum trioxide and other oxides did not have alterations in lung function (Walravens et al. 1979). In studies of rats and mice exposed to molybdenum trioxide for 2 years, hyaline degeneration of the nasal epithelium, squamous metaplasia of the epiglottis, and chronic inflammation (rats only) were observed (NTP 1997). However, no effects were observed following a 13-week exposure to similar concentrations (NTP 1997).

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



Hepatic Effects. Liver effects, which consisted of decreases in glycogen content, increases in aminotransferase activities, and increases in lipid content, have been observed at higher doses (≥300 mg/kg/day) that are often associated with body weight losses (Rana and Chauhan 2000; Rana and Kumar 1980b, 1980c; Rana et al. 1980, 1985). No hepatic effects have been observed at lower (≤60 mg/kg/day) doses (Bersenyi et al. 2008; Murray et al. 2014a).

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

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

rats exposed to approximately 25 mg molybdenum/kg/day as sodium molybdate (Pandey and Singh 2002; Zhai et al. 2013). Degeneration of the seminiferous tubules was also observed at similar molybdenum doses (Jeter and Davis 1954). Effects have also been observed in the female reproductive system (oocyte morphological alterations, abnormal rate of ovulation, and irregularities in the estrous cycle) at ≥1.5 mg molybdenum/kg/day in rats (Fungwe et al. 1990; Jeter and Davis 1954; Zhang et al. 2013).

Developmental Effects. Mixed results have been observed in animal developmental toxicity studies. Decreases in the number of live fetuses and fetal growth were observed in rats administered 14 mg molybdenum/kg as sodium molybdate (Pandey and Singh 2002). Interpretation of the results of this study is limited by the lack of information on the copper content of the diet and the lack of developmental effects reported in two high-quality studies in which rats were exposed to doses as high as 40 mg molybdenum/kg/day as sodium molybdate (Murray et al. 2014b, 2019).

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

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

1.3 MINIMAL RISK LEVELS (MRLs)

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

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

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

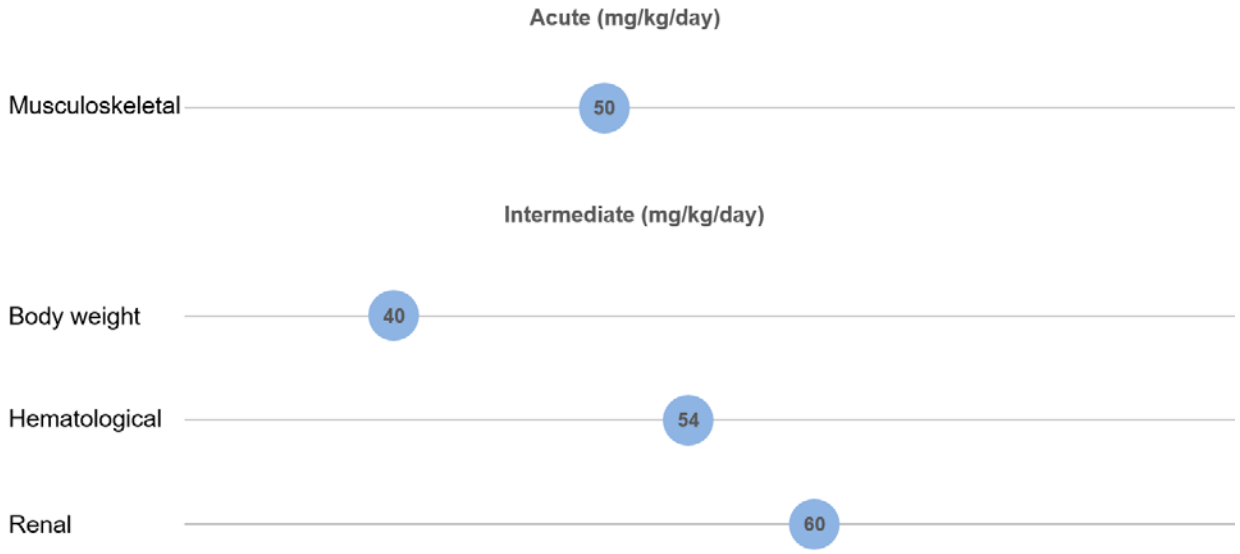
Exposure duration	MRL	Critical effect	Point of departure	Uncertainty and modifying factors	Reference
Inhalation exposure (mg molybdenum/m^3)					
Acute	Insufficient data for derivation of an MRL				
Intermediate	Insufficient data for derivation of an MRL				
Chronic (molybdenum trioxide)	0.002	Squamous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

[a]See Appendix A for additional information.

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

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

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



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:

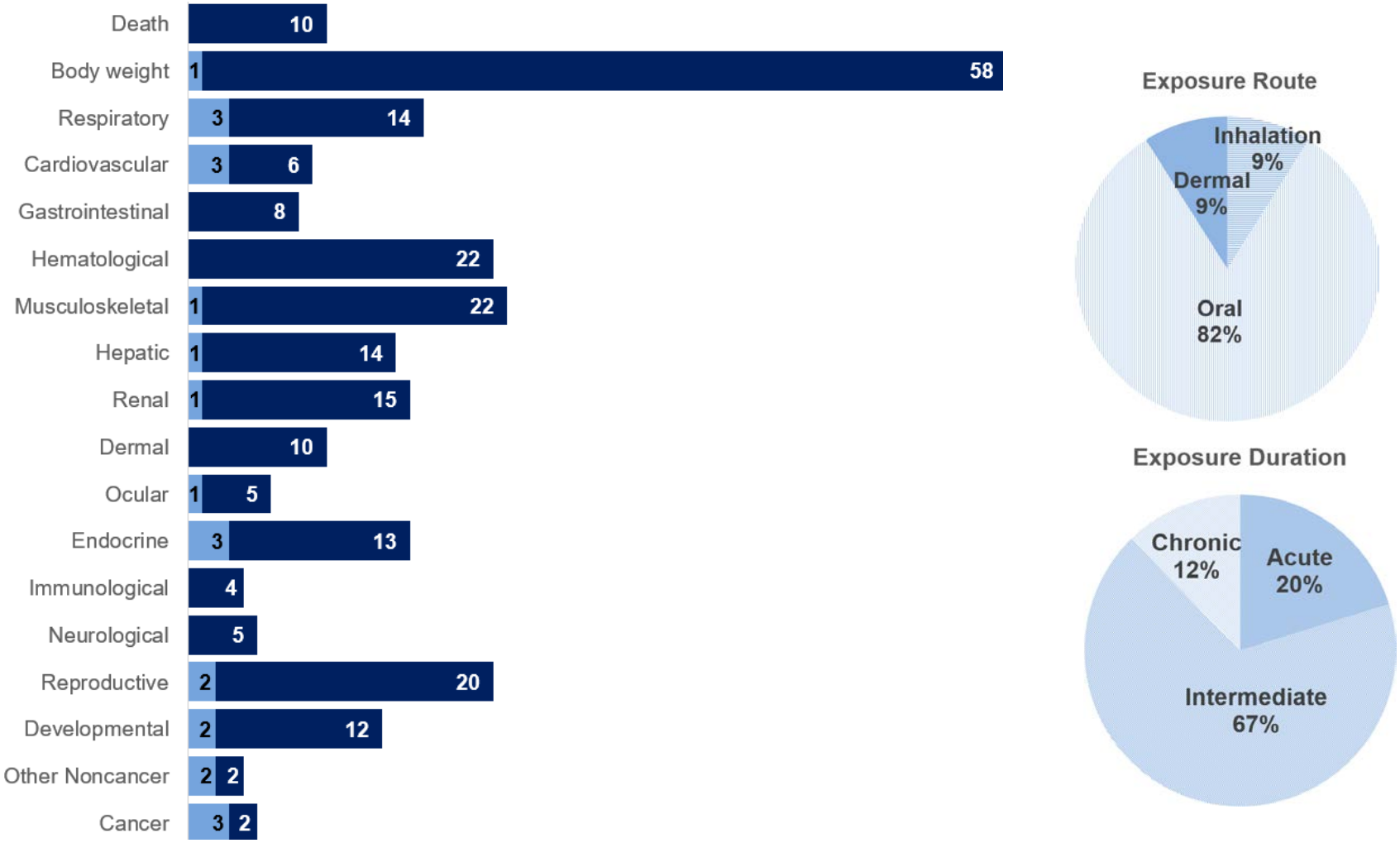
- **Respiratory Endpoints:** Respiratory effects are a presumed health effect for humans based on inadequate evidence in molybdenum oxide workers and a high level of evidence in rats and mice chronically exposed to airborne molybdenum trioxide.

- **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									

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
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			

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
					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									

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
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)

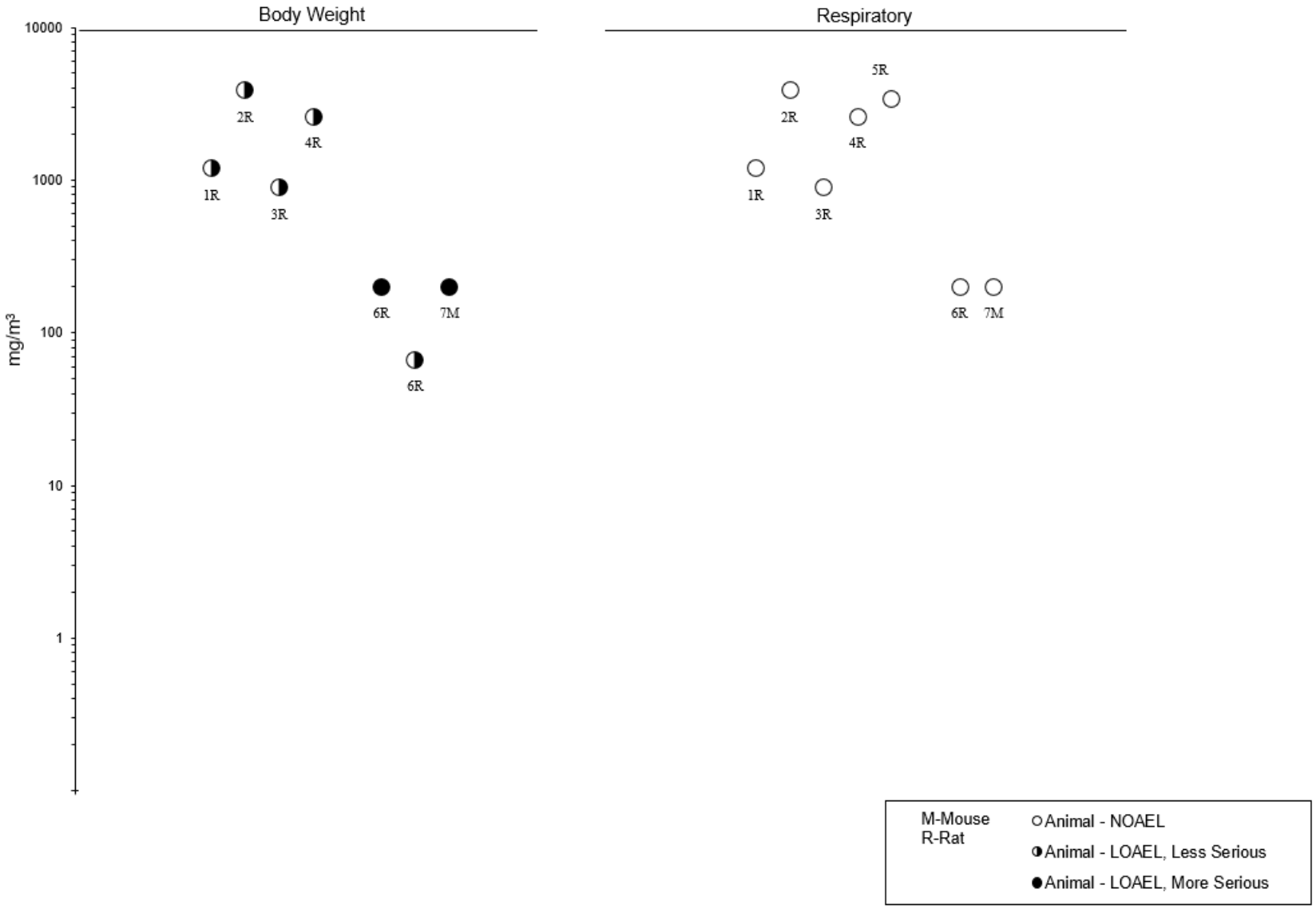


Figure 2-2. Levels of Significant Exposure to Molybdenum – Inhalation

Intermediate (15-364 days)

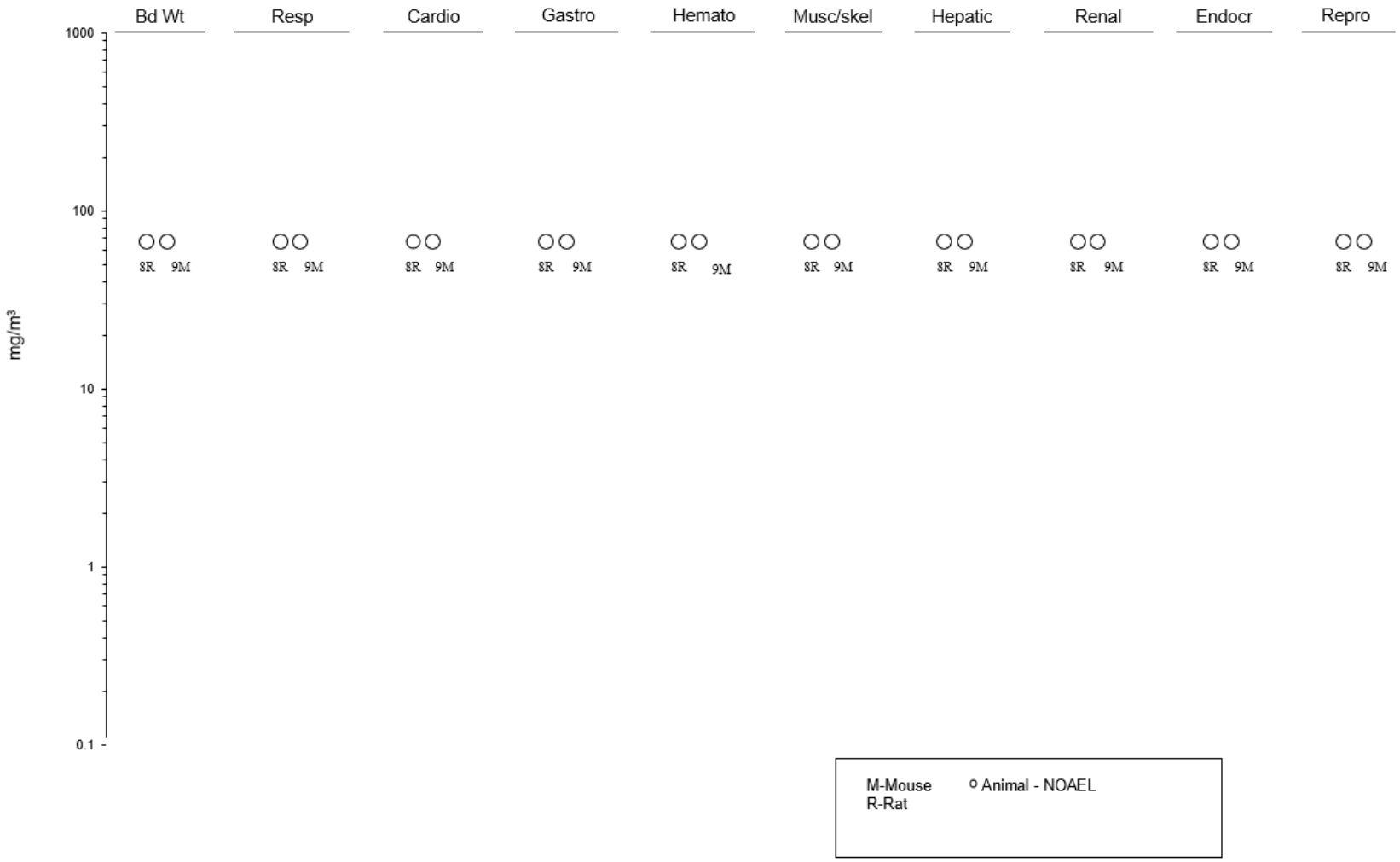


Figure 2-2. Levels of Significant Exposure to Molybdenum – Inhalation

Chronic (≥365 days)

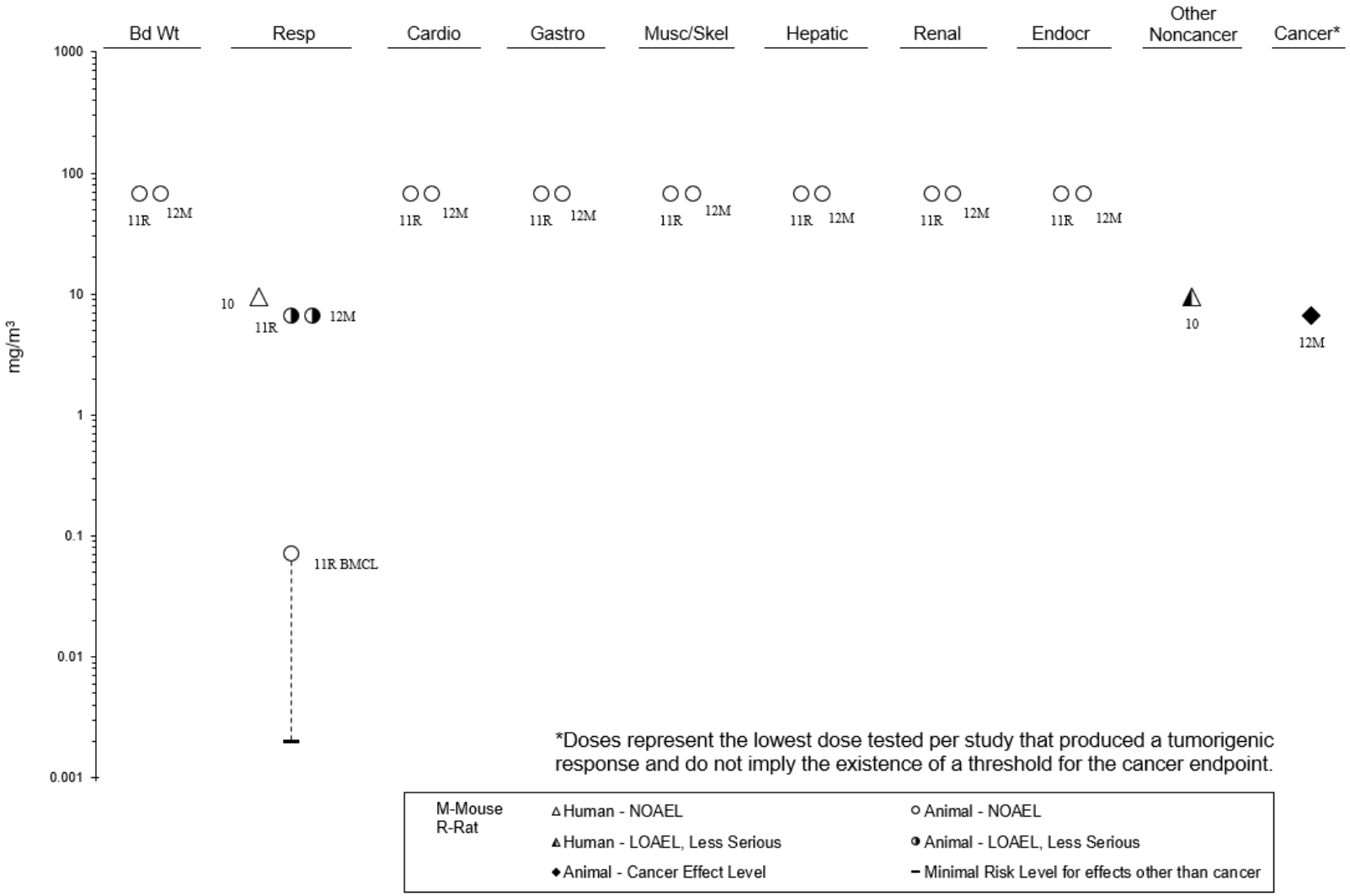


Table 2-2. Levels of Significant Exposure to Molybdenum – Oral

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)

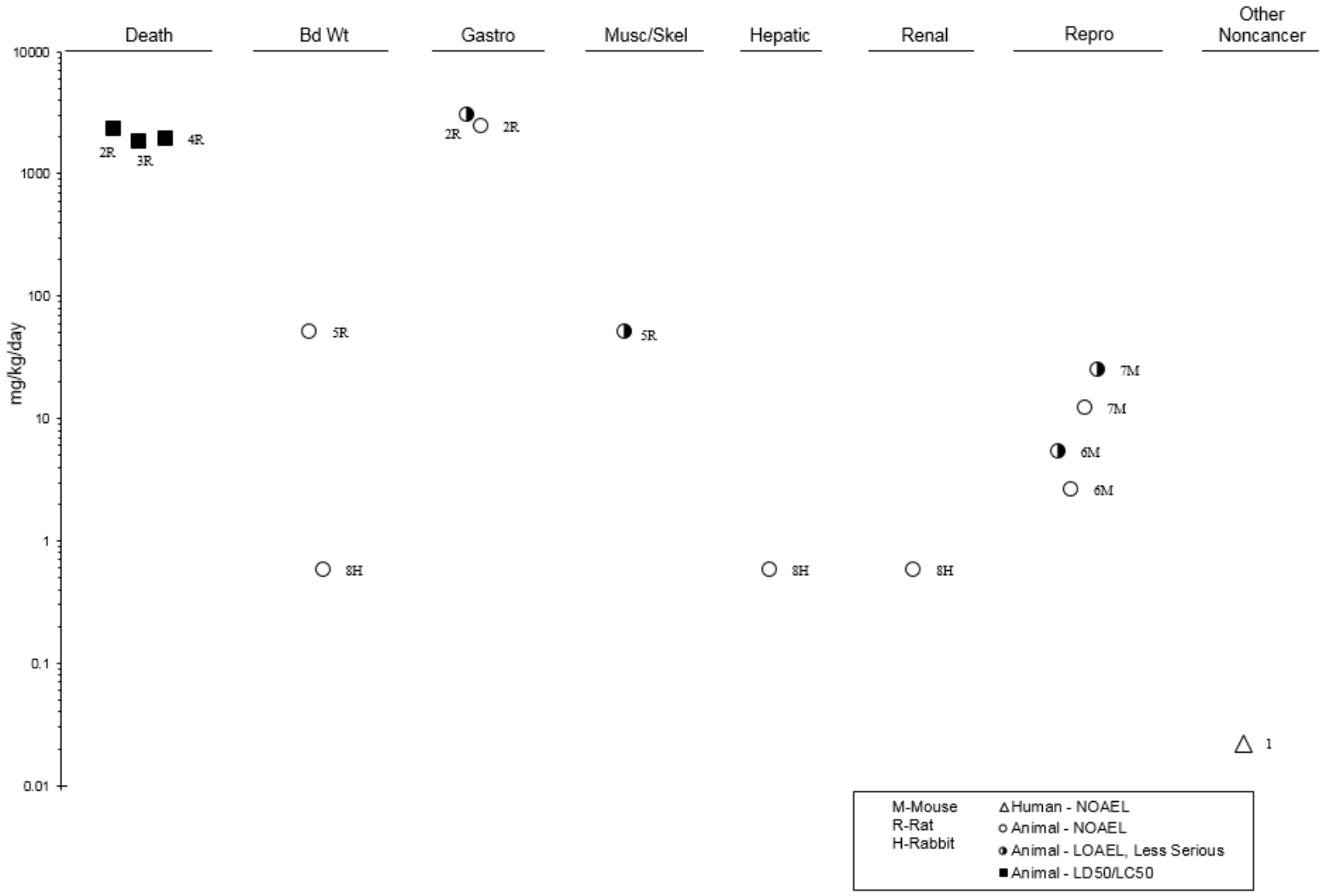


Figure 2-3. Levels of Significant Exposure to Molybdenum – Oral

Intermediate (15-364 days)

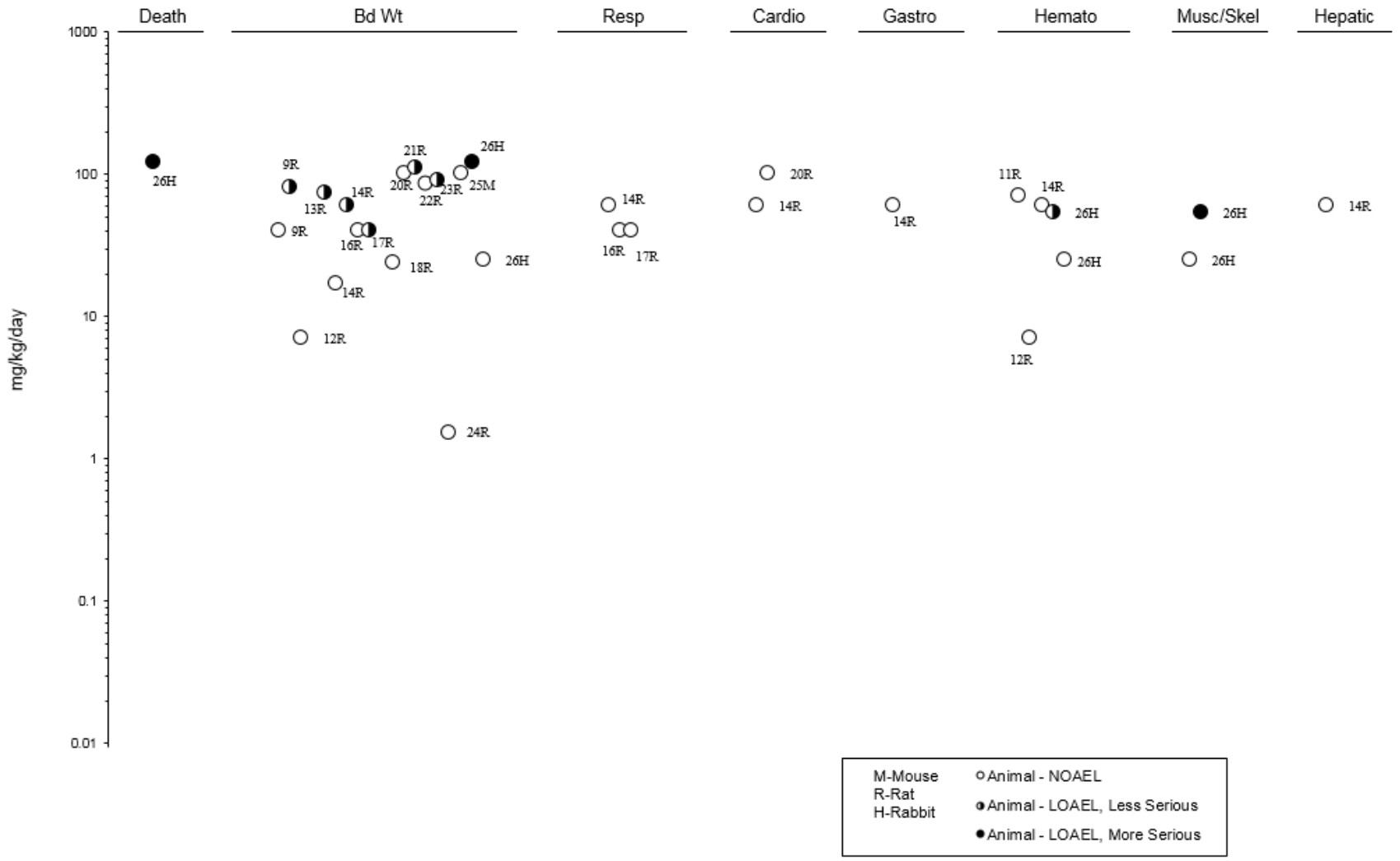


Figure 2-3. Levels of Significant Exposure to Molybdenum – Oral

Intermediate (15-364 days)

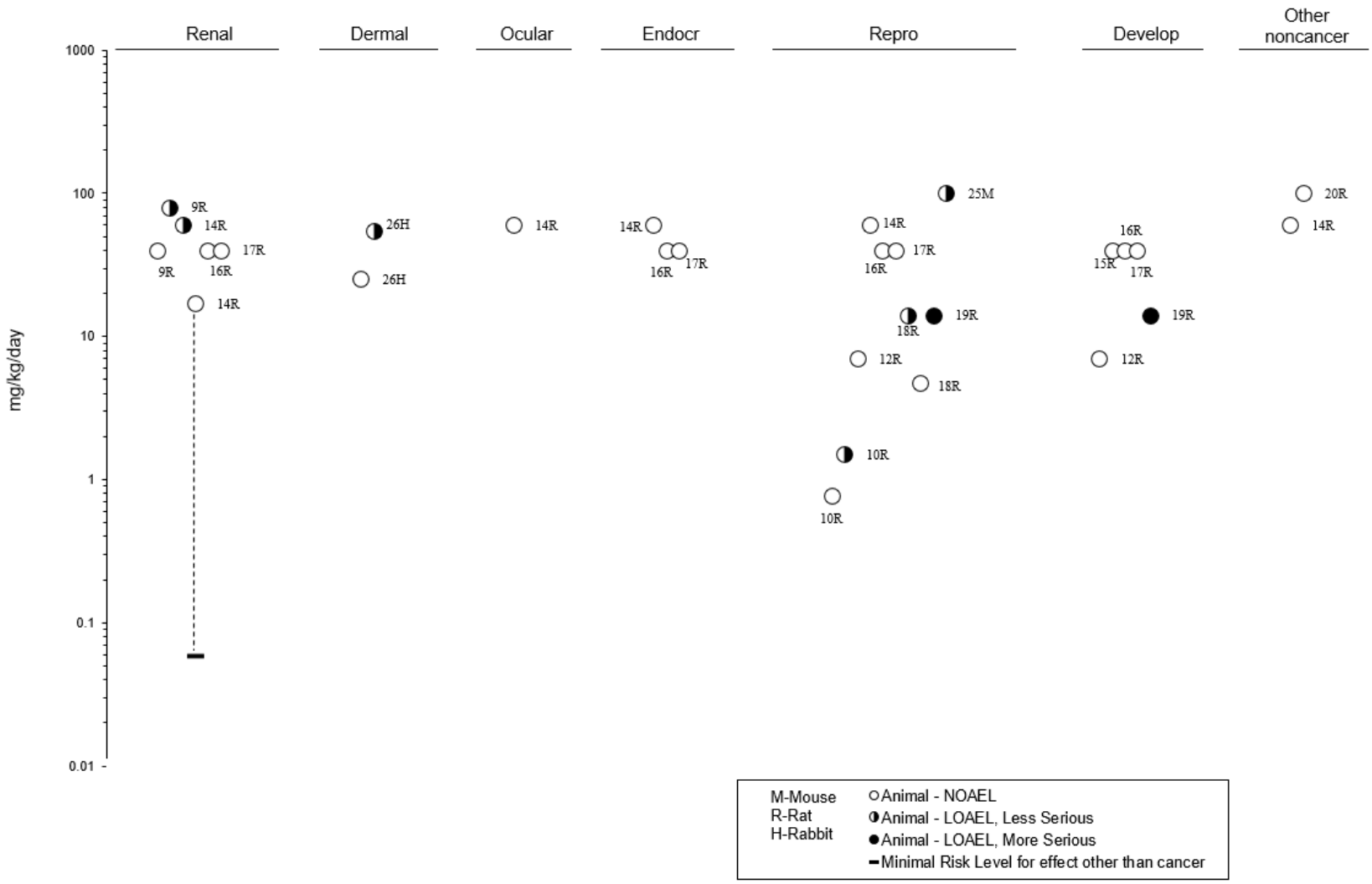


Figure 2-3. Levels of Significant Exposure to Molybdenum – Oral

Chronic (≥365 days)

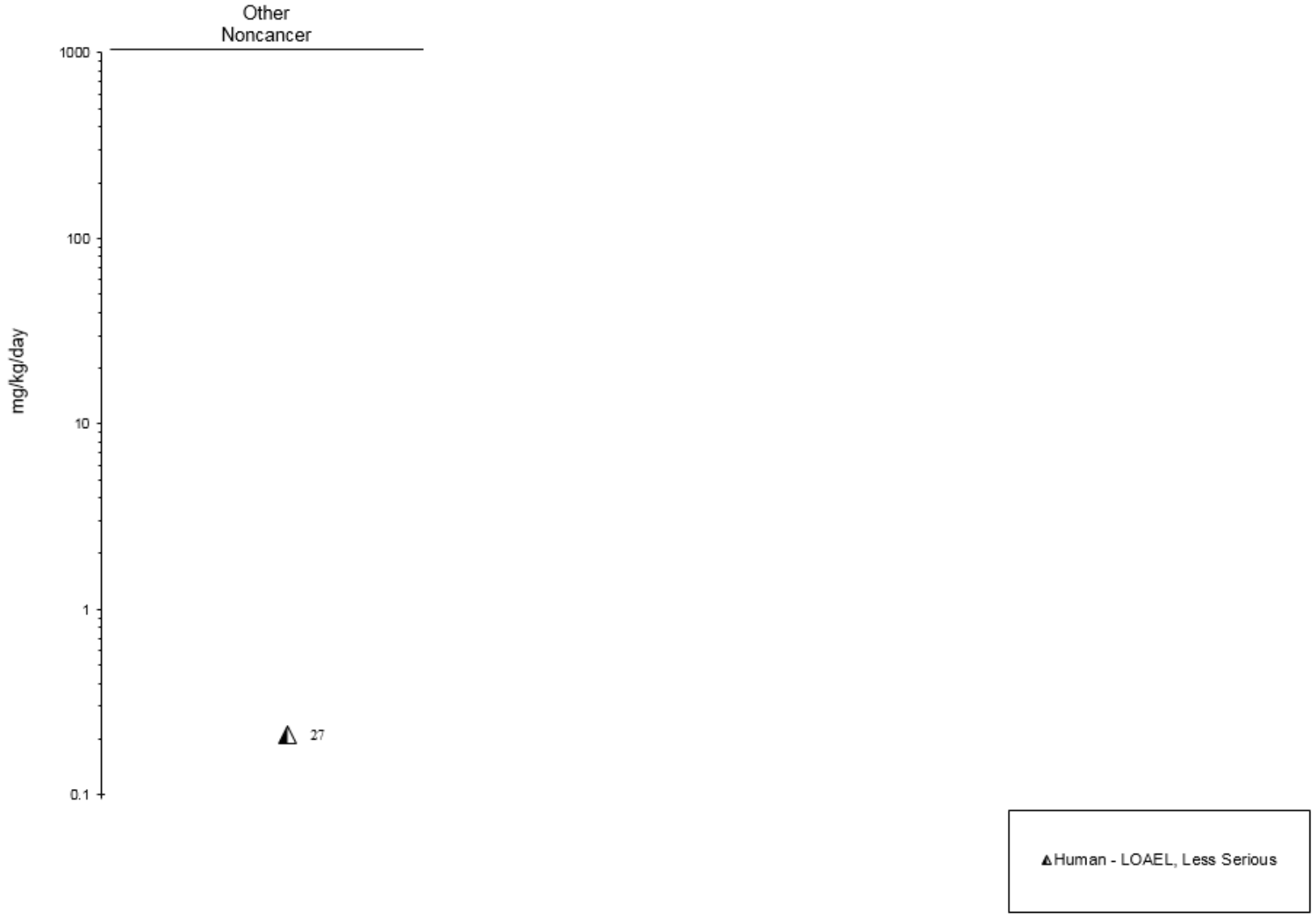


Table 2-3. Levels of Significant Exposure to Molybdenum – Dermal

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.

CHAPTER 3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

3.1 TOXICOKINETICS

- A number of factors can influence the oral absorption of molybdenum; absorption can range between 40 and 100%. The amount absorbed decreased with increasing doses and was lower when the molybdenum was ingested with a meal. There is evidence for absorption of airborne molybdenum, but no data on the amount absorbed. Molybdenum is poorly absorbed (approximately 0.2%) through the skin.
- Absorbed molybdenum is widely distributed throughout the body, with the highest concentrations found in the kidneys and liver.
- Molybdenum is not metabolized; however, it can undergo oxidation and reduction.
- Molybdenum is primarily excreted in the urine, with lesser amounts excreted in feces.

3.1.1 Absorption

Inhaled molybdenum particles that deposit in the respiratory tract are subject to three general distribution processes: (1) bronchial and tracheal mucociliary transport to the gastrointestinal tract; (2) transport to thoracic lymph nodes (e.g., lung, tracheobronchial, mediastinal); or (3) absorption into blood and/or lymph and transfer to other tissues (e.g., peripheral lymph tissues, liver, kidney). The above processes apply to all forms of deposited molybdenum, although the relative contributions of each pathway and rates associated with each pathway vary with the physical characteristics (e.g., particle size, solubility). Particles having diameters >5 μm are deposited primarily in the upper airways (extrathoracic, tracheobronchial regions) and are cleared from the respiratory tract primarily by mucociliary transport to the gastrointestinal tract (Bailey et al. 2007; ICRP 1994). Smaller particles (≤5 μm) are deposited primarily in the pulmonary region (terminal bronchioles and alveoli). Particles are cleared from the pulmonary region primarily by absorption, lymph drainage, macrophage phagocytosis and migration, and upward mucociliary flow. Dissolved molybdenum is absorbed into blood. The rate of absorption will depend on solubility. ICRP (2012) assigns molybdenum sulfide, oxides, and hydroxides to a "slow" classification in their absorption, which equates to an expected terminal absorption half-time of approximately 19 years (Bailey et al. 2007; ICRP 1994). More soluble forms of molybdenum, such as molybdenum trioxide ($Mo^{VI}O_3$), would be expected to undergo more rapid dissolution and absorption.

Quantitative estimates of absorption following inhalation exposure to molybdenum in humans or animals were not identified. Evidence for absorption of molybdenum trioxide is available from inhalation studies

on molybdenum trioxide conducted in rodents (Fairhall et al. 1945; NTP 1997). Fairhall et al. (1945) showed distribution to several tissues following inhalation exposure of guinea pigs to molybdenum trioxide. In rats and mice exposed to inhaled molybdenum trioxide (6.7–67 mg molybdenum/m^3, 6 hours/day, 5 days/week for 2 years), exposure-dependent increases in blood molybdenum were observed (NTP 1997). The respective blood molybdenum levels in the 0, 6.7, 20, and 67 mg molybdenum/m^3 groups were 0.221, 0.800, 1.774, and 6.036 μg/g in male rats, 0.059, 0.355, 0.655, and 2.411 μg/g in female rats, 0.102, 0.208, and 0.770 μg/g in male mice (no data were available for controls), and 0.043, 0.066, 0.198, and 0.523 μg/g for female mice.

Absorption of ingested molybdenum has been studied in human adults and infants (Cantone et al. 1993, 1997; Engel et al. 1967; Giussani et al. 1998, 2006, 2007; Novotny and Turnlund 2006, 2007; Robinson et al. 1973; Sievers et al. 2001a, 2001b; Turnlund et al. 1995a, 1995b; Werner et al. 1998; Yoshida et al. 2006). These studies fall into two general categories: mass balance studies and bioavailability studies. Mass balance studies estimate the absorption fraction from measurements of the difference between the ingested dose of molybdenum and fecal excretion (the difference being net absorption). Bioavailability studies estimate the absorption fraction from measurements of the plasma concentration of molybdenum following the oral dose. These methods provide estimates of net absorption in that absorbed molybdenum that is excreted into the gastrointestinal tract (e.g., biliary excretion) may not be accurately quantified from mass balance or bioavailability estimates. However, both approaches have been facilitated by the use of stable isotopes of molybdenum (^{95}Mo, ^{96}Mo), which allow measurement of plasma and excretion kinetics following concurrent intravenous and oral dosing. The use of stable isotopes also allows measurement of the administered molybdenum in plasma and excreta, distinct from background sources of molybdenum derived from other sources and preexisting body stores. By incorporating elimination kinetics data into mathematical models that include parameters representing absorption and fecal excretion of absorbed molybdenum, the absorption fraction can be estimated. In most reported stable isotope studies, the exact form of molybdenum administered was not reported. However, the isotope dosing material was typically prepared from an acid dissolution of metallic molybdenum (Mo^0). The resulting material dissolved in water most likely was a mixture of soluble molybdate anion ($Mo^{VI}O_4^{2-}$) and other soluble molybdenum oxide hydrates.

Balance and bioavailability studies conducted in humans have shown that the fraction of ingested molybdenum that is absorbed depends on numerous factors, including molybdenum dose level, fasting, diet, and nutritional status. Absorption was estimated to be 80–100% in replete fasted adults who ingested molybdenum dissolved in water or in a beverage (Giussani et al. 2006; Novotny and Turnlund

2006, 2007; Turnlund et al. 1995a). Absorption was 80–100% following a single dose of 20–40 µg molybdenum/kg dissolved in water and decreased with increasing dose level; absorption was 60% after a dose of 60 µg molybdenum /kg (Giussani et al. 2006). Absorption was lower when molybdenum was ingested with a meal (40–60%), when dissolved in black tea (20%), or when incorporated into vegetables cultivated with ^{96}Mo (30–60%), compared to when ingested without a meal (80–100%) (Giussani et al. 2006; Werner et al. 1998). Absorption was lower when molybdenum was incorporated into the diet (83%) compared to when it was administered in a beverage (90–94%) (Novotny and Turnlund 2007). Absorption appears to be affected by dietary molybdenum intake and molybdenum nutritional status. The absorption fraction was 90% in adults fed a diet containing 22 µg/day (approximately 0.3 µg molybdenum/kg/day), compared to 94% when fed a diet containing 467 µg molybdenum/day (approximately 7 µg molybdenum/kg/day) (Novotny and Turnlund 2007). Absorption in infants (gestational age 30–39 weeks) was 96–99% when a stable isotope of molybdenum was mixed with breast milk or infant formula (Sievers et al. 2001a, 2001b).

Long-term diet mass balance studies, without the aid of stable isotopes, have been conducted in adults and children (Engel et al. 1967; Robinson et al. 1973; Tipton et al. 1966). Because these studies cannot distinguish between the ingested dose of molybdenum and molybdenum excreted from body stores, these studies will underestimate the absorption fraction. A 50-week balance study conducted in two adult males (age 23 and 25 years) found absorption to range from 60 to 80% (Tipton et al. 1966). A 3-week balance study conducted in women (age 19–21 years) found absorption to range from 40 to 70% (Robinson et al. 1973). An 8-day balance study conducted in women (age 18–23 years) found absorption to range from 72 to 84% (Yoshida et al. 2006). Balance studies (18–30 days) conducted in female children (age 6–10 years) estimated the absorption fraction from diet to range from 67 to 85% (Engel et al. 1967).

Measurements of the time course of plasma molybdenum following oral doses of molybdenum indicate that absorption is relatively rapid, with peak concentrations in plasma attained within 100 minutes of dosing (Giusanni et al. 2006; Novotny and Turnlund 2007).

Studies of absorption and elimination kinetics conducted in swine provide estimates of absorption of ingested molybdenum. Based on cumulative urinary and fecal excretion measurements in swine dosed with a stable isotope of molybdenum, absorption was estimated to be between 80 and 90% (Bell et al. 1964). Studies conducted in rats have shown that tetrathiomolybdate ($Mo^{VI}S_4^{2-}$) is more poorly absorbed

when ingested in the diet; approximately 21% was absorbed when the copper content of the diet was 8 ppm (Mills et al. 1981b).

Roper (2009) evaluated the *in vitro* percutaneous absorption of sodium molybdate through human skin. Following an 8-hour application of 3.97 or 19.83 mg molybdenum/mL, the potentially absorbable doses were 0.21 and 0.16%, respectively.

Mechanisms that participate in absorptive transport of molybdenum in the gastrointestinal tract have not been characterized. Molybdate (MoO_4^{2-}) and sulfate (SO_4^{2-}) show mutually competitive inhibition for absorptive transport in rat small intestine, suggesting involvement of a common transporter for both anions (Cardin and Mason 1975, 1976). This transporter may be the Na^+/SO_4^{2-} symporter (NaS1 or SLC13A1) expressed in rodent small intestine and renal proximal tubule (Markovich and Aronson 2007; Murer et al. 1994). In humans, NaS1 is expressed in kidney but not small intestine, suggesting that mechanisms of absorptive transport in humans may be different from that of rodents (Lee at al. 2000).

3.1.2 Distribution

Very little information on the distribution on molybdenum following inhalation exposure is available. Following exposure of guinea pigs to inhaled molybdenum trioxide (150–300 mg/m^3, 1 hour/day, 5 days/week for 5 weeks), molybdenum was distributed to the lungs, liver, kidneys, and bone (Fairhall et al. 1945). Tissue levels decreased by approximately 20% in the 2-week postexposure period.

Absorbed molybdenum distributes to various tissues. Human autopsy studies have found that the kidney and liver have the highest amounts of molybdenum (Iyengar et al. 1978; Schroeder et al. 1970; Sorensen and Archambault 1963; Sumino et al. 1975; Tipton and Cook 1963; Tipton et al. 1965; Yoo et al. 2002; Zeisler et al. 1988). Based on a review of these data, Giussani (2008) estimated liver and kidney molybdenum concentrations to be approximately 0.5–1.5 µg molybdenum/g wet in liver (700–2,700 µg) and 0.2–0.4 µg molybdenum/g wet in kidney (55–120 µg). Coughtrey and Thorne (1983) reported relatively high concentrations (56 µg molybdenum/g) in bone, based on their recalculation of measurements of molybdenum in bone ash reported in Nusbaum et al. (1965) and Iyengar et al. (1978). However, these results are not supported by other studies (previously cited) and have been attributed to overestimation of tissue concentrations measured by arc emission spectrometry in the Nusbaum et al. (1965) and Iyengar et al. (1978) studies (Giussani 2008).

Results of studies in rats and guinea pigs exposed to oral molybdenum show that molybdenum is widely distributed (Bibr et al. 1977; Howell et al. 1993; Murray et al. 2014b; Pandey et al. 2002). Generally, the highest molybdenum tissue concentration is observed in the kidney. Molybdenum also is distributed to liver, spleen, brain, lungs, heart, bone, muscles, testes, epididymides, seminal vesicles, prostate, blood cells, and plasma.

Maternal-Fetal Transfer. Results of studies in humans and animals show that molybdenum is distributed to the fetus. In humans, maternal and fetal cord blood levels obtained from 33 maternal-fetal pairs at parturition show similar molybdenum levels (maternal: 1.44±0.75 µg/L, mean±standard deviation [SD]; fetal: 1.44±0.89 µg/L) (Bougle et al. 1989). Molybdenum concentrations in venous cord blood (flowing from the placenta to the fetus; 0.7±0.2 µg/L, mean±SD) were slightly higher than in arterial cord blood (flowing from the fetus to the placenta; 0.6±0.2 µg/L), indicating fetal retention of molybdenum (Krachler et al. 1999); the study did not evaluate whether there was a statistical difference between the molybdenum concentrations in venous and arterial blood.

Gestational exposure of rats to ammonium molybdate and thiomolybdate shows distribution of molybdenum to fetal liver, kidney, bone, and brain (Howell et al. 1993). Levels in liver, kidney, and bone were similar, with lower levels in brain. In rats, dose-dependent increases in placental and maternal liver content of molybdenum were observed following gestational exposure to molybdenum (sodium molybdate) in drinking water (5–100 mg molybdenum/L; equivalent to approximately 0.76–15 mg/kg/day, based on intermediate exposure to nonpregnant female rats) over the full dose range (Fungwe et al. 1989). However, neonatal whole-body levels of molybdenum reached a plateau at drinking water concentrations ≥50 mg/L (Fungwe et al. 1989). Results suggest that molybdenum levels in the fetus reach steady state more rapidly than in dams.

Maternal-Infant Transfer. Several studies have measured molybdenum in breast milk (Anderson 1992; Aquilio et al. 1996; Biego et al. 1998; Bougle et al. 1988; Casey and Neville 1987; Dang et al. 1984; Friel et al. 1999a; Krachler et al. 1998; Wappelhorst et al. 2002); the mean concentrations ranged from 0.02 to 24 µg/L. Breast milk concentrations are highest at the start of breast feeding and then decline (EFSA 2013). In the only study comparing maternal intake to breast milk levels, Wappelhorst et al. (2002) did not find a correlation between breast milk concentrations of molybdenum and maternal molybdenum intake. The mean concentration in breast milk was 72 µg/L and the mean maternal intake was 132 µg/day.

Bacteria and eukaryotes express cell membrane molybdate transporters, one of which (MoT_2) also appears to be expressed in humans (Tejada-Jimenez et al. 2007, 2011). In eukaryotes, this transporter participates in the delivery of molybdate into cells for incorporation into molybdopterin-cofactor (Moco), the biologically active prosthetic group in molybdenum-dependent enzymes (Schwarz et al. 2009). MoT_2 transport of molybdate is inhibited by sulfate, suggesting a common carrier for molybdate and sulfate. A sulfate-insensitive oxalate-sensitive molybdate transporter has been described in mammalian MEK-293T cells grown in culture (Nakanishi et al. 2013). Uptake of molybdate into human red blood cells involves participation of the Cl^{-1}/HCO_3^{-1} anion exchanger (Gimenez et al. 1993).

3.1.3 Metabolism

Molybdenum exists in several valence states and may undergo oxidation and reduction. The primary form of molybdenum that interacts with enzyme systems is Mo^{VI}, as the molybdate anion ($Mo^{VI}O_2^{2-}$) (Nakanishi et al. 2013). After molybdate is taken into a cell, it is incorporated into a molybdopterin to form molybdenum cofactor (Moco). Moco is a sulfur-molybdate complex that forms the prosthetic group in molybdenum-dependent enzymes (Mendel and Kruse 2012; Schwarz et al. 2009). Given that Moco is extremely sensitive to oxidation, it is believed that it is bound to a Moco-binding protein in the cell (Mendel and Kruse 2012). This stored Moco would be readily available to meet the cell's demand for molybdenum enzymes. Molybdate forms complexes with copper and binds to plasma proteins as a copper-molybdenum-sulfur (Cu-Mo-S) complex (Nederbragt 1980, 1982).

3.1.4 Excretion

Studies investigating the elimination and excretion of molybdenum following inhalation exposure were not identified.

Absorbed molybdenum is excreted in urine and feces in humans. Urine is the dominant excretion route, accounting for the excretion of approximately 75–90% of the absorbed dose (Giussani 2008; Novotny and Turnlund 2007). The fraction excreted in urine increases with increasing dietary intake (Novotny and Turnlund 2007). Urine also is the dominant excretory route for absorbed molybdenum in swine. Following an oral dose, approximately 90% of the dose was excreted in urine (Bell et al. 1964). To measure urinary and fecal excretion of molybdenum, Turnlund et al. (1995a, 1995b) exposed four healthy adult males to various doses of a radioactive isotope of molybdenum (24–1,378 μg ^{100}Mo/day) and administered intravenous doses of stable isotope of molybdenum (33 μg ^{97}Mo). Six days after exposure

to ^{100}Mo in the diet, 17.8% of the ^{100}Mo label was excreted in the urine at the lowest dose tested (total molybdenum dose of 24 μg/day). As the molybdenum dose increased, the amount excreted in the urine also increased; at the highest dose (1488 μg/day), 82.1% of the ^{100}Mo was excreted in the urine. A similar pattern of urinary excretion was found when ^{97}Mo was measured: 32.7% of the label at 24 μg/day and 86.7% at 1,488 μg/day. The percentage of the molybdenum dose excreted in the feces decreased with increasing doses. At the lowest dose tested, 9.4% of the ^{100}Mo dose was excreted in the feces; at the highest dose, 7.5% of the ^{100}Mo dose was excreted in the feces. In contrast, no consistent pattern of fecal ^{97}Mo excretion was found. When total molybdenum excretion was measured, the study found that 41% was excreted in feces and 59% was excreted in urine at the lowest dose tested and 6% was excreted in feces and 94% was excreted in urine at the highest dose tested. Fecal excretion of absorbed molybdenum is thought to result from biliary secretion. Studies conducted in bile-duct cannulated rats have shown that, following an intravenous dose of $Mo^{[V]}$ or $Mo^{[VI]}$, approximately 1% of the molybdenum dose was secreted into bile in a period of 4 hours (Lener and Bibr 1979).

The rate of elimination of molybdenum from plasma has been studied in human clinical studies (Cantone et al. 1997; Rosoff and Spencer 1964; Thompson et al. 1996; Werner et al. 2000). Elimination is approximately biphasic, with mean half-times of 30 minutes and 6.6 hours (Giussani 2008).

The whole-body elimination rate in rats is dose-dependent (Bibr and Lener 1973). Following oral administration of $Mo^{[VI]}$ at doses <3 μg molybdenum/kg, elimination was mono-phasic with a half-time of approximately 47 hours. Following doses >3 μg molybdenum/kg, the rate of elimination increased, with an increasing proportion of elimination contributed by a fast phase having a half-time of 6 hours.

Mechanisms that participate in the renal excretion of molybdenum have not been characterized. In sheep, reabsorption of filtered molybdate (MoO_4^{2-}) is saturable, which results in an increase in the fraction of filtered molybdate excreted as the plasma molybdate concentration increases and approaches or exceeds the tubular maximum (Ryan et al. 1987). In sheep and rat kidney, sodium-dependent reabsorptive transport of molybdate (MoO_4^{2-}) and sulfate (SO_4^{-2}) exhibit mutual inhibition (Ryan et al. 1987). This is consistent with participation of the Na^+/SO_4^{2-} symporter (NaS1 or SLC13A1) in the reabsorption of molybdate. This symporter is also expressed in the human renal proximal tubule (Markovich and Aronson 2007; Murer et al. 1994).

3.1.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

PBPK models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic endpoints.

Several multi-compartmental models of the kinetics of molybdenum in humans have been developed (Giussani 2008; Giussani et al. 1998, 2000; Novotny and Turnlund 2007; Thompson et al. 1996). The latest of these are the Giussani (2008) and Novotny and Turnlund (2007) models. Both models yield similar predictions when applied to the same dosing scenarios (Giusanni 2008). The Giussani (2008) model has been adopted for use by the International Commission on Radiological Protection (ICRP) and is described in this section.

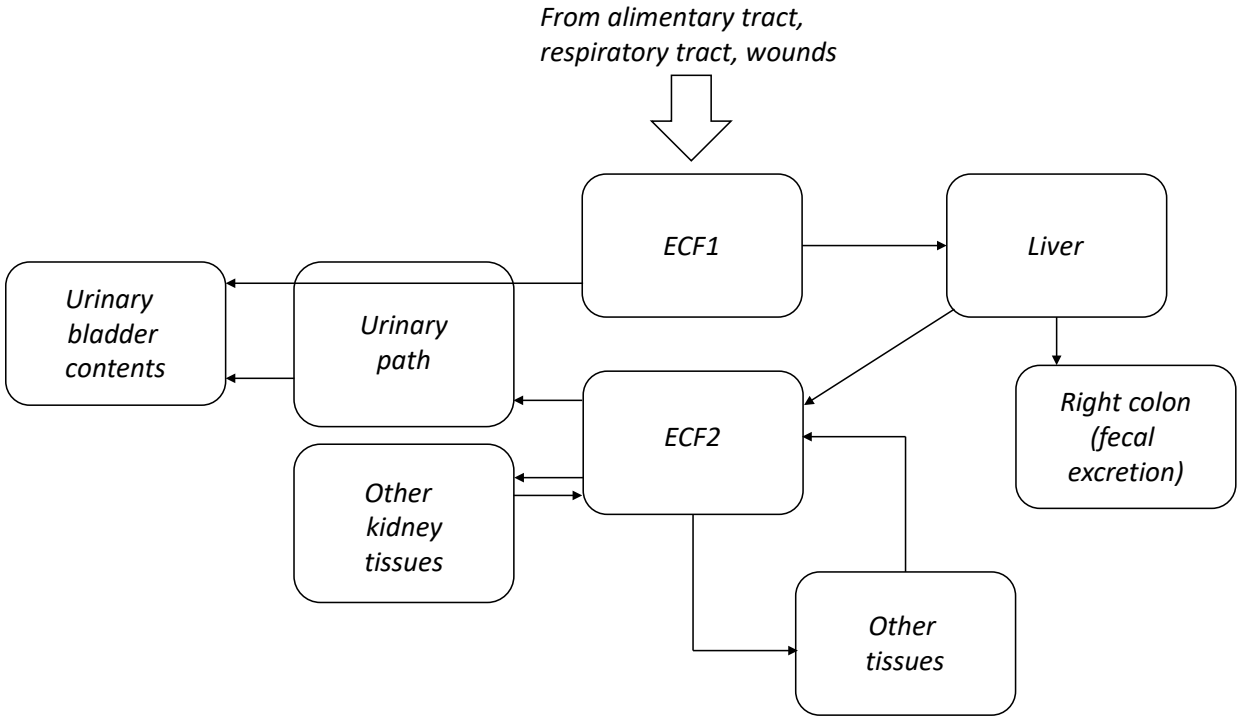
Giussani (2008) Model

Giussani (2008) developed a model of molybdenum kinetics in humans. The structure of the model is shown in Figure 3-1 and parameter values are presented in Table 3-1. Data used to derive and evaluate the model are described in Giusanni (2008) and included human clinical studies in which subjects were administered intravenous or oral doses of stable isotopes of molybdenum (Giusanni et al. 2006, 2007; Novotny and Turnlund 2006, 2007; Turnlund et al. 1995a; Werner et al. 1998, 2000). The Giussani (2008) model has been adopted for use by the ICRP and is described in this section.

The model consists of two central compartments representing extracellular fluids (ECF) and compartments representing liver, kidney (two subcompartments), and a lumped compartment representing all other tissues. All transfers of molybdenum between compartments are first order and governed by first-order rate coefficients (day^{-1}). The two ECF compartments represent fast and slow transfer pathways out of the ECF and were based on studies conducted in humans, which provide evidence for multi-phasic clearance of molybdenum from plasma (Giussani et al. 2007; Werner et al. 2000). The half-times for the two ECF compartments are approximately 30 minutes for ECF1 and 280 minutes for ECF2. Transfers

from the fast compartment (ECF1) are to liver, kidney, and urine. Transfers from the slow compartment (ECF2) are to urine, kidney, and other tissues; the slow compartment also receives molybdenum from the liver. Retention half-times in tissues are 41 days for liver, 14.5 days for kidney, and 21.5 days for the other tissue compartment. Excretion of absorbed molybdenum occurs in urine (88%) and transfer from liver to the gastrointestinal tract (12%).

Figure 3-1. The Proposed Systemic Model for Molybdenum Radionuclides



ECF = extracellular fluid

Source: Reprinted from Giussani (2008) with permission from Elsevier.

Table 3-1. Transfer Rates (Day^{-1}) for the Molybdenum Model

Transfer rate	Value (day^{-1})
ECF1 to ECF2	12.5
ECF1 to liver	14.2
ECF1 to urinary bladder contents	6.5
ECF2 to urinary path	1.7
ECF2 to other kidney tissues	0.115
ECF2 to other tissues	1.73
Liver to alimentary tract	0.0048

Table 3-1. Transfer Rates (Day^{-1}) for the Molybdenum Model

Transfer rate	Value (day^{-1})
Liver to ECF2	0.0122
Other kidney tissues to ECF2	0.0474
Other tissues to ECF2	0.0323
Urinary path to urinary bladder contents	1.40
Urinary bladder contents to urine	12
Modified parameters of the alimentary tract	
Stomach to small intestine (liquid form)	100
Stomach to small intestine (diet)	40
Small intestine to right colon (liquid form)	10
Small intestine to right colon (diet)	16
f_A (liquid form)[a]	0.9
f_A (diet)[a]	0.6

Source: Reprinted from Giussani (2008) with permission from Elsevier.

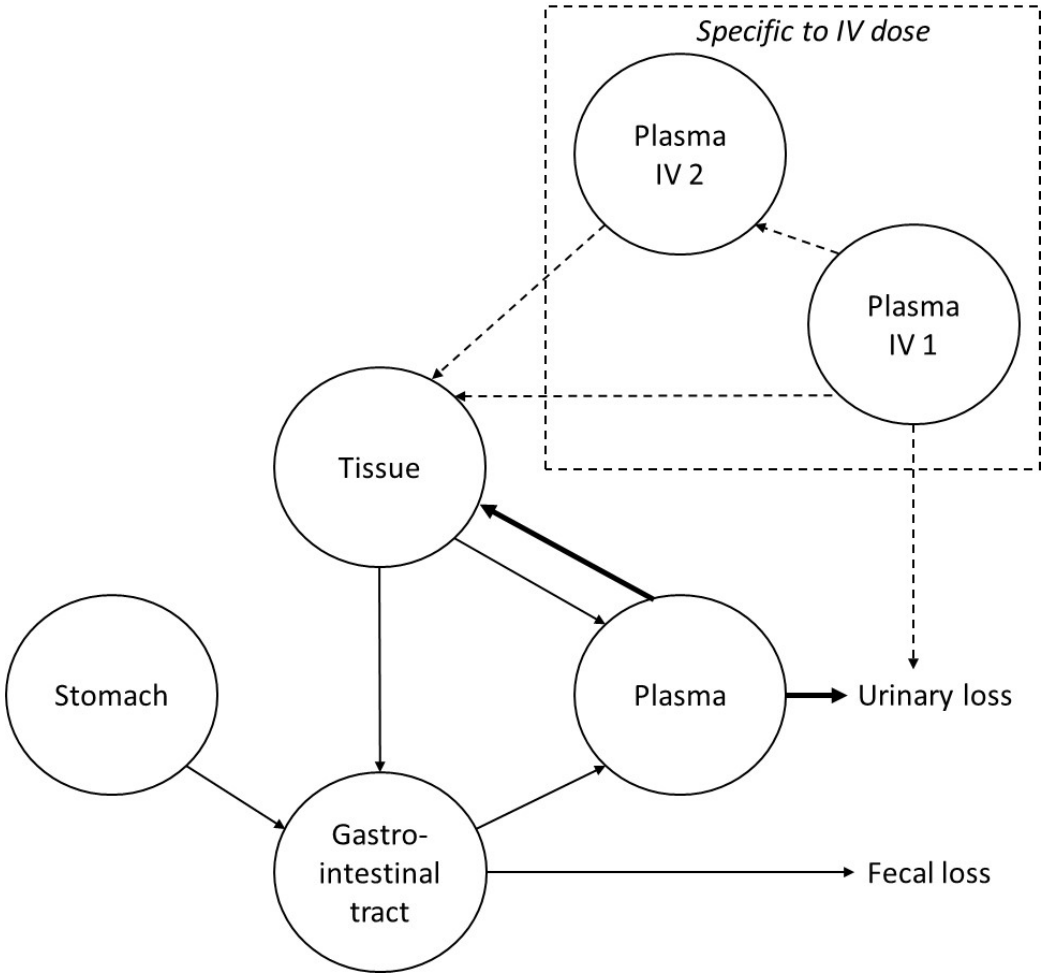
The model can simulate absorption from the gastrointestinal tract and respiratory tract. The absorption fraction for the gastrointestinal pathway uses an absorption fraction of 0.9 for molybdenum ingested in liquids and 0.6 for molybdenum ingested in the diet. The model predicts a steady state for constant dietary intake of molybdenum in adults, in which approximately 52% of the molybdenum body burden is in liver, 3% is in kidney, 45% is in other tissues, 53% of the daily dose is excreted in urine, and 47% of the daily dose is excreted in feces (Giussani 2008). The model is constructed to be able to interface with output from the ICRP Human Respiratory Tract Model (HRTM) (Bailey et al. 2007; ICRP 1994). The inputs to the Giussani (2008) model from the HRTM would be simulated transfers of molybdenum to the gastrointestinal tract (mucociliary transfer) and to blood (absorption from the respiratory tract), depending on the particle size and solubility of the inhaled molybdenum and other physiological factors (e.g., age, activity).

Novotny and Turnlund (2007) Model

The major difference between the structures of the Giussani (2008) and Novotny and Turnlund (2007) models is that the Novotny and Turnlund (2007) model has a single lumped compartment representing all tissues outside of the vasculature. The Novotny and Turnlund (2007) model illustrated in Figure 3-2 has two configurations: an intravenous configuration, which has two plasma compartments, representing fast

and slower clearance, and an oral configuration, which has a single plasma compartment. Molybdenum exchanges between plasma and a lumped tissue compartment. Urinary excretion is represented as a direct transfer from plasma. Absorbed molybdenum is also transferred to the gastrointestinal tract.

Figure 3-2. Diagram of the Compartment Molybdenum Model*



*Circles show distinct kinetic compartments and arrows show pathways of flow between compartments. Dashed lines show structures that are specific to the intravenous (IV) dosing. Bold arrows show paths that appear to be involved in molybdenum regulation as suggested by kinetic modeling.

Source: Novotny and Turnlund (2007), by permission of the American Society for Nutrition (via Oxford University Press)

Novotny and Turnlund (2006, 2007) conducted mass balance studies with subjects who ingested stable isotopes of molybdenum in the context of varying dietary intakes of molybdenum (22–1,490 µg molybdenum/day) and found that certain model parameters were dependent on dietary intake. These included, in association with increasing dietary intake, increases in the first-order rate coefficients for gastrointestinal absorption and urinary excretion and a decrease in the rate coefficients for transfer from

plasma to tissues. The largest adjustments were needed to simulate molybdenum kinetics in subjects who consumed >121 µg molybdenum/day and included a 70% decrease in the coefficient for transfer of molybdenum from plasma to tissues and a 660% increase in the rate coefficient for transfer from plasma to urine. These results suggest that high molybdenum intakes (>121 µg molybdenum/day) result in physiological adaptations that increase excretion of absorbed molybdenum (Novotny and Turnlund 2007).

3.1.6 Animal-to-Human Extrapolations

There are limited data to evaluate potential differences in the toxicity of molybdenum between laboratory animals and humans. Most of the available oral exposure studies were conducted in rats, and human data are mostly limited to a small number of cross-sectional studies. Within laboratory animal species, some differences have been observed between rats and rabbits, with rabbits appearing to be more sensitive than rats. However, the studies are not directly comparable due to differences in the copper content and other dietary constituents. In the absence of data to the contrary, it is assumed that the toxicity of molybdenum will be similar across species (excluding ruminants).

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Children may be more or less susceptible than adults to health effects from exposure to hazardous substances and the relationship may change with developmental age.

This section also discusses unusually susceptible populations. A susceptible population may exhibit different or enhanced responses to certain chemicals than most persons exposed to the same level of these chemicals in the environment. Factors involved with increased susceptibility may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters can reduce detoxification or excretion or compromise organ function.

Populations at greater exposure risk to unusually high exposure levels to molybdenum are discussed in Section 5.7, Populations with Potentially High Exposures.

There are limited data on the toxicity of molybdenum in children. In studies in rat pups maintained on a caries-promoting diet, administration of 50 mg molybdenum/kg/day as sodium molybdate resulted in an increase in buccal enamel lesions (Hunt and Navia 1975), but exposure to 8 mg molybdenum/kg/day did not result in increases in dental caries (Van Reen et al. 1962). Arrington and Davis (1953) exposed young (6 weeks of age at the start of the study) and mature rabbits to sodium molybdate in the diet for 30–84 days. Marked muscular/skeletal effects were observed in the young rabbits, but not in the mature rabbits. Since the investigators did not provide information on dietary intake, it is difficult to make direct comparisons across the studies.

An observational study did not find an association between maternal urinary molybdenum levels and newborn body weight or infant mental development (Shirai et al. 2010). However, another study did find an association between third-trimester maternal urinary molybdenum levels and infant psychomotor development indices (Vazquez-Salas et al. 2014). Two rat studies in which the copper content of the diet was adequate did not find significant alterations in fetal growth, survival, or malformations at maternal doses of 40 mg molybdenum/kg/day (Murray et al. 2014b, 2019). However, a third study reported decreases in growth and number of live fetuses in the offspring of male rats administered 14 mg molybdenum/kg as sodium molybdate 5 days/week for 60 days prior to mating with unexposed females (Pandey and Singh 2002).

Studies in laboratory animals have found that maintenance on a copper-deficient diet enhances the toxicity of molybdenum (Brinkman and Miller 1961; Franke and Moxon 1937; Johnson and Miller 1961; Sasmal et al. 1968; Valli et al. 1969; Van Reen 1959; Widjajakuma et al. 1973). Administration of additional copper results in a reversal of the adverse effect (Arrington and Davis 1953). Thus, individuals with low copper intakes may be unusually susceptible to the toxicity of molybdenum. Additionally, individuals with high dietary molybdenum intake, including individuals taking supplements containing high levels of molybdenum, may be at an increased risk from exposure to high levels of molybdenum in the environment.

Studies in rats suggest that the toxicity of molybdenum may be increased in animals maintained on a low protein diet. The magnitudes of the decrease in body weight gain (Bandyopadhyay et al. 1981; Cox et al. 1960) and decreases in femur breaking strength (Fejery et al. 1983) were greater in rats exposed to a low protein diet, as compared to those maintained on a diet with sufficient protein.

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as biomarkers of exposure, biomarkers of effect, and biomarkers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to molybdenum are discussed in Section 3.3.1. The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of a generalizable sample of the U.S. population to environmental chemicals using biomonitoring (see http://www.cdc.gov/exposurereport/). If available, biomonitoring data for molybdenum from this report are discussed in Section 5.6, General Population Exposure.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that (depending on magnitude) can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effect caused by molybdenum are discussed in Section 3.3.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.2, Children and Other Populations that are Unusually Susceptible.

3.3.1 Biomarkers of Exposure

Molybdenum levels can readily be measured in tissues, body fluids, and excreta. Dose-related increases in serum molybdenum levels were observed in rats and mice exposed via inhalation to molybdenum trioxide for 2 years (NTP 1997). In a study examining the relationship between plasma molybdenum levels and dietary intake, Turnland and Keyes (2004) reported a baseline plasma molybdenum level of 8.2±0.5 nmol/L; 25 days after the subjects were maintained on a low molybdenum diet (22 μg/day), the plasma molybdenum level was 5.1±0.5 nmol/L. Although a significant correlation between plasma molybdenum and dietary molybdenum was observed, comparison between plasma molybdenum levels at different dietary intakes showed that a significant increase in plasma molybdenum was not observed until the dietary intake exceeded 460 μg/day (6.6 mg/kg/day) and that tripling the intake resulted in a doubling of the plasma molybdenum levels. Urinary molybdenum levels were also significantly correlated to dietary intakes (Turnland and Keyes 2004) and appeared to be more responsive to changes in dietary intake. At all dietary concentrations, the urinary molybdenum levels were slightly lower than the dietary intakes (Turnland and Keyes 2004). The investigators concluded that plasma molybdenum levels are an indicator of dietary intake, but urinary levels had a more direct relationship with dietary intake.

Molybdenum levels were measured in urine samples collected during the NHANES study. The geometric mean urinary molybdenum levels in the United States in 2011–2012 was 37.1 μg/L and the creatinine-corrected value was 42.0 μg/g creatinine (CDC 2015); see Section 5.6 for additional information.

Although several studies have reported molybdenum levels in hair samples (DiPietro et al. 1989; Nagra et al. 1992; Paschal et al. 1989), no relationship between molybdenum exposure and hair levels has been established. Furthermore, Miekeley et al. (1998) demonstrated large interlaboratory differences in the molybdenum levels measured in hair.

3.3.2 Biomarkers of Effect

No biomarkers to characterize effects caused by molybdenum have been identified.

3.4 INTERACTIONS WITH OTHER CHEMICALS

The interaction between copper and molybdenum has been well-established in animals. The levels of copper in the diet have been shown to influence the toxicity of molybdenum. Marked toxicity has been

reported in studies in which the copper content of the diet was inadequate. Observed effects included mortality in rabbits (Valli et al. 1969; Widjajakuma et al. 1973), marked decreases in body weight gain and weight loss in rats and rabbits (Brinkman and Miller 1961; Johnson and Miller 1961; Sasmal et al. 1968; Valli et al. 1969; Van Reen 1959), and anemia in rats and rabbits (Brinkman and Miller 1961; Franke and Moxon 1937; Gray and Daniel 1954; Johnson et al. 1969; Valli et al. 1969). In general, these effects (or the severity of the effects) have not been observed when the diet contains an adequate level of copper (Mills et al. 1958; Murray et al. 2014a; Pandey and Singh 2002; Peredo et al. 2013). Exposure to high levels of copper has been shown to reduce the toxicity of molybdenum. Administration of high doses of copper to moribund rabbits resulted in a return to normal body weight gain and increases in hemoglobin levels within 2–3 weeks (Arrington and Davis 1953). Lyubimov et al. (2004) showed that administration of a high dose of copper prevented the molybdenum-induced testicular toxicity observed in rats fed a copper-adequate diet. Similarly, in an environmental exposure study of men at infertility clinics, Meeker et al. (2008) found a greater decline in sperm concentration in men with high molybdenum blood levels and copper blood levels below the median, as compared to when the men were not stratified by blood copper levels.

Kinetic studies have demonstrated differences in plasma, liver, and kidney copper and molybdenum concentrations in rats fed copper-deficient, copper-adequate, and copper-excessive diets (Nederbragt 1980). Administration of molybdenum results in increases in plasma, liver, and kidney copper levels in rats fed a copper-adequate diet (Nederbragt 1980); the increases in copper appear to be molybdenum-dose-related. Most of the rise in plasma copper levels was in the tightly-bound fraction, which is likely to be poorly available for copper metabolism. Excess copper in the diet resulted in a smaller increase in copper concentrations in plasma, liver, and kidneys and molybdenum concentrations in the liver and kidney, as compared to levels in rats fed a copper-adequate diet. Similarly, lower rises in liver copper and molybdenum and kidney molybdenum levels were observed in rats fed a copper-deficient and high-molybdenum diet, as compared to the copper-adequate diet. At the lowest molybdenum dose, kidney molybdenum levels were higher in the copper-deficient groups. In another study (Nederbragt 1982), kidney levels of copper and molybdenum were 5 and 3 times higher, respectively, in the copper-adequate groups as compared to the copper-deficient group. Two human studies have also evaluated the effect of molybdenum on copper levels. In one study, increases in serum and urine copper levels were found following a 10-day exposure to 0.022 mg molybdenum/kg/day (Deosthale and Gopalan 1974). Another study found no significant alterations in serum copper levels in humans exposed to 0.0003–0.02 mg molybdenum/kg/day for 24 days (Turnlund and Keys 2000).

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Molybdenum (Mo) is a naturally occurring metallic trace element found in natural minerals, but not as the free metal. Biologically, it is an important micronutrient in plants and animals, including humans. It is used widely in industry for metallurgical applications (EPA 1979).

Molybdenum metal is a dark-gray or black powder with a metallic luster (NLM 2020a). It is a transition element in Group 6 of the Periodic Table. It has oxidation states from -2 to +6. Commonly encountered compounds are those of molybdenum in oxidation state +6 (Mo(VI), MoO_3, molybdates) and +4 (Mo(IV), MoS_2). It does not occur naturally in the pure metallic form; it more commonly occurs in the mineral, molybdenite (Sebenik et al. 2012). Other naturally occurring molybdenum-containing minerals are powellite, wulfenite, ferrimolybdite, and ilsemannite; however, molybdenite is the primary commercial source of molybdenum. Molybdenum (VI) anions include molybdate (MoO_4^{-2}) with molybdenum at the center of a tetrahedron of four oxygen atoms, and polyberic anions ('isopolymolybdates') of which the most common are heptamolybdate ($Mo_7O_{24}^{6-}$) and octamolybdate ($Mo_8O_{26}^{4-}$) (EPA 1979). These anions occur in sodium and ammonium salts, often hydrated, which are the common sources of molybdenum in commerce and industrial applications.

There are 33 known isotopes of molybdenum. Seven isotopes occur naturally: mass numbers 92, 94, 95, 96, 97, 98, and 100. ^{98}Mo is the most abundant isomer, comprising approximately 24.3% (Rumble et al. 2018). Radioisotopes of masses 83–91, 93, 99, and 101–115 have been reported. The only one of major worldwide importance is Mo-99 (^{99}Mo), a 100% beta-emitting isotope with a 65.976-hour radioactive half-life that is used to produce technetium-99m (Tc-99^m or ^{99m}Tc) for medical scans (Doll et al. 2014; Parma 2009; Richards 1989).

Under physiological conditions (pH >6.5), the molybdate anion, $[MoO_4]^{2-}$, is the sole molybdenum species in aqueous media (Cruywagen 2000; Cruywagen et al. 2002). Molybdenum compounds (e.g., molybdenum trioxide and polymolybdates) transform rapidly to the $[MoO_4]^{2-}$ ion under environmentally relevant test conditions (Deltombe et al. 1974; Greenwood and Earnshaw 1997). Protonated forms, such as $[HMoO_4]^-$ and H_2MoO_4, are found at pH <5 (Smedley and Kinniburgh 2017). Molybdenum tends to be more mobile under alkaline conditions, but adsorption increases with decreasing pH (Goldberg et al. 2002).

Information regarding the chemical identity of molybdenum and molybdenum compounds is provided in Table 4-1.

Table 4-1. Chemical Identity of Molybdenum and Compounds

Characteristic	Information		
Chemical name	Molybdenum[a]	Molybdenum disulfide[b]	Molybdenum trioxide[c]
Synonym(s) and registered trade names[d]	MChVL; TsM1; Amperit 105.054; Amperit 106.2; Metco 63	Molybdenite (natural mineral); molybdenum(IV) sulfide; DAG 325; Molykote	Molybdenum(VI) oxide; molybdic acid anhydride; molybdic anhydride; molybdic oxide
Chemical formula	Mo	MoS_2	MoO_3
CAS Registry Number	7439-98-7	1309-56-4/1317-33-5 (natural mineral form)[e]; 12612-50-9 (synthetic form)	1313-27-5
Chemical name	Sodium molybdate[f]	Ammonium dimolybdate	Ammonium heptamolybdate tetrahydrate[g]
Synonym(s) and registered trade names[d]	Disodium molybdate; molybdic acid, disodium salt[e]	Ammonium molybdenum oxide[e]	Ammonium paramolybdate tetrahydrate; hexammonium molybdate
Chemical formula	Na_2MoO_4	$(NH_4)_2Mo_2O_7$	$(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$
CAS Registry Number	7631-95-0	27546-07-2	12054-85-2/12027-67-7 (anhydrous)[h]
Chemical name	Diammonium molybdate	Ammonium tetrathiomolybdate	
Synonym(s) and registered trade names[d]	Ammonium molybdate; molybdic acid, diammonium salt[i]	Tiomolibdate diammonium; ammonium molybdenum sulfide; ammonium tetrathiomolybdate; thiomolybdic acid, diammonium salt; Coprexa; TM; ATTM[j]	
Chemical formula	$(NH_4)_2MoO_4$	$(NH_4)_2MoS_4$	
CAS Registry Number	13106-76-8	15060-55-6	

[a]All information in this column obtained from NLM (2020a), unless otherwise noted.
[b]All information in this column obtained from NLM (2020b), unless otherwise noted.
[c]All information in this column obtained from NLM (2020c), unless otherwise noted.
[d]Additional synonyms and trade names may be queried using the Common Chemistry service from Chemical Abstracts Service (http://www.commonchemistry.org/).
[e]EPA 2019a.
[f]All information in this column obtained from NLM (2020d), unless otherwise noted.
[g]All information in this column obtained from NLM (2020e), unless otherwise noted.
[h]OECD 2013.
[i]EPA 2019b.
[j]NLM 2019.

CAS = Chemical Abstracts Service

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Metallic molybdenum, in the form of fine molybdenum powder, is considered nonflammable.

Information regarding the physical and chemical properties of molybdenum and molybdenum compounds is provided in Table 4-2. Much of the information presented was obtained from the chapter, Molybdenum and Molybdenum Compounds, in the Ullmann's Encyclopedia of Industrial Chemistry (Sebenik et al. 2012), or handbooks such as the CRC Handbook of Chemistry and Physics or the European Chemicals Agency (ECHA) registration dossiers.

Table 4-2. Physical and Chemical Properties of Molybdenum and Compounds[a]

Property	Information		
Chemical name	Molybdenum	Molybdenite (natural mineral)/molybdenum disulfide	Molybdenum trioxide
Molecular weight	95.94	160.07	143.95
Color	Dull gray	Black	White, turns slightly blue in light
Physical state	Powder	Crystalline solid	Crystalline solid
Melting point	2,617°C	>1,600°C (rhombohedral crystal); did not melt at 1,800°C[b]	801°C
Boiling point	4,612°C	No data	1,155°C
Density/specific gravity	10.22 g/cm^3	5.05 g/cm^3	4.692 g/cm^3 (21°C)
Odor	No data	Odorless	Odorless[c]
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water at 25°C	Insoluble; 5.5–12 mg/L at 20°C and pH 3.5–4.3[d]	Insoluble	490 mg/L (28°C)
Organic solvents	No data	Insoluble	Insoluble
Inorganic solvents	Dissolved by a mixture of concentrated nitric and concentrated hydrofluoric acids	Dissolves only in strongly oxidizing acids (e.g., aqua regia)	Soluble in aqueous alkali and ammonia; 14,000 mg/L in nitric acid (4 mol/L, 20°C)
Partition coefficients:			
Log K_{ow}	NA	NA	NA
Log K_{oc}	NA	NA	NA
Vapor pressure[e]:			
at 20°C	No data	No data	No data
at 2,469°C	7.5x10^{-3} mm Hg		
at 2,721°C	7.5x10^{-2} mm Hg		
at 3,039°C	0.75 mm Hg		
at 3,434°C	7.5 mm Hg		
at 3,939°C	75 mm Hg		
at 4,606°C	750 mm Hg		
Henry's law constant at 25°C	NA	NA	NA
Autoignition temperature	NA	NA	NA
Flashpoint	NA	NA	NA
Flammability limits	Not flammable	Not flammable	Not flammable[c]
Explosive limits	NA	NA	NA
Conversion factors	NA	NA	NA

Table 4-2. Physical and Chemical Properties of Molybdenum and Compounds[a]

Property	Information		
Chemical name	Sodium molybdate	Ammonium dimolybdate	Ammonium heptamolybdate tetrahydrate
Molecular weight	205.92	339.95	1,235.8
Color	White		White
Physical state	Crystalline powder[f]	Solid, powder[g]	Crystalline solid[f]
Melting point	687°C[f]	Decomposes from ca. 150°C[g]	Decomposition at 90°C[h]
Boiling point	Not applicable	Decomposes from ca. 150°C[f]	Decomposition at 90°C[h]
Density/specific gravity	3.5 g/cm[h]	2.97 at 20°C[g]	2.86 (20°C)[f]
Odor	Odorless[f]	Odorless[f]	Odorless[f]
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water	40 wt% (anhydrous salt in 100 g saturated solution, 25°C)	228.4 g/L (20°C, pH 6.8)[g]	206.5 g/L (20°C, tetrahydrate)[f]
Organic solvents	No data	No data	No data
Inorganic solvents	No data	No data	No data
Partition coefficients:			
Log K_{ow}	NA	NA	NA
Log K_{oc}	NA	NA	NA
Vapor pressure at 20°C	No data	No data	No data
Henry's law constant at 25°C	NA	NA	NA
Autoignition temperature	NA	No data	NA
Flashpoint	No data	No data	No data
Flammability limits	No data	Non flammable[g]	No data
Explosive limits	NA	NA	NA
Conversion factors	NA	NA	NA

Table 4-2. Physical and Chemical Properties of Molybdenum and Compounds[a]

Property	Information	
Chemical name	Diammonium molybdate	Ammonium tetrathiomolybdate
Molecular weight	196.01	260.28
Color	Colorless, white, or slightly greenish-yellowish[i]	Deep red[h]
Physical state	Crystalline solid[h]	Crystalline solid[h]
Melting point	No data	>300°C[j]
Boiling point	No data	No data
Density	1.4[i]	No data
Odor	Odorless[i]	No data
Odor threshold:		
Water	No data	No data
Air	No data	No data
Solubility:		
Water	>10,000 mg/L[k]; 39 wt% (in 100 g saturated solution, 25°C)	Insoluble (hygroscopic)[l]
Organic solvents	No data	No data
Inorganic solvents	No data	No data
Partition coefficients:		
Log K_{ow}	NA	No data
Log K_{oc}	No data	No data
Vapor pressure at 25°C	No data	NA
Henry's law constant at 25°C	NA	No data
Autoignition temperature	NA	NA
Flashpoint	NA	NA
Flammability limits	Not flammable[i]	No data
Explosive limits	NA	NA
Conversion factors	NA	NA

[a]All information was obtained from Sebenik et al. (2012) unless otherwise noted.
[b]Cannon 1959.
[c]NOAA 2015.
[d]ECHA 2019a.
[e]Lide 2005.
[f]OECD 2013.
[g]ECHA 2019b.
[h]Haynes et al. 2014.
[i]NJDOH 2009.
[j]Sigma-Aldrich 2015.
[k]ECHA 2019c.
[l]Alfa Aesar 2015.

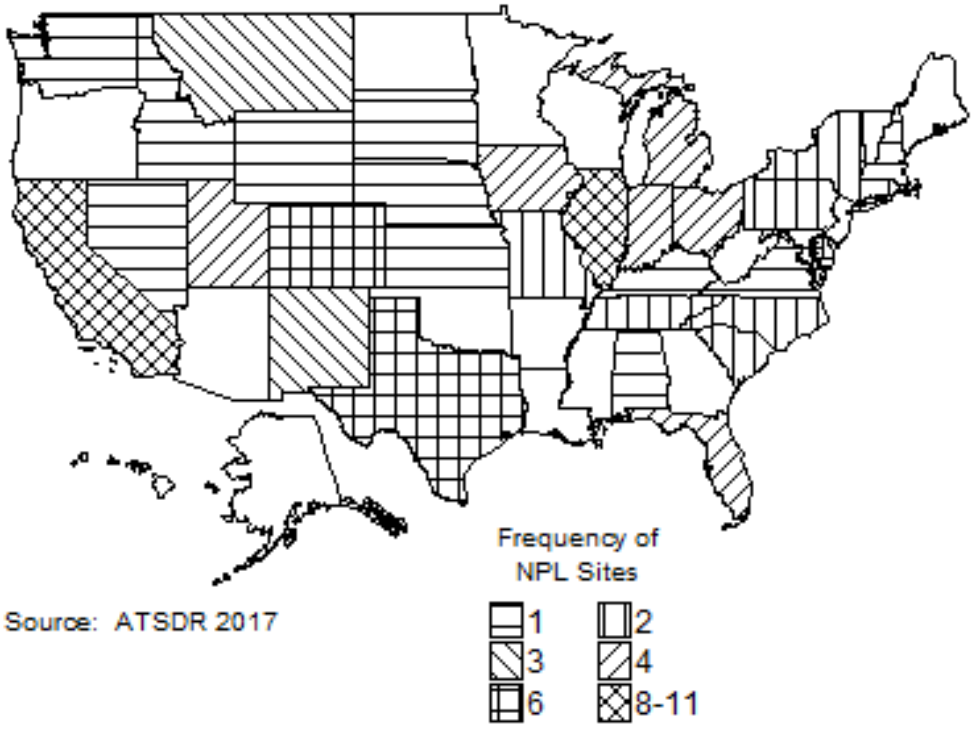
NA = not applicable

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Molybdenum has been identified in at least 86 of the 1,854 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2017). However, the number of sites in which molybdenum has been evaluated is not known. The number of sites in each state is shown in Figure 5-1. Of these sites, all are located within the United States.

Figure 5-1. Number of NPL Sites with Molybdenum Contamination



- The general population is primarily exposed to molybdenum through dietary intake.
- Inhalation exposure and ingestion of molybdenum from drinking water is typically low for the general population; however, water levels near mining operations may be higher and exposure may be greater for populations near these activities.
- Molybdenum compounds (e.g., molybdenum trioxide and polymolybdates) transform to the $[MoO_4]^{2-}$ ion under neutral or alkaline conditions; however, protonated forms, such as $[HMoO_4]^-$ and H_2MoO_4, are found at pH <5.

Molybdenum is a naturally occurring trace element found extensively in nature. Biologically, molybdenum plays an essential role as a micronutrient in plants and animals, including humans. It is also used widely in industry for metallurgical applications (EPA 1979). A radioactive isotope of molybdenum (^{99}Mo) is used as a source for producing metastable technetium-99 (^{99m}Tc), which is an important radiopharmaceutical that is used in the vast majority of high resolution medical imaging tests (Parma 2009). Important, naturally occurring molybdenum compounds are the minerals molybdenite, powellite, wulfenite, ferrimolybdite, and ilsemannite. When in the form of molybdate, a tetrahedral polyatomic anion, or other isopolyanions, it can be processed into salts used in industrial applications. The molybdate ion is the most common form of molybdenum found in the aqueous environment (EPA 1979).

If released to the atmosphere, molybdenum will be returned to earth by wet and dry deposition. In water, pH levels and oxidation/reduction conditions of the sediment govern the speciation of molybdenum and adsorption potential in natural aquifers. In the pH range of 3–5, molybdenum tends to exist as hydrogen molybdate and is adsorbed to sediment composed of clay and other oxic minerals (Fitzgerald et al. 2008). The adsorption and mobility of molybdenum in soils is also inversely correlated with pH. Adsorption of molybdenum to 36 surface and subsurface soils was maximized under acidic conditions (pH 2–5) and decreased rapidly at pH 5–8 (Goldberg et al. 2002). The availability of molybdenum to plants and vegetation is also affected by pH and soil properties. Since adsorption to soil decreases with increasing pH, it becomes more bioavailable for uptake to vegetation under nonacidic conditions.

Molybdenum is infrequently detected in ambient air, but is a natural constituent of water and soils. The earth's crust contains an average of 0.0001% (1 ppm) of molybdenum, and surface waters usually have molybdenum concentrations of <5 µg/L (EPA 1979). A decade-long study conducted by the U.S. Geological Survey (USGS) of >5,000 monitoring and drinking water wells from over 40 major aquifers in the United States reported a median molybdenum concentration of 1 µg/L (USGS 2011).

Anthropogenic activities such as mining operations may result in localized areas where molybdenum levels greatly exceed background levels.

The primary route of exposure for the general population to molybdenum is through the ingestion of food. NAS has estimated that the average dietary intakes (AVDIs) of molybdenum by adult men and women are 109 and 76 µg/day, respectively (NAS 2001). Other routes of exposure, such as inhalation of ambient air, ingestion of drinking water, and dermal exposure, are negligible for the general population; however, they may be important routes of exposure in certain occupational settings such as mining activities and

metallurgical applications where molybdenum is used. For example, molybdenum levels in air samples of two plants that produce molybdenum salts were 0.5–200 and 0.2–30 mg/m^3, depending upon the location of the sample and operation being performed (EPA 1979). Respirable dust samples contained molybdenum at levels of 0.471, 1.318, 0.142, and 0.318 mg/m^3 during mining, crushing, milling, and open pit operations, respectively, at a Colorado mine (EPA 1979).

The extensive nationwide use of radioactive ^{99}Mo in generators that produce ^{99m}Tc for nuclear medicine imaging scans can expose medical staff and the public in medical facilities to low levels of ionizing radiation. The extent of those exposures is limited by U.S. Nuclear Regulatory Commission (USNRC) and agreement state regulations (USNRC 2016a, 2016b).

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

Molybdenum is a naturally occurring trace element that can be found extensively in nature. Biologically, it plays an important role as a micronutrient in plants and animals, including humans. It is also used widely in industry for metallurgical applications (USGS 2015a).

Molybdenum does not occur naturally in the pure metallic form, but is in minerals, principally as oxide or sulfide compounds (Barceloux 1999; EPA 1979). Important naturally occurring molybdenum compounds are the minerals molybdenite (MoS_2, the predominant source), powellite, wulfenite, ferrimolybdite, and ilsemannite. Molybdenum may also form molybdate, a tetrahedral poly atomic anion, or other isopolyanions, which can form salts used in industrial applications. The earth's crust contains an average of 0.0004% (4 ppm) of molybdenum (Sebenik et al. 2012). Deposits that are economically feasible for mining contain ≥200 ppm of molybdenum, with lower concentrations obtained as a byproduct of copper mining (EPA 1979).

Molybdenite (MoS_2) is the principal mineral from which molybdenum is obtained. Mining and milling of crude ore produce molybdenite concentrate containing ≥90% of MoS_2, almost all of which is converted to technical-grade molybdenum trioxide. Molybdenum trioxide is the base material for the production of a variety of chemical compounds, ferromolybdenum, and purified molybdenum (EPA 1979).

Roasting molybdenite concentrate in a multiple hearth furnace at temperatures up to 600°C produces technical-grade molybdenum trioxide. This can be further purified by sublimation or selective recrystallization at about 1,000–1,100°C (Sebenik et al. 2012).

Worldwide mine production of molybdenum was estimated to be 258,000 metric tons in 2013, with approximately 92% produced, in descending order, by China, the United States, Chile, Peru, Mexico, and Canada. The United States accounted for 24% of world production with 60,700 metric tons in 2013, down slightly from 61,500 metric tons in 2012. Primary molybdenum operations accounted for 53% of total U.S. molybdenum production, while byproduct production made up 47% of the total in 2013. All U.S. molybdenum concentrates and products are from the mining of ore (USGS 2015a). U.S. production of molybdenum increased roughly 8% in 2014 to 65,500 metric tons (USGS 2015b). U.S. production of molybdenum for 2018 was 41,900 metric tons (USGS 2019). The USGS Mineral Industry Survey for molybdenum reported that domestic production for the first 3 months of 2019 was 3,620 metric tons (January), 3,420 metric tons (February) and 3,650 metric tons (March) (USGS 2019).

Table 5-1 contains a list the number of facilities per state that produced, processed, or used molybdenum trioxide in 2017, as well as information on the amount of molybdenum trioxide on site and related activities and uses (TRI17 2018).

Table 5-1. Facilities that Produce, Process, or Use Molybdenum Trioxide

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AL	5	100	99,999	7, 10, 12
AR	2	100,000	999,999	7
AZ	3	100,000	9,999,999	1, 4, 7, 9
CA	16	1,000	9,999,999	1, 2, 3, 7, 9, 10, 12, 13
CO	1	100,000	999,999	1, 6, 12, 13
DE	1	0	99	12
GA	1	0	0	0
IA	3	1,000,000	9,999,999	1, 3, 4, 6, 9
ID	1	10,000	99,999	12
IL	8	10,000	999,999	1, 5, 6, 7, 10
IN	7	1,000	999,999	1, 5, 6, 7, 8, 9, 10
KS	4	0	999,999	2, 3, 8, 10
KY	5	10,000	999,999	1, 2, 3, 4, 6, 7, 10
LA	27	0	49,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13

Table 5-1. Facilities that Produce, Process, or Use Molybdenum Trioxide

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
MD	1	100,000	999,999	7
ME	1	10,000	99,999	1, 5, 6
MI	4	0	99,999	1, 5, 6, 7, 10
MN	3	10,000	9,999,999	1, 7, 9, 10, 11, 13
MS	2	10,000	999,999	1, 5, 7, 10
MT	3	10,000	999,999	1, 2, 3, 5, 10, 12, 13
ND	2	10,000	99,999	10
NE	1	10,000	99,999	10
NJ	2	100,000	999,999	10
NM	2	10,000	999,999	10
NV	1	10,000	99,999	12
OH	8	1,000	999,999	1, 6, 7, 8, 9, 11, 13
OK	4	10,000	999,999	1, 4, 5, 7, 10, 13
OR	1	10,000	99,999	7
PA	17	100	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12
TX	40	0	99,999,999	1, 2, 3, 4, 6, 7, 8, 9, 10, 11, 12
UT	3	100	999,999	10, 11
WA	3	1,000	999,999	7, 10, 11, 12
WI	1	10,000	99,999	10, 11
WV	2	10,000	9,999,999	2, 3, 7, 10
WY	3	10,000	999,999	10

[a]Post office state abbreviations used.
[b]Amounts on site reported by facilities in each state.
[c]Activities/Uses:

1. Produce
2. Import
3. Used Processing
4. Sale/Distribution
5. Byproduct
6. Reactant
7. Formulation Component
8. Article Component
9. Repackaging
10. Chemical Processing Aid
11. Manufacture Aid
12. Ancillary
13. Manufacture Impurity
14. Process Impurity

Source: TRI17 2018 (Data are from 2017)

Molybdenum-99 (^{99}Mo) is a radioactive form of molybdenum and the only molybdenum radioisotope of commercial importance. It is produced in nuclear reactors, and then processed, packaged, and shipped to medical facilities throughout the world, where the ^{99}Tc progeny into which it transforms is eluted and injected into patients for imaging purposes (e.g., cardiac stress tests).

^{99}Mo was produced in one of eight nuclear reactors (mainly at the Chalk River complex in Canada) using highly enriched uranium, and then commercialized at five processing facilities and six generator manufacturing facilities. The availability of those reactors was reduced by the closure of the Chalk River facility, and this impacted the supply stream. The United States has established a high national priority on assuring an adequate supply of ^{99}Mo and urged manufacturers to switch from using highly enriched uranium (HEU) to low enriched uranium (LEU) to reduce the use of HEU for civilian applications (Ballinger 2010; The White House 2012; USNRC 2015; Van Noorden 2013). At a NAS symposium in 2017, several companies discussed their plans to produce ^{99}Mo in the United States (NAS 2018).

Currently, ^{99}Mo can be produced by placing HEU or LEU targets in an operating nuclear reactor and allowing the neutron flux to produce ^{99}Mo and its radioactive precursors. The quantity of ^{99}Mo peaks after approximately 6 days, at which time, the target is removed, processed, and prepared for shipment. New facilities for producing ^{99}Mo from LEU in the United States are being planned (Welsh et al. 2015).

5.2.2 Import/Export

Molybdenum-containing exports rose from 49,900 metric tons in 2010 to 55,300 metric tons in 2014, while imports for consumption rose from 19,700 metric tons in 2010 to 23,600 metric tons in 2014 (USGS 2015b). Imports of molybdenum (excluding ore) were 22,190 metric tons in 2018 and exports totaled 44,700 metric tons (USGS 2019). These data, along with U.S. production volumes, are summarized in Table 5-2.

Table 5-2. Molybdenum U.S. Production, Import, and Export Data from 2010 to 2014 and 2018 in Metric Tons

	2010[a]	2011[a]	2012[a]	2013[a]	2014[a]	2018[b]
Total U.S. production	59,400	63,700	61,500	60,700	65,500	41,900
U.S. imports for consumption	19,700	21,100	19,800	20,200	23,600	22,219[c]
U.S. exports for consumption	49,900	56,700	48,900	53,100	55,300	44,700[d]

[a]USGS 2015b.
[b]USGS 2019.
[c]Excludes imports of ore and concentrate.
[d]Includes ores and concentrates.

5.2.3 Use

Molybdenum is used primarily in metallurgical applications, including as an alloying agent in cast iron, steel, and superalloys to enhance properties such as hardenability, strength, toughness, and wear- and corrosion-resistance. Molybdenum is commonly used in combination with other alloy metals like chromium, cobalt, manganese, nickel, niobium, and tungsten. The leading form of molybdenum used by industry, particularly in stainless steel production, is molybdenum trioxide (USGS 2015a).

Molybdenum is used significantly as a refractory metal and molybdenum compounds in a variety of non-metallurgical chemical applications, such as catalysts, lubricants, and pigments. For example, MoS_2 is used along with cobalt during the desulfurization process of petroleum (Sebenik et al. 2012). Most molybdenum nitride catalysts are nitrogen deficient due to thermodynamically unfavorable conditions at atmospheric pressure; however, molybdenum nitride was recently produced in a high temperature and pressure environment by solid state ion exchange. Testing found its catalytic activity to be 3 times that of MoS_2 and its selectivity to hydrogenation to be 3 times that of MoS_2 for hydrodesulfurizing dibenzo-thiophene (Wang et al. 2015). As green technology is becoming more popular, molybdenum has become increasingly important in areas like biofuels, catalysts, ethanol, solar panels, and wind power (USGS 2015a).

A radioactive isotope of molybdenum, ^{99}Mo, is used as a source to produce the metastable radioisotope technetium-99m (^{99m}Tc), which is used in the vast majority of medical imaging tests performed today (Doll et al. 2014; Parma 2009; Richards 1989). It was estimated that 85% of all medical radioisotope procedures use ^{99m}Tc and that about 50,000 ^{99m}Tc-based diagnostic procedures are performed in the United States each day, resulting in about 13 million procedures annually (Parma 2009).

Molybdenum concentrate produced by U.S. mines is roasted, exported for conversion, or purified to lubricant-grade molybdenum disulfide. Purified MoS_2 is used directly as a solid or in coatings that are bonded onto the metal surface by burnishing, vapor deposition, or bonding processes that use binders, solvents, and mechanochemical procedures (Stiefel 2011).

Metallurgical applications accounted for about 87% of total molybdenum use in 2013. The principle non-metallurgical use was in catalysts, primarily catalysts used in petroleum refining. Molybdenum compounds are also used to produce pigments (USGS 2015a).

5.2.4 Disposal

Recycling is the most environmentally acceptable means of disposal for stable molybdenum (USGS 2015b). Because molybdenum is difficult to remove from waste water, it often is adsorbed to biosolids in municipal waste water treatment facilities. Biosolids are beneficial and are often used as fertilizer or compost for agricultural applications. In the United States, the land application ceiling limit for molybdenum in biosolids is 75 mg/kg (EPA 2018b).

A ^{99m}Tc generator containing a depleted uranium shield or sufficient residual ^{99}Mo radioactivity to be considered radioactive can be disposed of by shipping to an authorized licensee following USNRC agreement state requirements along with those of the Department of Transportation (USNRC 2015). If the ^{99}Mo is allowed to decay sufficiently (typically ≥10 half-lives) and the internal shield is lead or tungsten, then disposal should follow state and local requirements.

5.3 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ ≥10 full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005).

Molybdenum mining, milling, and smelting, along with its association with uranium mining and milling, copper mining and milling, shale oil production, oil refining, and coal-fired power plants, have resulted in major releases to the environment (EPA 1979).

5.3.1 Air

Estimated releases of 83,484 pounds (~37.87 metric tons) of molybdenum trioxide to the atmosphere from 188 domestic manufacturing and processing facilities in 2017, accounted for about 4.23% of the estimated total environmental releases from facilities required to report to the TRI (TRI17 2018). These releases are summarized in Table 5-3.

Table 5-3. Releases to the Environment from Facilities that Produce, Process, or Use Molybdenum Trioxide[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AL	5	59	0	0	8,295	0	4,539	3,815	8,354
AR	2	105	0	0	0	4,398	105	4,398	4,503
AZ	3	7,400	0	0	14,011	5	7,400	14,016	21,416
CA	16	638	43	0	11,305	70,649	10,152	72,484	82,635
CO	1	26	0	0	0	0	26	0	26
DE	1	14	0	0	2	0	14	2	15
GA	1	0	0	0	0	0	0	0	0
IA	3	8,650	6,100	0	5,705	0	15,500	4,955	20,455
ID	1	3	0	0	22,265	0	22,268	0	22,268
IL	8	18,361	2,685	0	16,464	2,449	21,046	18,913	39,959
IN	7	394	12,002	0	420,655	3,091	73,394	362,748	436,142
KS	4	250	0	0	5	0	255	0	255
KY	5	297	0	0	1,071	21	307	1,082	1,390
LA	27	6,761	1,733	81,533	279,468	9,012	258,237	120,270	378,507
MD	1	500	6,500	0	250	0	7,250	0	7,250
ME	1	147	0	0	0	0	147	0	147
MI	4	5	44	0	0	0	49	0	49
MN	3	124	5	0	227	0	129	227	356
MS	2	85	740	0	3,100	0	825	3,100	3,925
MT	3	129	0	0	24	0	129	24	153
ND	2	3	0	0	46	0	3	46	49
NE	1	0	0	0	0	0	0	0	0
NJ	2	0	0	0	13,620	0	0	13,620	13,620
NM	2	3	0	0	0	0	3	0	3
NV	1	1	0	0	42,143	0	42,144	0	42,144
OH	8	281	2,029	50,320	547	83	50,606	2,654	53,259
OK	4	3,501	20	0	0	46,900	3,521	46,900	50,421

Table 5-3. Releases to the Environment from Facilities that Produce, Process, or Use Molybdenum Trioxide[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
OR	1	17	0	0	1,266	0	1,153	130	1,283
PA	17	25,837	743	0	25,890	340	46,536	6,274	52,810
TX	40	9,616	6,224	54,360	659,999	0	593,414	136,784	730,199
UT	3	12	0	0	60	0	12	60	72
WA	3	260	0	0	7	0	260	7	267
WI	1	0	0	0	0	0	0	0	0
WV	2	0	0	0	0	0	0	0	0
WY	3	5	0	0	0	0	5	0	5
Total	188	83,484	38,868	186,213	1,526,424	136,948	1,159,428	812,509	1,971,937

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI17 2018 (Data are from 2017)

The primary source of molybdenum emissions to the atmosphere is coal combustion. In 1970, it was estimated that 550 metric tons of molybdenum were released via coal combustion in the United States, in comparison to 900 metric tons estimated from all air pollution sources (EPA 1979). A total of 909 metric tons of molybdenum can be emitted from a single 1,000 megawatt power plant per year (EPA 1979). Historical concentrations of molybdenum in fly ash from coal combustion were reported to range from 7 to 160 mg/kg (Barceloux 1999). Advances in sorbent and air pollution control technology such as fabric filters and electrostatic precipitators in power plants have resulted in a reduction of atmospheric emissions of molybdenum and other metals as compared to emissions from decades ago (Cho and Wu 2004; EPA 2009a). A report from the EPA, which compiled data on 73 coal combustion residues (CCR),

typically found molybdenum levels of 8–30 µg/g (mg/kg) in fly ash and scrubber sludges and about 1–10 µg/g (mg/kg) in gypsum (EPA 2009a). The study reported that no correlation was observed in molybdenum content and coal type or air pollution control system employed.

5.3.2 Water

Estimated releases of 38,868 pounds (~17.63 metric tons) of molybdenum trioxide to surface water from 188 domestic manufacturing and processing facilities in 2017, accounted for about 1.97% of the estimated total environmental releases from facilities required to report to the TRI (TRI17 2018). This estimate includes releases to waste water treatment and publicly owned treatment works (POTWs) (TRI17 2018). These releases are summarized in Table 5-3.

Per year, it has been estimated that natural processes result in the release of $3.6x10^{10}$ g of molybdenum into surface waters (EPA 1979).

Aqueous effluents from industries with a high presence of molybdenum, including molybdenum mining, milling, and smelting; uranium mining and milling; copper mining and milling; shale oil production; oil refining; and coal-fired power plants, contain molybdenum at concentrations ranging from 100 to 800,000 µg/L (EPA 1979). Molybdenum levels in leachate samples obtained from a landfill located in Caledonia, Wisconsin ranged from 1.28 to 16 µg/L (WDNR 2013).

Effluent concentrations of molybdenum from three molybdenum mining and milling operations (two in Colorado, one in New Mexico) ranged on the order of 1,000–10,000 µg/L. In 1972, a mine in Colorado released approximately 100,000 kg of molybdenum into a receiving stream. Releases of molybdenum from coal power plants to surface waters in the United States average about 1,800 metric tons/year. A uranium mill in Colorado reported leaking of the tailings ponds containing 860,000 µg/L molybdenum in 1965. Some uranium operations in New Mexico reported as much as 1,000 µg/L molybdenum in aqueous effluents. Copper milling operations have reported molybdenum effluent concentrations as high as 30,000 µg/L (EPA 1979).

Frasacoli and Hudson-Edwards (2018) compiled monitoring data on molybdenum levels in mining-affected areas in different parts of the world, which included groundwaters, nearby rivers, and tailing pore water. The largest levels of molybdenum were observed in mine waste from a coal mine located in Poland (2,332,000 µg/L). Groundwater from an area near 13 nonactive mines in Mexico ranged from

<5 to 150 µg/L. Tailing pore water from an inactive mining operation in Manitoba, Canada had molybdenum levels of <5–1,100 µg/L. Molybdenum concentrations from tailings channel water from an active copper mining facility in Chile ranged from 2,670 to 3,900 µg/L. Mine drainage samples obtained from an operational mine in Peru had molybdenum levels of 0.001–13.9 ppm (1–13,900 µg/L) (Skierszkan et al. 2016).

5.3.3 Soil

Estimated releases of 1,526,424 pounds (~692.37 metric tons) of molybdenum trioxide to soil from 188 domestic manufacturing and processing facilities in 2017, accounted for about 77.41% of the estimated total environmental releases from facilities required to report to the TRI (TRI17 2018). An additional 186,213 pounds (~84.46 metric tons), accounted for about 9.44% of the total environmental emissions, were released via underground injection (TRI17 2018). These releases are summarized in Table 5-3.

Metals, such as molybdenum, may leach into soil via municipal solid waste incineration bottom ash (IMOA 2015).

5.4 ENVIRONMENTAL FATE

5.4.1 Transport and Partitioning

Air. Molybdenum released to the air by industrial processes will be subject to atmospheric deposition (IMOA 2015). Deposition from the atmosphere is only a minor source to terrestrial and aquatic environments (Fitzgerald et al. 2008).

Water. Molybdenum can be leached into the aquatic environment near industrial use areas via direct release or atmospheric wet deposition by rain (IMOA 2015). The pH of water, along with the composition and redox conditions of the sediment, greatly affect the speciation and adsorption behavior of molybdenum in natural waterbodies. Molybdenum accumulation in the sediment phase is favored under conditions of low pH and in sediments with low redox potential and high iron and organic matter content (Fitzgerald et al. 2008). In more favorable reducing geochemical conditions, solid-phase iron and manganese oxyhydroxides tend to undergo dissolution, and sorbed molybdenum may be released back into the water phase.

Sediment and Soil. In a seasonally anoxic basin, the distribution of molybdenum in the pore water of sediments was relatively uniform. In a perennially oxic basin, however, there was a redistribution of molybdenum in the sediment-water interface subsequent to deposition. This was determined to be a consequence of adsorption of molybdenum to iron oxyhydroxides at a rate of 36 cm^3/molecule-second in the first 1–2 cm depth (IMOA 2015).

Geological uplift and atmospheric deposition result in the molybdenum enrichment of surface soils (IMOA 2015). Molybdenum concentrations are found to be the highest in the topsoil layer, due to strong binding to natural organic matter. Goldberg et al. (2002) studied the adsorption potential of molybdenum as a function of pH on 36 surface and subsurface soil samples from 27 soil series belonging to six different soil orders, which provided a wide range of soil physical-chemical characteristics such as organic carbon content, cation exchange capacity, and iron content. In general, maximum adsorption occurred under acidic pH conditions (pH 2–5) in which molybdenum adsorbed to oxyhydroxide mineral surfaces and sorption decreased rapidly from pH 5 to 8 and was minimal in all soils at pH >9. Skierszkan et al. (2016) studied the stable isotopic composition of molybdenum and zinc in mine wastes and noted a large variation in δ^{98}Mo (a measure of how the isotopic composition in the liquid or solid waste differed from a National Institute of Standards and Technology [NIST] standard solution) as a function of adsorption. At lower pH, adsorption of molybdenum is greatest, and the molybdenum isotope profile shifts toward heavier isotopic composition, as the adsorption process preferentially removes lighter isotopes. In contrast, zinc has the opposite behavior as it is more mobile under acidic conditions and adsorption is enhanced under alkaline conditions with lighter zinc isotopes more prominent. These results suggest the possibility of using isotopic composition as a method to understand attenuation mechanisms such as adsorption and molybdate precipitation during the weathering process.

Other Media. As reviewed by Regoli et al. (2012), the bioaccumulation factor (BAF) ranged from 30.1 to 71.6 (average of 49) in fish exposed to molybdenum levels <65 ug/L. At higher molybdenum levels (up to 766 µg/L), the BAF ranged from 0.4 to 9.9 (average 1.4). A laboratory study in rainbow trout found a similar inverse relationship between molybdenum concentration in the water and bioconcentration factor (BCF) (Regoli et al. 2012). A 60-day exposure to 880 µg/L resulted in tissue levels below the limit of detection. Exposure to 11,100 µg/L for 28 days resulted in whole-body molybdenum levels of 0.53 mg/kg fish; the calculated average BCF was 0.05. In another study, fish in a creek near a molybdenum tailings pile had measured BCFs of <100 after a 2-week exposure (CCME 1999). The accumulation data show that the BAF decreases with increasing molybdenum levels. At low

molybdenum concentrations, there is an active accumulation of essential metals in organisms (and often non-essential metals via the same uptake mechanisms) to ensure that metabolic requirements are met. This active uptake process decreases when organisms are exposed to higher metal concentrations. At higher concentrations, organisms with active regulation mechanisms are even limiting their uptake by excretion of excess metals. EPA published a framework for metals risk assessment that discusses the difference in interpreting BCF and BAF values for organic versus inorganic compounds (EPA 2017a). It was generally concluded that the most recent scientific data on bioaccumulation do not currently support the use of BCF and BAF values when applied as generic threshold criteria when assessing the hazardous potential of metals. Moreover, single-value BCF/BAF data are most applicable to site-specific assessments; for more general regional or national assessments, the media chemistry and metal concentrations for a particular species should be considered for BCF/BAF studies.

5.4.2 Transformation and Degradation

As a naturally occurring trace element, molybdenum can be found extensively in nature. The predominant form of molybdenum in natural waters is as the molybdate anion, $[MoO_4]^{2-}$ (Barceloux 1999), while naturally occurring molybdenum salts are the dominant form in dry environments (EPA 1979).

Air. No information regarding the chemical forms of molybdenum in the atmosphere and their transformations could be located. It is generally assumed that metals, especially those from combustion sources, exist in the atmosphere as oxides since metallic species are readily attacked by atmospheric oxidants.

Water. The speciation of molybdenum in aqueous media as a function of pH and molybdenum concentration, has been thoroughly investigated and reported upon in open literature. As discussed in Chapter 4, at pH >6.5, the sole molybdenum species is the molybdate anion, $[MoO_4]^{2-}$ (Cruywagen 2000; Cruywagen et al. 2002). Molybdenum compounds transform rapidly into the $[MoO_4]^{2-}$ ion under environmentally relevant conditions (Greenwood and Earnshaw 1997). In low redox environments, the molybdate anion can be reduced to molybdenum disulfide or molybdenite (Fitzgerald et al. 2008).

Sediment and Soil. Molybdenum is found naturally in soil as the minerals molybdenite, powellite, wulfenite, ferrimolybdite, and ilsemannite (EPA 1979; Fitzgerald et al. 2008).

The predominant form of molybdenum in wet soil is as the molybdate anion, $[MoO_4]^{2-}$ (Barceloux 1999).

Other Media. No data for the degradation of molybdenum in other media were located.

5.5 LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to molybdenum depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of molybdenum in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on molybdenum levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

Table 5-4 shows the typical limits of detection that are achieved by commonly employed analytical methods in environmental media. Smedley and Kinniburgh (2017) compiled a list of ranges for molybdenum in environmental matrices from primary references, including analytical detection limits. The American Public Health Association publishes analytical methods for molybdenum and other metals in aqueous samples and the EPA publishes laboratory analytical methods and procedures to test for analytes in air, water, solids, and hazardous waste. An overview summary of the range of concentrations detected in environmental media is also presented in Table 5-5.

Table 5-4. Lowest Limit of Detection Based on Standards[a]

Media	Detection limit	Reference
Air	0.48 ng/m^3	EPA 1999 (Method IO-3.3)
Drinking water	0.3 µg/L	EPA 1994 (Method 200.8)
Surface water and groundwater	0.3 µg/L; 8 µg/L	APHA 1989 (Method 3120B); EPA 1994 (Method 200.8)
Soil	0.000090–0.0023 mg/kg	Campillo et al 2002
Sediment	0.000090–0.0023 mg/kg	Campillo et al. 2002
Whole blood	~0.1 ng/mL (µg/L)	Keyes and Turnland (2002)

[a]Detection limits based on using appropriate preparation and analytics. These limits may not be possible in all situations.

Table 5-5. Summary of Environmental Levels of Molybdenum

Media	Low	High	For more information
Outdoor air (µg/m^3)	0.2	8.05	Section 5.5.1
Surface water (µg/L)	<1	157	Section 5.5.2
Groundwater (µg/L)	1	4,700	Section 5.5.2
Drinking water (µg/L)	<1	>40	Section 5.5.2
Food (ppb)	<1	1,800	Section 5.6
Soil (mg/kg)	<0.05	94.7	Section 5.5.3

Detections of molybdenum in air, water, and soil at NPL sites are summarized in Table 5-6.

Table 5-6. Molybdenum Levels in Water, Soil, and Air of National Priorities List (NPL) Sites

Medium	Median[a]	Geometric mean[a]	Geometric standard deviation[a]	Number of quantitative measurements	NPL sites
Water (µg/L)	340	229	14.4	16	10
Soil (mg/kg)	57	56.2	0.00794	7	6
Air (µg/m$^{3)}$	0.0655	0.0515	2.30	4	2

[a]Concentrations found in ATSDR site documents from 1981 to 2017 for 1,854 NPL sites (ATSDR 2017). Maximum concentrations were abstracted for types of environmental media for which exposure is likely. Pathways do not necessarily involve exposure or levels of concern.

5.5.1 Air

Molybdenum concentrations in ambient air have been reported to range from below detection limits to 0.03 mg/m^3 (EPA 1979). Concentrations of molybdenum in ambient air of urban areas, 0.01–0.03 µg/m^3, are higher than those found in rural areas, 0.001–0.0032 µg/m^3 (Barceloux 1999). Data from the EPA Air Quality System Database reported 24-hour concentrations of molybdenum at several locations in the United States for 2018 (EPA 2018c). These data are summarized in Table 5-7.

Table 5-7. 24-Hour Molybdenum Concentrations (µg/m^3) in Air Samples (2018 Data)

State (sample type)	Arithmetic mean	99th percentile	75th percentile	50th Percentile	10th Percentile
California (TSP)	0.0007	0.0015	0.0007	0.0007	0.0007
California (TSP)	0.0008	0.0019	0.0007	0.0007	0.0007
California (TSP)	0.0009	0.0016	0.0015	0.0007	0.0007
California (TSP)	0.0015	0.0053	0.0019	0.0007	0.0007
California (TSP)	0.0010	0.0023	0.0015	0.0007	0.0007
California (TSP)	0.0030	0.0063	0.0042	0.0028	0.0007
California (TSP)	0.0037	0.0068	0.0047	0.0038	0.0007
California (TSP)	0.0008	0.0016	0.0007	0.0007	0.0007
California (TSP)	0.0009	0.0023	0.0007	0.0007	0.0007
California (TSP)	0.0008	0.0019	0.0007	0.0007	0.0007
California (TSP)	0.0008	0.0021	0.0007	0.0007	0.0007
California (TSP)	0.0013	0.0042	0.0015	0.0007	0.0007
California (TSP)	0.0010	0.0026	0.0015	0.0007	0.0007
California (TSP)	0.0010	0.0025	0.0015	0.0007	0.0007
California (TSP)	0.0015	0.0046	0.0019	0.0007	0.0007
California (TSP)	0.0007	0.0014	0.0007	0.0007	0.0007
California (PM_{10})	2.0000	2.0000	2.0000	2.0000	2.0000
California (PM_{10})	2.0000	2.0000	2.0000	2.0000	2.0000
California (PM_{10})	0.0002	0.0020	0.0000	0.0000	0.0000
California ($PM_{2.5}$)	0.0003	0.0030	0.0000	0.0000	0.0000
California ($PM_{2.5}$)	0.0001	0.0030	0.0000	0.0000	0.0000
California ($PM_{2.5}$)	0.0003	0.0030	0.0000	0.0000	0.0000
California ($PM_{2.5}$)	0.0003	0.0030	0.0000	0.0000	0.0000
California ($PM_{2.5}$)	0.0003	0.0020	0.0000	0.0000	0.0000
California ($PM_{2.5}$)	0.0013	0.0043	0.0017	0.0010	0.0004
Michigan (TSP)	0.0011	0.0026	0.0016	0.0010	0.0002
Michigan (TSP)	3.0787	49.5000	1.4000	0.9000	0.5000
Michigan (PM_{10})	0.9935	2.2000	1.5000	0.9000	0.4000
Michigan (PM_{10})	1.0057	2.6000	1.4000	0.8000	0.4000
Michigan (PM_{10})	1.1778	2.4000	1.5000	1.1000	0.4000
Texas ($PM_{2.5}$)	0.0005	0.0040	0.0010	0.0000	0.0000

Table 5-7. 24-Hour Molybdenum Concentrations (µg/m^3) in Air Samples (2018 Data)

State (sample type)	Arithmetic mean	99th percentile	75th percentile	50th Percentile	10th Percentile
Texas ($PM_{2.5}$)	0.0006	0.0030	0.0010	0.0000	0.0000
Texas ($PM_{2.5}$)	0.0006	0.0020	0.0010	0.0000	0.0000
Vermont ($PM_{2.5}$)	0.0726	0.4700	0.1100	0.0400	0.0100
Vermont (PM_{10})	0.0655	0.2700	0.1100	0.0400	0.0000
Vermont (PM_{10})	0.1955	0.3800	0.2700	0.1500	0.0900
Vermont (PM_{10})	0.1787	0.5900	0.3000	0.1000	0.0400

PM_{10} = particulate matter ≤10 µm in diameter; $PM_{2.5}$ = particulate matter ≤2.5 µm in diameter; TSP = total suspended particulate

Source: EPA 2018c

5.5.2 Water

It has been reported that concentrations of molybdenum are generally <1.0 µg/L in surface waters (USGS 2006) and 1.0 µg/L in drinking water (USGS 2011). Groundwaters contain about 1.0 µg/L (USGS 2011). Smedley and Kinniburgh (2017) compiled ranges of molybdenum levels in rain water, stream water, rivers, lakes, estuaries, and oceans. Most surface water levels were <1 µg/L; however, there was wide variability, with levels tending to be higher with increasing salinity of the body of water (for example, molybdenum levels in the Salton Sea, California were reported as high as 37 µg/L).

A USGS study of surface water from 51 of the nation's major river basins was conducted from 1991 to 2002 (USGS 2006). The median concentration of molybdenum in 2,773 surface water samples was <1.0 µg/L, with a maximum concentration of 157 µg/L. There were eight samples (approximately 0.29% of the total) that exceeded the health-based screening level of 40 µg/L for molybdenum.

In a study of surface waters collected from 197 sampling stations in Colorado, molybdenum was found at concentrations <10 µg/L in 87% of the 299 samples. Samples that contained concentrations >5 µg/L were concluded to be the result of proximity to mineralization or mining and milling operations (EPA 1979). However, another study comparing surface waters draining highly mineralized areas to those with baseline molybdenum areas found that molybdenum mineralization did not contribute significantly to

concentrations in surface waters. The waters from streams draining the highly mineralized areas rarely had molybdenum concentrations above 1–2 µg/L (EPA 1979).

Huang et al. (2010) discussed surface water concentrations of metals including molybdenum in the Gyama Valley, an area impacted by four metal mining operations. Molybdenum concentrations ranged from <0.6 (detection limit) to 10.4 µg/L in the Gyamaxung-chu stream/river.

DOI (1967) collected river and lake water samples from 100 sampling stations around the United States from 1962 to 1967. The samples were taken from areas susceptible to contamination, including highly populated areas, industrial areas, recreational use areas, and state and national boundaries. Molybdenum was detected in the water samples at maximum concentrations >100 µg/L at 38 of the sample sites, while 26 sites had mean molybdenum concentrations >50 µg/L.

Molybdenum levels of 9.3–10.4 µg/L for open oxic seawater and 0.67–3.74 µg/L in euxinic waters of the Black Sea were reported (Smedley and Kinniburgh 2017). Kulathilake and Chatt (1980) reported the molybdenum concentration in the Atlantic Ocean as 7.2–7.9 µg/L. Another study reported that the molybdenum concentration in the North Atlantic ranged from 0.5 to 1.0 µg/L (Chan and Riley 1966). In the Pacific Ocean, measured molybdenum concentrations included 8.8 µg/L in the Eastern Pacific (Kiriyama and Kuroda 1984) and 1.5 µg/L in the Western Pacific (Nakata et al. 1983). Kawabuchi and Kuroda (1969) reported a mean molybdenum concentration of 7.7 µg/L in Tokyo Bay. Molybdenum concentrations measured in the English Channel ranged from 12 to 16 µg/L (Chan and Riley 1966), while the Irish Sea was reported to have a mean molybdenum concentration of 8.4 µg/L (Riley and Taylor 1968).

A comprehensive groundwater monitoring study conducted from 1992 to 2003 by the USGS of 5,183 monitoring and drinking-water wells representative of over 40 principal aquifers in humid and dry regions and in various land-use settings reported that the median concentration of molybdenum in 3,063 samples was 1.0 µg/L, with a maximum value of 4,700 µg/L (USGS 2011). Approximately 1.5% of the groundwater samples had molybdenum levels exceeding the health-based screening level of 40 µg/L (USGS 2011). Levels of molybdenum tended to be greatest in glacial unconsolidated sand and gravel aquifers as compared to other major aquifer groups in the study.

A report issued by the Wisconsin Department of Natural Resources found elevated levels of molybdenum in private supply wells and groundwater monitoring wells near the We Energies Oak Creek power plant

located in Caledonia, Wisconsin (WDNR 2013). Molybdenum levels in 21 private well samples exceeded the state of Wisconsin groundwater enforcement standard of 40 µg/L. It was not determined whether the elevated levels of molybdenum were naturally occurring or were a consequence of the activities of the power plant and the coal ash fill areas located nearby the plant.

In January of 2017, the EPA published the final results of the third Unregulated Contaminant Monitoring Rule (UCMR 3) program. Molybdenum levels >1 µg/L were measured in 25,377 out of 62,981 analyzed drinking water samples, and 151 samples had levels greater than the health-based screening level of 40 µg/L. In 40 of the 4,922 public water systems tested, at least one measurable level above 40 µg/L was found (EPA 2017b). Concentrations as high as 1,400 µg/L have been detected in drinking waters in areas impacted by mining and milling operations (USGS 2011).

In a study of finished drinking water supplies from the 100 largest cities in the United States in 1964, median and maximum molybdenum concentrations of 1.4 and 68 µg/L, respectively, were reported (USGS 1964). Another study reported a mean molybdenum concentration of 8 µg/L in samples collected from 161 drinking water sources from 44 states in the United States (Hadjimarkos 1967). Molybdenum levels measured onsite at 12 public water facilities across England and Wales ranged from below the detection limit (0.03 µg/L) to 1.51 µg/L over an 18-month collection period (Smedley et al. 2014). Corresponding molybdenum levels in tap water from 24 residences in three towns (North Wales, the English Midlands, and South East England) served by these public water facilities ranged from <0.03 to 1.00 µg/L. The study indicated that there was little variability in molybdenum concentrations when comparing levels in tap water versus respective water supply facilities, construction ages of the residences (i.e., new homes versus older homes), and pre-flush versus post-flush tap samples, suggesting that water distribution pipework has a negligible effect on supplied tap water levels of molybdenum.

Drinking water may also be affected by industrial contamination, as water treatment facilities are ineffective at removing molybdenum from source waters. In tap waters samples collected in 1971 from Golden, Colorado, a community that derives its water supply from a stream draining a molybdenum mine and mill, the mean molybdenum concentration was reported to be 440 µg/L. However, after the mine closed in 1974, the mean concentration in drinking water samples decreased to 150 µg/L by January 1975, 60 µg/L by June 1975, and 30 µg/L by 1977 (EPA 1979).

5.5.3 Sediment and Soil

Globally, most soils contain molybdenum at concentrations between 0.6 and 3.5 mg/kg, although total concentrations in soils can vary widely depending on geological composition, soil horizon, or industrial contamination. Statistical analysis of 4,841 samples of soil collected from a depth of 0–5 cm in the conterminous United States showed molybdenum levels ranging from <0.05 to 75.7 mg/kg (USGS 2014). The 5th, 25th, 50th, 75th, and 95th percentile concentrations were 0.24, 0.51, 0.78, 1.14, and 2.27 mg/kg, respectively (USGS 2014). From 4,780 samples of C horizon (substratum) soils in the United States, the molybdenum levels were reported as ranging from <0.05 to 94.7 mg/kg and the 5th, 25th, 50th, 75th, and 95th percentile concentrations were 0.20, 0.51, 0.83, 1.27, and 2.88 mg/kg, respectively (USGS 2014). A review of 25,673 deep soil samples from the British Geological Survey reported molybdenum concentrations of <0.6–885 mg/kg, with a median value of 1.4 mg/kg (Smedley and Kinniburgh 2017). The Forum of European Geological Surveys (FOREGS), under the International Union of Geological Sciences/International Association of Geochemistry (IUGS/IAGC) Global Geochemical Baselines Programme, collected 840 topsoil samples from 26 European countries and reported molybdenum concentrations ranging from <0.1 to 21.3 mg/kg (mean 0.943 mg/kg) (FOREGS 2005).

Above average molybdenum soil concentrations may occur in areas containing molybdenum-rich rock formations or in areas of industrial contamination. Natural sources sampled, including soils covering a mineralized area, soil derived from a marine black shale, alluvial soils on the eastern footslopes of Sierra Nevada, and soils formed from volcanic ash in Kauai, Hawaii, contained mean molybdenum concentrations of 76, 12, 17.4, and 14.9 mg/kg, respectively. Soils sampled near industrial contamination, such as soils downstream from a molybdenum mine and mill in Colorado, soil irrigated with water contaminated by a uranium mill, and soils 2 miles from a molybdenum smelter in Pennsylvania, had mean molybdenum concentrations of 59, 61, and 29 mg/kg, respectively (EPA 1979).

Typical molybdenum concentrations found in stream sediments were reported to range from 1 to 5 mg/kg (EPA 1979). Sediments in streams that drain water from natural deposits of molybdenum in the United States have been reported to have molybdenum concentrations ranging from 10 to 200 ppm (10–200 mg/kg). Another study reported molybdenum levels of up to 300 mg/kg in sediments derived from black marine shales in England. Stream sediment collected from water below a molybdenum mine and mill in Colorado had molybdenum concentrations ranging from 50 to 1,800 mg/kg (mean of 530 mg/kg). Molybdenum content in stream sediments have been shown to reflect mineralization, as the concentration increases with decreasing sediment grain size (EPA 1979). FOREGS collected 848 freshwater sediment

samples from 26 European countries and reported molybdenum concentrations ranging from 0.12 to 117 mg/kg (mean 1.34 mg/kg) (FOREGS 2005). An analysis of 65,477 stream sediments in the British Geological Survey G-Base reported a range of molybdenum concentrations of <0.1–309 mg/kg, with a median of 0.4 mg/kg (Smedley and Kinniburgh 2017). Sediment samples collected from river/streams in Tibet close in proximity to mining operations had molybdenum levels of 9.1–20.8 mg/kg (Huang et al. 2010).

5.5.4 Other Media

In a study detecting and comparing trace elements in the milk of guinea pigs (n=87), dairy cattle (n=48), horses (n=35), and humans (n=84), the average molybdenum concentrations measured were 26, 22, 16, and 17 µg/L, respectively (Anderson 1992). Average concentrations of molybdenum detected in six kinds of milk, including cow's milk-based formula, breast milk, soya milk, bottled milk, dried milk, and evaporated milk, were 18, 4, 160, 34, 35, and 29 µg/L, respectively (Biego et al. 1998). Most of the molybdenum is in the cream fraction (Archibald 1951).

Food derived from aboveground plants, such as legumes, leafy vegetables, and cauliflower generally has a relatively higher concentration of molybdenum in comparison to food from tubers or animals. Beans, cereal grains, leafy vegetables, legumes, liver, and milk are reported as the richest sources of molybdenum in the average diet (Barceloux 1999).

Typical concentrations of molybdenum in plants are 1–2 mg/kg; however, a range of tenths to hundreds of mg/kg have been reported (EPA 1979). Tobacco contains molybdenum concentrations of 0.3–1.76 mg/kg (Barceloux 1999).

5.6 GENERAL POPULATION EXPOSURE

Molybdenum exposure to the general population via ambient air and drinking water is expected to be negligible compared with exposure through food (Barceloux 1999). Molybdenum does not occur naturally in the pure metallic form. It is principally found as oxide or sulfide compounds (Barceloux 1999; EPA 1979). Therefore, almost all exposure is to a molybdenum compound rather than the metal alone. The average dietary intake of molybdenum in the United States by adult men and women are 109 and 76 µg/day, respectively (NAS 2001). A study of the dietary intake of adult residents in Denver, Colorado reported a mean molybdenum ingestion rate of 180 µg/day (range 120–240 µg/day) (Barceloux

1999). Daily intakes ranged from 74 to 126 µg molybdenum in a study of older children and adults in the northeastern United States (Barceloux 1999).

The European Food Safety Authority (EFSA) used dietary intake studies to derive estimates of which foods were most responsible for molybdenum intake in European populations (EFSA 2013). Cereals and cereal-based products (including bread) are the largest contributors to molybdenum intake in a Western diet; these products contribute one-third to one-half of the total molybdenum intake. Other contributors to total molybdenum intake include dairy products and vegetables.

A summary of molybdenum concentrations positively identified in foods analyzed during the FDA Total Diet Study (TDS) of 2006–2011 and 2013–2014 is summarized in Table 5-8 (FDA 2017). The data for molybdenum arose from Market Basket Surveys conducted in 2010 and 2011 and 2013–2014, in which 382 store-bought foods purchased in four geographic regions of the United States (northeast, southeast, central, and west) were analyzed. Only those food items in which the molybdenum content of at least one sample was above the detection limit of the analytical method are reported. Another survey of levels of molybdenum in food found the highest molybdenum concentrations in legumes; grains and grain products; nuts; meat, fish, and poultry (including liver); eggs; and milk, yogurt, and cheese (76.7, 30.0, 29.5, 8.9, 6.3, and 4.6 µg/100 g, respectively) (Pennington and Jones 1987).

Table 5-8. Molybdenum Levels Detected in Foods in the 2006–2011 and 2013–2014 Market Basket Surveys[a]

Food	Number of samples	Positive detections	Mean (mg/kg)	Median (mg/kg)	Maximum (mg/kg)	LOD (mg/kg)	LOQ (mg/kg)
Liver (beef/calf), pan-cooked with oil	8	8	1.500	1.400	1.700	0.700	3.000
Pinto beans, dry, boiled	8	8	1.300	1.270	1.600	0.700	3.000
Pork and beans, canned	8	1	0.088	0	0.700	0.700	3.000
Peanut butter, smooth/creamy	8	3	0.508	0	1.900	0.900	3.000
Shredded wheat cereal	8	5	0.554	0.883	0.984	0.700	3.000
Raisin bran cereal	8	1	0.088	0	0.701	0.700	3.000
Crisped rice cereal	8	8	0.898	0.837	11.300	0.700	3.000
Granola with raisins	8	6	0.589	0.772	0.815	0.700	3.000
Oat ring cereal	8	8	1.300	1.300	1.400	0.700	3.000
Collards, fresh/frozen, boiled	8	2	0.262	0	1.600	0.500	2.000
Chili con carne with beans, canned	8	2	0.179	0	0.730	0.700	3.000
Refried beans, canned	8	2	0.254	0	1.100	0.800	3.000

Table 5-8. Molybdenum Levels Detected in Foods in the 2006–2011 and 2013–2014 Market Basket Surveys[a]

Food	Number of samples	Positive detections	Mean (mg/kg)	Median (mg/kg)	Maximum (mg/kg)	LOD (mg/kg)	LOQ (mg/kg)
White beans, dry, boiled	8	8	1.100	1.116	1.800	0.700	3.000
Granola bar, with raisins	8	1	0.164	0	1.300	0.800	3.000
Candy bar, chocolate, nougat, and nuts	8	1	0.115	0	0.922	0.800	3.000

[a]Trace values were defined as results ≥LOD and <LOQ. Results ≥LOD and <LOQ (trace values) were used as reported when calculating the means.

LOD = limit of detection; LOQ = limit of quantification

Source: FDA 2017 (Data were initially released in 2014 and revised April 2017.)

Molybdenum is an essential dietary element and is often included in nutritional supplements. Based on data from NHANES, the median molybdenum intake from dietary supplements was about 23 and 24 µg/day for men and women who reported supplement use, respectively. Dietary supplements generally contain molybdenum in the form of sodium molybdate or ammonium molybdate (Momcilovic 1999; NAS 2001), although the molybdenum can also be in the form of molybdenum chloride, molybdenum glycinate, and molybdenum amino acid chelate (NIH 2019).

It was reported in 1979 that in the United States, the average human intake of molybdenum via drinking water was <5 µg/day (EPA 1979). Drinking water coming from sources close to areas with high molybdenum contamination from industrial effluents may contain a higher concentration of molybdenum (>50 µg/L) (EPA 1979).

Urinary levels of molybdenum were measured for the U.S. population from NHANES studies from 1999 to 2016 (CDC 2019) and are summarized in Table 5-9.

Table 5-9. Urinary Molybdenum Levels in U.S. Adults

Survey years	Geometric mean	50th percentile	95th percentile	Sample size
		Urinary molybdenum (µg/L)[a]		
1999–2000	41.7 (36.7–47.4)	46.6 (40.5–52.5)	168 (143–206)	1,299
2001–2002	41.1 (38.3–44.1)	47.6 (43.7–51.2)	150 (130–166)	1,560
2003–2004	35.9 (34.0–38.0)	40.3 (37.6–42.1)	133 (119–144)	1,543
2005–2006	41.3 (38.7–44.0)	46.0 (41.7–49.6)	153 (135–171)	1,520
2007–2008	40.8 (38.7–43.0)	44.5 (42.2–47.8)	152 (145–164)	1,857

Table 5-9. Urinary Molybdenum Levels in U.S. Adults

Survey years	Geometric mean	50th percentile	95th percentile	Sample size
2009–2010	39.6 (37.5–41.8)	42.0 (39.8–43.9)	144 (130–163)	2,019
2011–2012	34.1 (31.8–36.5)	37.3 (33.6–39.8)	136 (120–146)	1,715
2013–2014	30.8 (28.58–33.3)	32.7 (28.3–36.0)	129 (116–137)	1,811
2015–2016	32.0 (29.9–34.1)	35.9 (33.1–37.8)	124 (112–136)	1,793
Creatinine corrected urinary molybdenum (µg/g creatinine)				
1999–2000	39.6 (36.9–42.6)	38.5 (36.1–41.0)	122 (116–147)	1,299
2001–2002	39.3 (36.8–42.0)	39.6 (36.4–42.1)	123 (109–139)	1,559
2003–2004	36.9 (35.0–38.9)	37.0 (35.7–38.4)	118 (101–134)	1,543
2005–2006	41.2 (39.3–43.1)	40.5 (38.8–42.7)	119 (103–132)	1,520
2007–2008	43.5 (42.1–44.9)	42.9 (41.3–44.7)	122 (110–132)	1,857
2009–2010	41.9 (40.0–43.9)	41.2 (39.4–43.0)	127 (115–141)	2,019
2011–2012	38.6 (37.5–42.2)	40.0 (36.0–43.6)	118 (108–131)	1,261
2013–2014	35.9 (33.7–38.2)	36.9 (35.1–38.4)	97.8 (88.5–111)	1,810
2015–2016	34.9 (33.3–36.6)	36.3 (34.4–38.1)	97.4 (85.5–102)	1,791

[a]Limit of detection for survey years 1999–2001, 2001–2002, 2003–2004, 2005–2006, 2007–2008, 2009–2010, 2011–2012, 2013–2014, 2015–2016 were 0.8, 0.8, 1.5, 0.92, 0.92, 0.99, 0.8, and 0.8 µg/L, respectively.

Source: CDC 2019

Paschal et al. (1998) analyzed the levels of molybdenum and 12 other metals in the urine of 496 residents of the United States obtained from the NHANES III survey conducted from 1988 to 1994. The specimens randomly selected were from a broad spectrum of the population (e.g., both urban and rural communities, both males and females, and persons aged 6–88 years from all major ethnicities). The geometric mean molybdenum concentration of the samples was 46.8 µg/L and the 25th, 50th, 75th, and 95th percentiles were 27.9, 56.5, 93.9, and 168.0, µg/L, respectively. The creatinine-adjusted 25th, 50th, 75th, and 95th percentiles were 30.9, 45.7, 64.3, and 133.8 µg/g, respectively, with a geometric mean of 39.6 µg/g.

Molybdenum levels in whole blood are typically <5 ng/mL in the general population; however, blood samples from persons from areas with natural molybdenum deposits or from molybdenum mining areas may have concentrations of up to 150 µg/mL (Barceloux 1999).

Blood samples collected from 18 miners at a molybdenum mine in New Mexico had plasma molybdenum levels <5 µg/L in 12 of the 18 samples and 6–18 µg/L in the remaining 6 samples. The concentration of molybdenum in urine collected from 11 of the miners ranged from 20 to 74 µg/L. It was noted that

molybdenum levels in urine and blood of miners mainly exposed to molybdenite may not be above average, since molybdenite is a relatively insoluble compound (EPA 1979).

In a survey of a molybdenite mining, crushing, and milling operation in Colorado, mean molybdenum levels in respirable dust samples were 0.471, 1.318, 0.142, and 0.318 mg/m^3 during mining, crushing, milling, and open pit operations, respectively (EPA 1979). In settled dust and air samples collected from a molybdenum smelting operation, concentrations of molybdenum, in the form of molybdenum trioxide, were 57–61% and 3–33 mg/m^3, respectively (EPA 1979). Forty air samples collected above a crucible in a molybdenum trioxide smelting plant contained a mean molybdenum concentration of 0.22 mg/m^3, while air samples collected in the breathing zone of workers had molybdenum concentrations ranging from 1.4 to 5.4 mg/m^3 (EPA 1979). The air concentrations of molybdenum in two plants that produce molybdenum salts were 0.5–200 and 0.2–30 mg/m^3 (EPA 1979). More recent monitoring data for mining and milling operations were not located; current levels may be lower due to possible changes in occupational standards, engineering and administrative controls, and personal protective equipment requirements.

Workers involved in metal refining and metal working may be exposed to airborne particulates containing molybdenum. In a study assessing the exposure of a group of 20 workers performing welding, polishing, and assembly of stainless steel constructions, molybdenum was detected in personal air samplers at concentrations of 0.27–9.7, 0.03–4.2, and 0.14–0.60 µg/m^3, respectively. Stationary air samplers in the facility detected course (equivalent aerodynamic diameter [EAD] 2–10 µm) and fine (EAD <2 µm) molybdenum particles at concentrations of 0.015–0.087 and 0.093–0.54 µg/m^3, respectively (Kucera et al. 2000).

The National Occupational Exposure Survey (NOES) conducted by NIOSH in 1983 estimated that 245,024 workers employed at 15,996 facilities were potentially exposed to molybdenum (pure, powder, and unknown forms) in the United States (RTECS 2009). The NOES database does not contain information on the frequency, concentration, or duration of exposure; the survey provides only estimates of workers potentially exposed to chemicals in the workplace.

The extensive nationwide use of radioactive ^{99}Mo in generators that produce ^{99m}Tc for nuclear medicine imaging scans can expose medical staff and the public in medical facilities to low levels of ionizing radiation. The extent of those exposures is limited by the USNRC and agreement state regulations (USNRC 2016a, 2016b).

Breast milk and infant formula are the primary sources of molybdenum in infants aged 0–6 months (NAS 2001). The primary source of dietary molybdenum intake among children in the United States is milk (EPA 1979). Several studies have measured molybdenum levels in human breast milk; average molybdenum levels ranged from 1.5 to 17 µg/L (Anderson 1992; Aquilio et al. 1996; Biego et al. 1998; Bougle et al. 1988). As shown in Table 5-10, the highest molybdenum concentrations occur within the first week after birth and tend to be higher in the mothers of term infants, as compared to preterm infants (Aquilio et al. 1996; Bougle et al. 1988).

Table 5-10. Molybdenum Levels in Breast Milk in Mothers of Term and Preterm Infants

	Molybdenum levels in breast milk (µg/L)		
Lactation day	Term infants	Preterm infants	Reference
2–6	6.8	3.9[a]	Aquilio et al. 1996
12–16[b]	5.7	2.4[a]	
21[c]	3.6	1.9[a]	
3–5	10.2	4.0[a]	Bougle et al. 1988
7–10[d]	4.8	3.7	
14[d]	1.5	1.4	
30[d]	2.6	1.9	
60[e]	No data	1.2	

[a]Significantly different from term infant levels ($p<0.05$).
[b]Significantly different from molybdenum concentration at 2-6 days ($p<0.01$).
[c]Significantly different from molybdenum concentration at 2-6 days ($p<0.05$).
[d]Significantly different from molybdenum concentration for whole group at 3-5 days ($p<0.01$).
[e]Significantly different from molybdenum concentration at for whole group at 3-5 days ($p<0.05$).

Krachler and colleagues studied the trace element concentrations in human milk during the course of lactation (Krachler et al. 1998; Rossipal and Krachler 1998). In total, 79 samples of human milk from 46 healthy mothers were sampled in Austria in 1995 and 1996 at 1–293 days after the mothers gave birth (Rossipal and Krachler 1998). In colostrum milk (1–3 days postpartum), the molybdenum concentration was 8.88±3.74 µg/L. In samples collected 42–60 days postpartum, the concentration was 1.43±1.77 µg/L, and at 97–293 days, the milk contained 1.78±1.62 µg/L. In a later study, the same group analyzed a further set of samples of colostrum milk only (Krachler et al. 1999). Previous results were confirmed, with the mean concentration being reported as 7.0±3.8 µg/L (median 5.7 µg/L, range 3.4–18.8 µg/L). Another study from Europe reported molybdenum concentrations in human milk (Wappelhorst et al. 2002). In samples taken daily in 2002 from 19 mothers from Germany, Poland, and

the Czech Republic, for sample periods between 2 and 8 weeks for each mother and covering weeks 3–68 of lactation, the median molybdenum concentration was 0.53 µg/L (mean 0.72 µg/L, range 0.27–1.61 µg/L). Data on molybdenum concentrations in human milk are also available from Japan (Hattori et al. 2004). In 17 samples provided by three mothers during days 96 and 327 after delivery, the molybdenum concentrations ranged from 1.97 to 8.93 µg/L, with an estimated average of ~4.3 µg/L (estimated from three median values given for the individual mothers). In comparison, the concentration of molybdenum in formula milk after preparation is reported as 2.38±0.75 µg/L (n=6). In Canada, 20 samples of mother's milk were analyzed for molybdenum in the context of a balance study on low-birth-weight infants on parenteral and enteral nutrition (Friel et al. 1999b). The median molybdenum concentration is reported as 5 µg/L, with a range of 2.1–23 µg/L.

Urinary levels of molybdenum in children 6–11 and 12–19 years old were measured during the NHANES study assessing exposure from 1999 to 2016 (CDC 2019) and in children 3–5 years of age during NHANES 2015–2016; these data are summarized in Table 5-11.

Table 5-11. Urinary Molybdenum Levels in U.S. Children and Adolescents

Survey years	Geometric mean	50th percentile	95th percentile	Sample size
	Urinary molybdenum (µg/L)[a]			
1999–2000				
Age 6–11 years	78.2 (61.0–100)	84.8 (67.7–105)	267 (159–840)	310
Age 12–19 years	54.3 (47.6–62.0)	60.6 (52.2–70.3)	188 (146–216)	648
2001–2002				
Age 6–11 years	63.3 (53.4–75.0)	69.2 (63.0–77.6)	197 (161–291)	368
Age 12–19 years	60.6 (55.5–66.2)	65.7 (58.7–73.1)	179 (155–227)	762
2003–2004				
Age 6–11 years	62.2 (56.7–68.3)	71.3 (55.7–84.1)	181 (138–235)	290
Age 12–19 years	52.5 (49.0–56.3)	59.6 (55.5–65.1)	143 (130–156)	725
2005–2006				
Age 6–11 years	65.6 (56.6–76.0)	73.5 (62.8–85.5)	181(154–205)	355
Age 12–19 years	59.1 (53.7–65.1)	63.8 (57.9–69.4)	173 (148–202)	701
2007–2008				
Age 6–11 years	69.3 (60.8–79.0)	72.8 (62.1–83.9)	235 (169–282)	394
Age 12–19 years	64.1 (58.6–70.2)	68.6 (63.7–80.2)	174 (151–196)	376
2009–2010				
Age 6–11 years	65.0 (57.8–73.2)	69.7 (61.1–84.2)	218 (180–263)	378
Age 12–19 years	52.4 (47.5–57.7)	58.5 (51.4–65.6)	178 (151–201)	451

Table 5-11. Urinary Molybdenum Levels in U.S. Children and Adolescents

Survey years	Geometric mean	50th percentile	95th percentile	Sample size
2011–2012				
Age 6–11 years	58.4 (51.5–66.2)	65.1 (52.8–74.5)	211 (187–283)	399
Age 12–19 years	46.4 (40.2–53.7)	51.0 (44.2–64.8)	163 (145–173)	390
2013–2014				
Age 6–11 years	51.7 (47.1–56.6)	54.7 (49.3–61.9)	182 (159–210)	402
Age 12–19 years	48.2 (41.5–55.8)	55.9 (49.0–64.8)	156 (136–180)	451
2015–2016				
Age 3–5 years	47.3 (43.9–50.8)	51.6 (45.8–61.1)	191 (146–218)	486
Age 6–11 years	56.2 (51.3–61.5)	57.5 (50.2–69.1)	173(165–224)	379
Age 12–19 years	47.7 (43.3–52.6)	53.0 (45.9–57.0)	149 (135–166)	402
Creatinine corrected urinary molybdenum (µg/g creatinine)				
1999–2000				
Age 6–11 years	85.9 (73.7–100)	79.3 (71.6–88.4)	214 (154–1,040)	310
Age 12–19 years	41.9 (39.3–44.6)	40.5 (37.7–44.4)	112 (78.4–185)	648
2001–2002				
Age 6–11 years	77.2 (73.1–81.5)	77.6 (71.8–84.5)	185 (165–219)	368
Age 12–19 years	43.4 (40.8–46.1)	44.1 (40.8–47.2)	106 (94.8–118)	762
2003–2004				
Age 6–11 years	72.5 (65.2–80.7)	73.5 (65.1–79.9)	160 (129–257)	290
Age 12–19 years	37.5 (35.4–39.8)	38.9 (36.9–41.8)	81.0 (74.3–102)	725
2005–2006				
Age 6–11 years	81.0 (71.9–91.3)	78.6 (72.1–89.0)	201(160–261)	355
Age 12–19 years	45.5 (42.5–48.7)	45.7 (41.3–49.2)	109 (95.0–131)	701
2007–2008				
Age 6–11 years	90.4 (81.8–99.8)	88.2 (79.2–101)	274 (224–354)	394
Age 12–19 years	50.1 (47.2–53.2)	50.1 (44.2–53.4)	129 (99.5–138)	376
2009–2010				
Age 6–11 years	88.6 (81.9–95.4)	89.0 (79.2–95.4)	195 (178–216)	378
Age 12–19 years	49.0 (45.3–53.0)	50.7 (44.6–56.2)	126 (96.4–134)	451
2011–2012				
Age 6–11 years	83.5 (76.1–91.6)	81.7 (74.3–91.2)	259 (185–300)	398
Age 12–19 years	44.4 (40.8–48.4)	43.7 (39.1–48.0)	109 (92.4–131)	390
2013–2014				
Age 6–11 years	77.0 (73.5–80.8)	73.5 (70.0–81.4)	184 (164–225)	402
Age 12–19 years	43.6 (40.3–47.2)	44.0 (39.1–47.3)	113 (95.9–140)	451

Table 5-11. Urinary Molybdenum Levels in U.S. Children and Adolescents

Survey years	Geometric mean	50th percentile	95th percentile	Sample size
2015–2016				
Age 3–5 years	109 (102–116)	107 (98.4–117)	275 (239–329)	485
Age 6–11 years	79.7 (75.5–84.1)	79.6 (69.9–86.7)	200(171–229)	379
Age 12–19 years	44.6 (41.9–47.5)	45.0 (41.8–48.7)	107 (89.3–133)	402

[a]Limit of detection for survey years 1999–2001, 2001–2002, 2003–2004, 2005–2006, 2007–2008, 2009–2010, 2011–2012, 2013–2014, 2015–2016 were 0.8, 0.8, 1.5, 0.92, 0.92, 0.99, 0.8, and 0.8 µg/L, respectively.

NHANES = National Health and Nutrition Examination Survey

Source: CDC 2019; NHANES data are periodically updated, and the most recent information can be found at https://cdc.gov/exposurereport/index.html.

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Workers in an industrial setting such as mining, metal refining, and metal working can be exposed to significant levels of molybdenum (Kucera et al. 2000). Populations living close to areas with high molybdenum contamination from industrial effluents and high mineral deposits are at risk for higher exposures (EPA 1979).

^{99}Mo generators are the major source of ionizing radiation exposure to nuclear medicine staff in medical facilities that perform ^{99m}Tc diagnostic imaging scans (Ahasan 2004).

CHAPTER 6. ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of molybdenum is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the adverse health effects (and techniques for developing methods to determine such health effects) of molybdenum.

Data needs are defined as substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.1 INFORMATION ON HEALTH EFFECTS

Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to molybdenum that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of molybdenum. The number of human and animal studies examining each endpoint is indicated regardless of whether an effect was found and the quality of the study or studies.

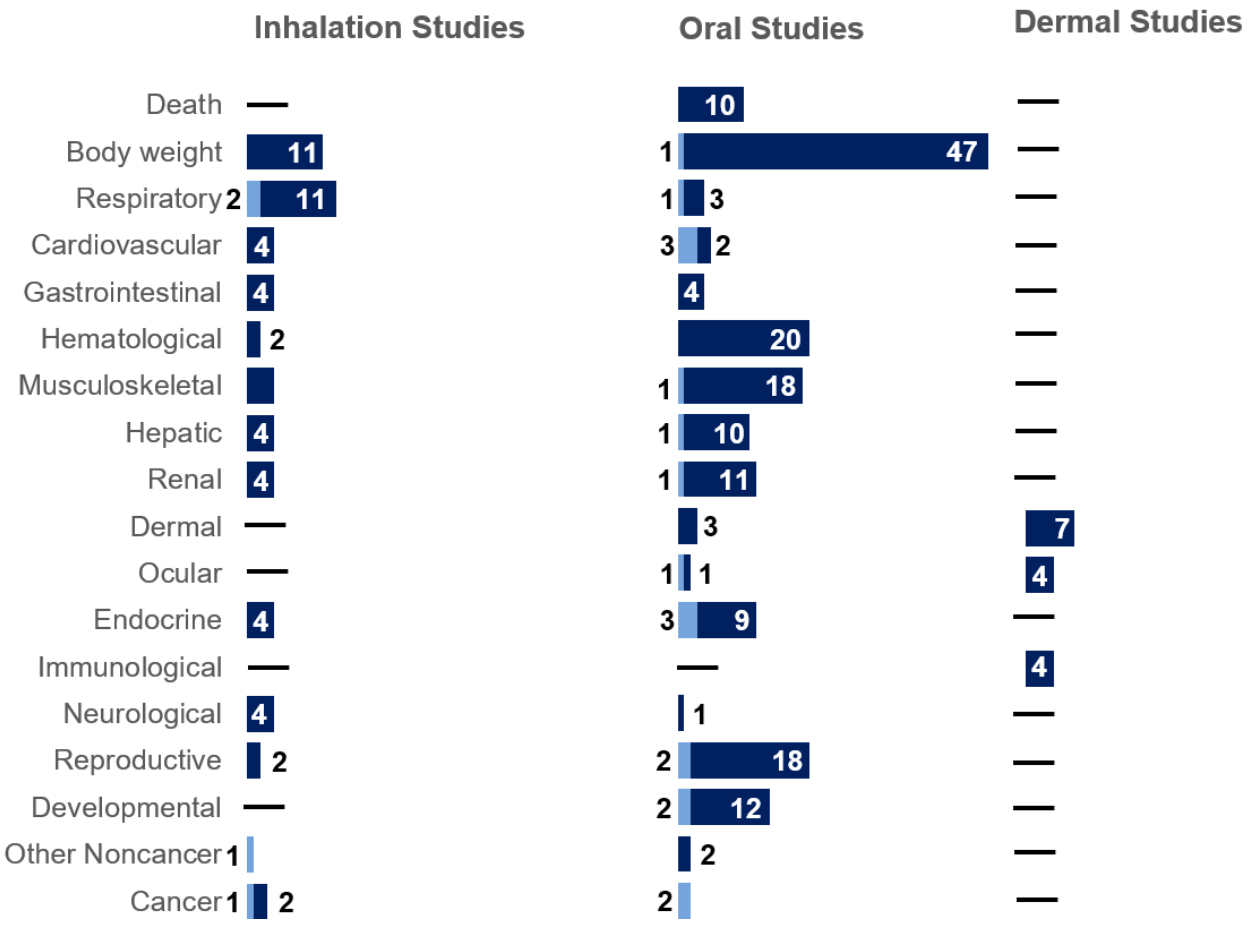
6.2 IDENTIFICATION OF DATA NEEDS

Missing information in Figure 6-1 should not be interpreted as a "data need." A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Figure 6-1. Summary of Existing Health Effects Studies on Molybdenum By Route and Endpoint*

Potential body weight, hematological, musculoskeletal, and reproductive effects were the most studied endpoints

The majority of the studies examined oral exposure in **animals** (versus **humans**)



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect and studies may have examined more than one endpoint.

Acute-Duration MRLs. No data were located regarding health effects after acute inhalation exposure to molybdenum in humans. In laboratory animals, the inhalation exposure data are limited to studies of molybdenum trioxide conducted in rats and mice (NTP 1997); however, the studies only examined the nasal cavity and body weight. Although increased mortality and decreases in body weight gain were observed, the studies are not adequate for identifying the primary target of toxicity. Thus, they were not considered adequate for derivation of an acute-duration inhalation MRL. Additional studies examining a wide-range of endpoints and several different molybdenum compounds would be useful for characterizing the hazard of molybdenum following acute inhalation exposure.

In an acute oral exposure experiment, no alterations in uric acid levels were observed in volunteers (Deosthale and Gopalan 1974); the study did not examine other potential endpoints. A small number of studies have examined the acute oral toxicity in laboratory animals, and none of them examined a wide-range of endpoints. One study found an increase in serum triglyceride levels in rabbits but did not find any histological alterations in the liver or kidneys (Bersenyi et al. 2008). Three acute laboratory animal studies have reported reproductive effects (Bersenyi et al. 2008; Zhai et al. 2013; Zhang et al. 2013). However, interpretation of the results is limited by the lack of statistical analyses (Bersenyi et al. 2008) or limited information on molybdenum and copper intake (Zhai et al. 2013; Zhang et al. 2013). Additionally, reproductive effects have not been reported in high-quality intermediate-duration studies (Murray et al. 2014a, 2019). Given these limitations, the database was not considered suitable for derivation of an acute-duration oral MRL. Additional studies that report molybdenum doses and copper content of the diet, and evaluate a wide range of endpoints, including the reproductive system, are needed.

Intermediate-Duration MRLs. The available data on the toxicity of molybdenum following intermediate-duration inhalation exposure are limited to 90-day studies of molybdenum trioxide examining a wide range of potential targets of toxicity in rats and mice (NTP 1997). No adverse effects were observed in these studies, and the studies were not considered suitable for derivation of an intermediate-duration inhalation MRL for molybdenum. Additional studies testing higher concentrations and several molybdenum compounds may identify sensitive targets.

A number of studies have examined the intermediate-duration toxicity of ingested molybdenum. Among studies in which the laboratory animals were provided a diet with adequate levels of copper, a number of targets of toxicity were identified including the kidney, hematological system, reproductive system, and the developing organism (Bompart et al. 1990; Fungwe et al. 1990; Jeter and Davis 1954; Lyubimov et al. 2004; Murray et al. 2014a, 2019; Pandey and Singh 2002). The lowest LOAEL values were identified for

reproductive and developmental effects. However, these values were identified in lower quality studies and were not confirmed in higher quality studies; thus, they were not considered suitable as a point of departure (POD) for an MRL. An intermediate-duration oral MRL was derived based on kidney effects in a high-quality study (Murray et al. 2014a). Additional studies are needed to confirm that the kidney is the most sensitive target of oral molybdenum toxicity.

Chronic-Duration MRLs. Two occupational exposure studies have reported mixed results on the effect of molybdenum on the respiratory tract (Ott et al. 2004; Walravens et al. 1979). There is insufficient information on the specific molybdenum compounds involved and limited data on exposure levels. Chronic exposure studies in rats and mice have identified the respiratory tract as a sensitive target of molybdenum trioxide toxicity (NTP 1997), and an inhalation MRL was derived based on the findings in the animal studies. Additional studies are needed to evaluate the inhalation toxicity of other molybdenum compounds.

A number of studies have evaluated the chronic toxicity of ingested molybdenum in humans. Studies of populations potentially exposed to high concentrations of molybdenum have evaluated potential alterations in uric acid levels (EPA 1979; Koval'skiy et al. 1961); there are a number of limitations with both of these studies restricting their usefulness in evaluating the chronic toxicity of molybdenum in humans. Epidemiological studies that examined the potential of molybdenum to induce adverse health effects presumably involved background environmental exposure (Meeker et al. 2008, 2010; Mendy et al. 2012; Schroeder and Kraemer 1974; Shiue and Hristova 2014; Vazquez-Salas et al. 2014; Yorita Christensen 2013). Although some of these studies reported statistically significant associations between biomarkers of molybdenum exposure (plasma or urine levels) and adverse effects, the studies do not establish causality and there may have been factors other than molybdenum exposure. No laboratory animal studies evaluated the chronic oral toxicity of molybdenum. Additional studies examining a wide range of potential endpoints are needed to identify the hazards associated with chronic ingestion of high levels of molybdenum and establish dose-response relationships; these data could be used to derive a chronic-duration oral MRL.

Health Effects.

Reproductive. A study of men at an infertility clinic found associations between blood molybdenum levels and altered sperm parameters and reproductive hormone levels (Meeker et al. 2008, 2010). These studies do not establish causality. Oral exposure studies in laboratory animals have provided mixed results on whether the reproductive system is a target of

molybdenum toxicity (Bersenyi et al. 2008; Fungwe et al. 1990; Lyubimov et al. 2004; Murray et al. 2014a, 2019; Pandey and Singh 2002; Zhai et al. 2013; Zhang et al. 2013). High-quality studies did not find any significant alterations in sperm parameters, estrous cycling, or male or female reproductive tissue (Murray et al. 2014a, 2019), and no effects on fertility were found in a 2-generation study (Murray et al. 2019). In contrast, other studies have found alterations in estrous cycling (Fungwe et al. 1990), sperm parameters (Pandey and Singh 2002; Zhai et al. 2013), oocytes (Zhang et al. 2013), and male fertility (Pandey and Singh 2002). Interpretation of the results of these studies was limited by inadequate information on molybdenum doses (the investigators did not provide adequate information on body weight or water consumption, which could be used to estimate doses) or did not report the copper content of the commercial diet used. Additional studies are needed to provide insight into the apparent conflicting results for reproductive toxicity.

Immunotoxicity. The immunotoxicity of molybdenum has not been adequately addressed. No inhalation or oral exposure studies addressed immune function; intermediate- and chronic-duration inhalation studies did not find histological alterations in the thymus or spleen (NTP 1997). Very low levels of positive results of patch tests were observed in patients undergoing hip or knee replacements (Koster et al. 2000; Menezes et al. 2004; Zeng et al. 2014). In animals, contact sensitization was observed in a guinea pigs in a sensitization assay with molybdenum pentachloride (Boman et al. 1979); other studies with other molybdenum compounds—ammonium dimolybdate, molybdenum trioxide, and sodium molybdate—have not found evidence of skin sensitization (Allan et al. 1996, 1996b, 1996c, 1996d). Studies examining immune function and systemic immunological endpoints (e.g., changes in white cell populations, cytokine levels, macrophage infiltration) would be useful in evaluating whether this is a target of molybdenum toxicity; it would be useful if the studies evaluated different molybdenum compounds.

Mechanisms of Action. The mechanisms of molybdenum toxicity are poorly understood. Although there are data suggesting that molybdenum toxicity may be related to alterations in copper utilization, it is also likely that other mechanisms, such as oxidative damage, are also involved. Studies examining the mode of action are needed to support the identification of critical endpoints and derivation of MRLs.

Epidemiology and Human Dosimetry Studies. A small number of epidemiology studies were identified for molybdenum; however, most of these studies presumably involved background environmental exposure to molybdenum. Two occupational exposure studies found conflicting results regarding the respiratory toxicity of molybdenum (Walravens et al. 1979; Ott et al. 2004). Additional studies of worker populations examining a wide range of potential endpoints, including the respiratory tract, would provide valuable information on the toxicity of inhaled molybdenum. General population studies have identified a number of potential targets of toxicity of ingested molybdenum including blood pressure (Shiue and Hrisova 2014), liver (Mendy et al. 2012), the reproductive system (Meeker et al. 2008, 2010), and the developing organism (Shirai et al. 2010); however, none of the studies established causality. Studies of populations exposed to high levels of molybdenum in drinking water or from foods grown in molybdenum-rich soil would provide support for establishing sensitive targets of molybdenum toxicity.

Biomarkers of Exposure and Effect.

Exposure. Molybdenum levels can be measured in blood, tissues, and excreta, and background urinary levels of molybdenum have been established in healthy individuals (CDC 2019). Blood and urinary levels have been shown to increase in response to increased molybdenum ingestion (Turnland and Keyes 2004), although plasma molybdenum levels are likely to be reflective of recent dietary intake. Studies that quantified the relationship between blood and/or urinary levels and intake would provide valuable information on screening and comparison with adverse effect levels. Studies evaluating biochemical and/or genomic biomarkers of exposure would also be useful for evaluating potential inhalation and/or oral exposure.

Effect. No biomarkers of effect were identified. The available data have identified the following sensitive targets: respiratory tract (inhalation only), kidney, and possibly the reproductive system. Studies examining the possible relationship between blood or urinary levels of molybdenum with these adverse health effects could facilitate medical surveillance leading to early detection and possible treatment.

Absorption, Distribution, Metabolism, and Excretion. For humans, detailed quantitative information is available regarding the absorption, distribution, and excretion of ingested molybdate ($Mo^{[VI]}O_4^{2-}$) and molybdenum incorporated into food. Although molybdate is most likely the dominant chemical species of molybdenum in the body, there are no data for humans on toxicokinetics following

exposures to other forms of molybdenum that could occur in the environment, such as Mo^{IV} compounds. No quantitative information is available on the toxicokinetics of molybdenum in humans following chronic oral exposure. There is no information on inhalation, and dermal toxicokinetic data are limited to an *in vitro* percutaneous absorption study (Roper 2009). A study conducted in mice showed that molybdenum is absorbed following inhalation exposure to molybdenum trioxide (NTP 1997).

Limited information was identified on the relative bioavailability of different molybdenum compounds following inhalation or oral exposure. It is likely that the solubility of the molybdenum compound would greatly influence the amount that is absorbed through the lungs or gastrointestinal tract. Studies examining relative bioavailability would provide valuable information on extrapolating data across molybdenum compounds and species.

Studies conducted in humans have provided data for the development of PBPK models of molybdenum kinetics in humans (Giussani 2008; Novotny and Turnlund 2007). Models have not been developed for rodents or other animal species that could be used in dosimetry extrapolation of animal bioassay results.

Comparative Toxicokinetics. The available data on the toxicity of molybdenum in humans and laboratory animals suggest that they have similar targets of toxicity; however, there are limited epidemiology data. The available data suggest similarities in the absorption, distribution, and elimination of ingested molybdenum in humans and rats. Additional studies are needed to compare the toxicokinetics of inhaled molybdenum and to assess whether there are species differences.

Children's Susceptibility. Two epidemiological studies have examined possible developmental effects associated with maternal urinary molybdenum levels (Shirai et al. 2010; Vazquez-Salas et al. 2014); interpretation of the results of these studies is limited. Studies in laboratory animals have not reported alterations in pup survival, body weight, occurrence of malformations, or developmental landmarks in rats orally exposed to molybdenum (Jeter and Davis 1954; Murray et al. 2014, 2019). There are limited data on the toxicity of molybdenum in children; studies are needed to evaluate whether the susceptibility of children differs from adults.

Physical and Chemical Properties. The physical-chemical properties of molybdenum are provided in Chapter 4. No data needs are identified.

Production, Import/Export, Use, Release, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The TRI is updated yearly and should provide a list of industrial production facilities and emissions.

Environmental Fate. Molybdenum is a naturally occurring trace element that can be found extensively in nature (EPA 1979). Its transport and partitioning are well understood. No data needs are identified.

Bioavailability from Environmental Media. Biologically, molybdenum plays an important role as a micronutrient in plants and animals, including humans (EPA 1979). Its bioavailability is well documented. No data needs are identified.

Food Chain Bioaccumulation. Measured BCFs of molybdenum in fish suggest that bioaccumulation in aquatic organisms is not high. No data needs are identified.

Exposure Levels in Environmental Media. Reliable monitoring data for the levels of molybdenum in contaminated media at hazardous waste sites are needed so that the information obtained on levels of molybdenum in the environment can be used in combination with the known body burden of molybdenum to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. Exposure to molybdenum to the general population is almost entirely through food. Food derived from aboveground plants, such as legumes, leafy vegetables, and cauliflower generally has a relatively higher concentration of molybdenum in comparison to food from tubers or animals. Beans, cereal grains, leafy vegetables, legumes, liver, and milk are reported as the richest sources of molybdenum in the average diet. Nutritional supplements are also a source of dietary exposure. Drinking water coming from sources close to areas with high molybdenum contamination from industrial effluents may contain a higher concentration of molybdenum. Exposure to molybdenum in an industrial setting such as mining can be significant (Barceloux 1999; EPA 1979; Momcilovic 1999; NAS 2001).

This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. There are limited data on estimates of molybdenum exposure in children. Milk is reported to be the primary source of dietary molybdenum intake among children in the United States (Biego et al. 1998; EPA 1979); however, this is based on older data. More recent monitoring data would be valuable in assessing whether molybdenum exposure sources vary between children and adults.

6.3 ONGOING STUDIES

No ongoing studies on the toxicity of molybdenum or its toxicokinetic properties were identified in the National Institute of Health (NIH) RePORTER (2019) database.

CHAPTER 7. REGULATIONS AND GUIDELINES

Pertinent international and national regulations, advisories, and guidelines regarding molybdenum in air, water, and other media are summarized in Table 7-1. This table is not an exhaustive list, and current regulations should be verified by the appropriate regulatory agency.

ATSDR develops MRLs, which are substance-specific guidelines intended to serve as screening levels by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites. See Section 1.3 and Appendix A for detailed information on the MRLs for molybdenum.

Table 7-1. Regulations and Guidelines Applicable to Molybdenum

Agency	Description	Information	Reference
	Air		
EPA	RfC	No data	IRIS 2003
WHO	Air quality guidelines	Not listed	WHO 2010
	Water & Food		
EPA	Drinking water standards and health advisories for molybdenum		EPA 2018a
	1-Day health advisory (10-kg child)	0.08 mg/L	
	10-Day health advisory (10-kg child)	0.08 mg/L	
	DWEL	0.2 mg/L	
	Lifetime health advisory	0.04 mg/L	
	National primary drinking water regulations	Not listed	EPA 2009b
	RfD (molybdenum)	$5x10^{-3}$ mg/kg/day[a]	IRIS 2003
WHO	Drinking water quality guidelines	Not established[b]	WHO 2017
FDA	Substances added to food	Not listed[c]	FDA 2018
USNRC	Annual limit on intake, oral ingestion		NRC 2018
	^{99}Molybdenum compounds except oxides, hydroxides, and molybdenum disulfide	$2x10^{3}$ µCi	
	Cancer		
HHS	Carcinogenicity classification	No data	NTP 2016
EPA	Carcinogenicity classification	No data	IRIS 2003
IARC	Carcinogenicity classification		IARC 2018
	Molybdenum trioxide	Group 2B[d]	
	Occupational		
OSHA	PEL (8-hour TWA) for general industry, shipyards and construction (molybdenum, as molybdenum)		OSHA 2018a, 2018b, 2018c
	Soluble compounds	5 mg/m^3	
	Insoluble compounds, total dust	15 mg/m^3	

Table 7-1. Regulations and Guidelines Applicable to Molybdenum

Agency	Description	Information	Reference
NIOSH	REL (up to 10-hour TWA)	Not established[e]	NIOSH 2016a, 2016b
	IDLH (molybdenum, as molybdenum)		
	Soluble compounds	1,000 mg Mo/m^3	NIOSH 1994a
	Insoluble compounds	5,000 mg Mo/m^3	NIOSH 1994b
USNRC	Annual limit on intake, inhalation		NRC 2018
	^{99}Molybdenum compounds except oxides, hydroxides, and molybdenum disulfide	3x10^3 µCi	
	Derived air concentration		
	^{99}Molybdenum compounds except oxides, hydroxides, and molybdenum disulfide	1x10^{-6} µCi/mL	
	Emergency Criteria		
EPA	AEGLs-air	No data	EPA 2016
DOE	PACs-air		DOE 2018b
	PAC-1[f]		
	Molybdenum	30 mg/m^3	
	Ammonium heptamolybdate	2.6 mg/m^3	
	Ammonium molibdate	3.5 mg/m^3	
	Ammonium molybdate(VI) tetrahydrate	2.8 mg/m^3	
	Diammonium dimolybdate	2.6 mg/m^3	
	Diammonium molybdate	3.1 mg/m^3	
	Disodium molybdate	3.2 mg/m^3	
	Molybdenum carbide	34 mg/m^3	
	Molybdenum dioxide	40 mg/m^3	
	Molybdenum hexacarbonyl	83 mg/m^3	
	Molybdenum pentachloride	4.3 mg/m^3	
	Molybdenum trioxide	2.3 mg/m^3	
	Molybdenum(IV) sulfide	50 mg/m^3	
	Sodium molybdate dihydrate	3.8 mg/m^3	
	PAC-2[f]		
	Molybdenum	330 mg/m^3	
	Ammonium heptamolybdate	230 mg/m^3	
	Ammonium molibdate	290 mg/m^3	
	Ammonium molybdate(VI) tetrahydrate	30 mg/m^3	
	Diammonium dimolybdate	29 mg/m^3	
	Diammonium molybdate	22 mg/m^3	
	Disodium molybdate	17 mg/m^3	
	Molybdenum carbide	360 mg/m^3	
	Molybdenum dioxide	430 mg/m^3	
	Molybdenum hexacarbonyl	920 mg/m^3	
	Molybdenum pentachloride	410 mg/m^3	
	Molybdenum trioxide	43 mg/m^3	

Table 7-1. Regulations and Guidelines Applicable to Molybdenum

Agency	Description	Information	Reference
	Molybdenum(IV) sulfide	260 mg/m^3	
	Sodium molybdate dihydrate	34 mg/m^3	
	PAC-3[f]		
	Molybdenum	2,000 mg/m^3	
	Ammonium heptamolybdate	1,400 mg/m^3	
	Ammonium molibdate	1,700 mg/m^3	
	Ammonium molybdate(VI) tetrahydrate	180 mg/m^3	
	Diammonium dimolybdate	170 mg/m^3	
	Diammonium molybdate	130 mg/m^3	
	Disodium molybdate	100 mg/m^3	
	Molybdenum carbide	2,200 mg/m^3	
	Molybdenum dioxide	2,600 mg/m^3	
	Molybdenum hexacarbonyl	5,500 mg/m^3	
	Molybdenum pentachloride	2,400 mg/m^3	
	Molybdenum trioxide	260 mg/m^3	
	Molybdenum(IV) sulfide	1,600 mg/m^3	
	Sodium molybdate dihydrate	210 mg/m^3	

[a]The RfD is based on a LOAEL of 0.14 mg/kg/day for increased uric acid levels in humans (Koval'skiy et al. 1961).
[b]Reason for not establishing guideline value: occurs in drinking water at concentrations well below those of health concern.
[c]The Substances Added to Food inventory replaces EAFUS and contains the following types of ingredients: food and color additives listed in FDA regulations, flavoring substances evaluated by FEMA or JECFA, GRAS substances listed in FDA regulations, substances approved for specific uses in food prior to September 6, 1958, substances that are listed in FDA regulations as prohibited in food, delisted color additives, and some substances "no longer FEMA GRAS."
[d]Group 2B: possibly carcinogenic to humans.
[e]In 1988, NIOSH provided comments to OSHA in which NIOSH questioned whether proposed PELs for particular substances, including the TWA 5 mg/m^3 PEL for molybdenum (soluble compounds as molybdenum), were adequate to protect workers from recognized health hazards. At that time, NIOSH also concluded that the documentation cited by OSHA was inadequate to support a proposed PEL of 10 mg/m^3 for particular substances including molybdenum (insoluble compounds as molybdenum) (NIOSH 2018).
[f]Definitions of PAC terminology are available from U.S. Department of Energy (DOE 2018a).

AEGL = acute exposure guideline level; DOE = Department of Energy; DWEL = drinking water equivalent level; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; FEMA = Flavor and Extract Manufacturers Association; GRAS = generally recognized as safe; HHS = Department of Health and Human Services; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; JECFA = Joint FAO/WHO Expert Committee on Food Additives; LOAEL = lowest-observed-adverse-effect level; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = protective action criteria; PEL = permissible exposure limit; REL = recommended exposure limit; RfD = oral reference dose; TWA = time-weighted average; USNRC = U.S. Nuclear Regulatory Commission; WHO = World Health Organization

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APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified route and duration of exposure. MRLs are based on noncancer health effects only; cancer effects are not considered. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the NOAEL/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (≥365 days) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive substance-induced endpoint considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

APPENDIX A

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Human Health Sciences, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published MRLs. For additional information regarding MRLs, please contact the Division of Toxicology and Human Health Sciences, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S102-1, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Molybdenum
CAS Numbers: 7439-98-7
Date: May 2020
Profile Status: Final
Route: Inhalation
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration inhalation MRL for molybdenum due to the limited number of endpoints examined in the only available animal studies.

Rationale for Not Deriving an MRL: The database on the acute inhalation toxicity of molybdenum is limited to several 4-hour studies in rats exposed to ammonium dimolybdate (Jackson et al. 1991a), molybdenum trioxide (Jackson et al. 1991b, 1991d; Leuschner 2010), or sodium molybdate (Jackson et al. 1991c) and a 14-day study in rats and mice exposed to molybdenum trioxide (NTP 1997). No effects on lethality or the respiratory tract (most only examined the lungs) were observed at concentrations of 1,200 mg molybdenum/m^3 and higher (Jackson et al. 1991a, 1991b, 1991c, 1991d; Leuschner 2010); several of the studies reported decreases in body weight on days 2–3 post-exposure (Jackson et al. 1991b, 1991c, 1991d). The NTP (1997) study evaluated the effect of molybdenum trioxide on the nasal cavity and on body weight in rats and mice exposed 6 hours/day, 5 days/week for 14 days. No adverse effects were observed in the nasal cavity. However, weight loss was observed at the highest concentration tested (200 mg molybdenum/m^3); decreases in body weight gain were observed in male rats exposed to 67 mg molybdenum/m^3 and in female rats and mice exposed to 200 mg/m^3. Given the limited number of endpoints examined, the decrease in body weight gain was not considered a suitable basis for an acute-duration inhalation MRL because the database is inadequate for identifying the critical target of molybdenum toxicity following acute-duration inhalation exposure.

Agency Contacts (Chemical Managers): G. Daniel Todd

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Molybdenum
CAS Numbers: 7439-98-7
Date: May 2020
Profile Status: Final
Route: Inhalation
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration inhalation MRL for molybdenum due to the lack of studies identifying a critical target of toxicity.

Rationale for Not Deriving an MRL: Information on the intermediate-duration toxicity of molybdenum is limited to 90-day studies of molybdenum trioxide in rats and mice conducted by NTP (1997) that examined a wide range of potential targets, including reproductive endpoints. No toxicologically significant alterations were observed at concentrations of molybdenum trioxide as high as 67 mg/m^3. Consistent with ATSDR's practice of not using free-standing NOAELs as a POD, an intermediate-duration inhalation MRL was not derived.

Agency Contacts (Chemical Managers): G. Daniel Todd

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Molybdenum trioxide
CAS Numbers: 1313-27-5
Date: May 2020
Profile Status: Final
Route: Inhalation
Duration: Chronic
MRL 0.002 mg molybdenum/m^3
Critical Effect: Respiratory effect, squamous metaplasia of the epiglottis in female rats
Reference: NTP 1997
Point of Departure: $BMCL_{10}$ of 1.60 mg molybdenum/m^3 ($BMCL_{HEC}$ of 0.071 mg Mo/m^3)
Uncertainty Factor: 30
LSE Graph Key: 11
Species: Rat

MRL Summary: A chronic-duration inhalation MRL of 0.002 mg molybdenum/m^3 was derived for molybdenum trioxide based on an increased incidence of squamous metaplasia of the epiglottis in female rats exposed to 6.7 mg molybdenum/m^3 as molybdenum trioxide 6 hours/day, 5 days/week for 2 years (NTP 1997). The MRL is based on a $BMCL_{10}$ of 1.60 mg molybdenum/m^3 (human equivalent concentration [HEC] of 0.071 mg molybdenum/m^3) and a total uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustments and 10 for human variability).

Selection of the Critical Effect: There are limited data on the toxicity of inhaled molybdenum in humans. A study of workers at a molybdenite roasting facility exposed to molybdenum trioxide and other oxides found no alterations in lung function but did find increases in serum uric acid levels (Walravens et al. 1979); the TWA molybdenum concentration was 9.46 mg molybdenum/m^3. Another study of workers exposed to ultrafine molybdenum trioxide dust reported respiratory symptoms (dyspnea and cough), radiographic abnormalities, and impaired lung function (Ott et al. 2004); the study did not provide monitoring data. Confidence in these cohort studies was considered very low (see Appendix C for additional information).

Data on the chronic toxicity of molybdenum in laboratory animals is limited to 2-year studies in rats and mice exposed to molybdenum trioxide (NTP 1997). In these studies, NTP (1997) examined a wide range of potential targets of toxicity. Adverse effects were limited to the respiratory tract, specifically the nasal respiratory and olfactory epithelium, epiglottis, and lungs. The respiratory tract was considered the critical target of molybdenum trioxide toxicity.

Selection of the Principal Study: The NTP (1997) study was selected as the principal study.

Summary of the Principal Study:

NTP. 1997. Toxicology and carcinogenicity studies of molybdenum trioxide (CAS No. 1313-27-5) in F344/N rats and B6C3F1 mice (inhalation studies). National Toxicology Program, Research Triangle Park, NC. NT PTR 462.

Groups of male and female F344/N rats and B6C3F1 mice (50/sex/species/group) were exposed to target concentrations of 0, 10, 30, or 100 mg/m^3 molybdenum trioxide (0, 6.7, 20, and 67 mg molybdenum/m^3) 6 hours/day, 5 days/week for 106 (rats) or 105 (mice) weeks; actual concentrations were within 15% of the target level. The average mass median aerodynamic diameter particle sizes (and geometric standard deviation, σ_g) were 1.5 (1.8), 1.6 (1.8), and 1.7 (1.8) μm for the 6.7, 20, and 67 mg/m^3 concentrations,

respectively. The following parameters were used to assess toxicity: twice daily cage-side observations, body weights (weekly for 12 weeks, at 15 weeks, monthly thereafter, and at termination), and histopathological examination of major tissues and organs. In addition, bone density and femoral curvature studies were conducted in 10 animals/sex/species/group.

No significant alterations in survival rates or body weight gain and no toxicologically significant alterations in bone density or curvature were found. Non-neoplastic lesions were only observed in the nose, larynx, and lungs; a summary of the type of lesions and incidences is presented in Table A-1. The severity of the respiratory lesions was concentration related. Significant increases in the incidence of alveolar/bronchiolar carcinoma and/or adenoma were observed in mice: carcinoma in male mice at ≥6.7 mg/m^3, adenoma or carcinoma (combined) in male mice at 6.7 and 20 mg/m^3, adenoma in female mice at ≥20 and 67 mg/m^3, and adenoma or carcinoma (combined) in female mice at 67 mg/m^3. In rats, the incidence of alveolar/bronchiolar adenoma or carcinoma (combined) was increased in males; however, the incidences (0/50, 1/49, 1/49, 4/60) were within the range of historical controls and NTP considered this to be equivocal evidence of carcinogenic activity.

Table A-1. Incidence of Non-Neoplastic Respiratory Tract Lesions in Rats and Mice Exposed to Molybdenum Trioxide for 2 Years

	Concentration (mg molybdenum/m^3)			
	0	6.7	20	67
Male rats				
Hyaline degeneration of nasal respiratory epithelium	2/50	7/49	48/49[a]	49/50[a]
Squamous metaplasia of epiglottis	0/49	11/48[a]	16/49[a]	39/49[a]
Chronic lung inflammation in alveolus	2/50	3/50	25/50[a]	47/50[a]
Female rats				
Hyaline degeneration of nasal respiratory epithelium	1/48	13/49[a]	50/50[a]	50/50[a]
Hyaline degeneration of nasal olfactory epithelium	39/48	47/49[b]	50/50[a]	50/50[a]
Squamous metaplasia of epiglottis	0/49	18/49[a]	29/49[a]	49/50[a]
Chronic lung inflammation	14/50	13/50	43/50[a]	49/50[a]
Male mice				
Nasal suppurative inflammation	2/50	6/50	10/49[b]	8/50[b]
Nasal olfactory epithelium atrophy	3/50	5/50	3/49	10/50[b]
Hyaline degeneration of nasal respiratory epithelium	11/50	13/50	11/49	41/50[a]
Squamous metaplasia of epiglottis	0/50	26/49[a]	37/48[a]	49/50[a]
Laryngeal hyperplasia	1/50	3/49	6/48	41/50
Histiocyte infiltration in the lungs	2/50	16/50[a]	9/49[b]	9/50[b]
Alveolar epithelial metaplasia	0/50	32/50[a]	36/49[a]	49/50[a]
Female mice				
Hyaline degeneration of nasal respiratory epithelium	26/49	23/50	28/49	48/49[a]
Hyaline degeneration of nasal olfactory epithelium	22/49	14/50	14/49	36/49[a]

Table A-1. Incidence of Non-Neoplastic Respiratory Tract Lesions in Rats and Mice Exposed to Molybdenum Trioxide for 2 Years

	Concentration (mg molybdenum/m^3)			
	0	6.7	20	67
Squamous metaplasia of epiglottis	1/49	36/50[a]	43/49[a]	49/50[a]
Laryngeal hyperplasia	1/49	1/50	7/49	35/50
Alveolar epithelial metaplasia	2/50	26/50[a]	39/49[a]	46/49[b]

[a]Significantly different from controls; p≤0.01.
[b]Significantly different from controls; p≤0.05.

Source: NTP 1997

Selection of the Point of Departure for the MRL: The MRL was based on a $BMCL_{10}$ of 1.60 mg molybdenum/m^3 for squamous metaplasia of the epiglottis in female rats.

Benchmark dose (BMD) modeling was conducted for the respiratory tract lesions with statistically significant increases in incidence at ≥6.7 mg/m^3 (squamous metaplasia of the epiglottis in male and female rats and mice, hyaline degeneration of the nasal respiratory and olfactory epithelium in female rats, histiocyte infiltration in the lungs in male mice, and alveolar epithelial metaplasia in male and female mice). The incidence data (Table A-1) provided adequate fit for four endpoints (squamous metaplasia in male rats, female rats, and female mice and hyaline degeneration of the nasal respiratory epithelium in female rats). The results of the BMD modeling are presented in the Benchmark Dose Modeling subsection and are summarized in Table A-2.

Table A-2. Summary of Benchmark Dose Modeling

Endpoint	Selected model	BMC_{10} (mg Mo/m^3)	$BMCL_{10}$ (mg Mo/m^3)
Squamous metaplasia of the epiglottis in male rats	Multistage, 2-degree (Table A-4 and Figure A-1)	4.36	3.53
Hyaline degeneration of the respiratory epithelium in female rats	Log-logistic (Table A-5 and Figure A-2)	5.87	4.82
Squamous metaplasia of the epiglottis in female rats	Weibull (Table A-6 and Figure A-3)	1.97	1.60
Squamous metaplasia of the epiglottis in male mice	Gamma (Table A-7 and Figure A-4)	1.30	1.06

BMC = benchmark concentration; BMCL = 95% lower confidence limit on the benchmark concentration

A summary of the potential POD values is presented in Table A-3. Because there are dosimetric differences in regional respiratory tract deposition of aerosols between animal species, a comparison was made between the human equivalent concentration PODs (POD_{HEC}). The lowest POD_{HEC}, $BMCL_{HEC}$ of 0.071 mg molybdenum/m^3 for squamous metaplasia of the epiglottis in female rats, was selected as the POD for the MRL.

Table A-3. Summary of PODs and HECs

Endpoint	PODs (mg Mo/m^3)	RDDR values[a]	HECs[b] (mg Mo/m^3)
Squamous metaplasia of the epiglottis in male rats	3.53 (BMCL)	0.459	0.28
Hyaline degeneration of the respiratory epithelium in female rats	4.82 (BMCL)	0.248	0.21
Hyaline degeneration of the olfactory epithelium in female rats	6.7 (LOAEL)	0.248	0.30
Squamous metaplasia of the epiglottis in female rats	1.60 (BMCL)	0.248	0.071
Squamous metaplasia of the epiglottis in male mice	1.06 (BMCL)	0.441	0.08
Histiocyte infiltration in the lungs of male mice	6.7 (LOAEL)	1.046	1.3
Alveolar epithelial metaplasia in male mice	6.7 (LOAEL)	1.046	1.3
Squamous metaplasia of the epiglottis in female mice	6.7 (LOAEL)	0.367	0.44
Alveolar epithelial metaplasia in female mice	6.7 (LOAEL)	3.067	3.7

[a]RDDR values specific for each region of the respiratory tract (extrathoracic, tracheobronchial, and pulmonary) were calculated using EPA's RDDR calculator with reference body weights of 0.40, 0.25, 0.040, and 0.035 kg for male rats, female rats, male mice, and female mice, respectively, and reported particle sizes and particle size distributions.
[b]HEC calculated by multiplying the duration-adjusted POD (POD x 6 hours/24 hours x 5 days/7days) by the RDDR value.

BMCL = 95% lower confidence limit on the benchmark concentration; HEC = human equivalent concentration; LOAEL = lowest observed adverse effect level; POD = point of departure; RDDR = regional deposited dose ratio for the specific region of the respiratory tract

Adjustment for Intermittent Exposure: The PODs were adjusted for intermittent exposure (6 hours/day, 5 days/week).

Calculation of Human Equivalent Concentration: HECs were calculated for each potential POD by multiplying the duration-adjusted POD by the regional deposited dose ratio (RDDR) for the specific region of the respiratory tract. The RDDR is a factor used to adjust particulate exposure concentration in animals to a predicted concentration in humans that would be associated with the same dose delivered to a specific region of the respiratory tract or to the blood (EPA 1994). The RDDRs were calculated using EPA's RDDR calculator with reference body weights of 0.40, 0.25, 0.040, and 0.035 kg for the male rats, female rats, male mice, and female mice, respectively, the reported particle sizes, and particle size distributions. The particles were assumed to be monodispersed given that the σ_g was 1.8.

Uncertainty Factor: The $BMCL_{HEC}$ is divided by a total uncertainty factor (UF) of 30.

- 3 for extrapolation from animals to humans with dosimetric adjustments
- 10 for human variability

$$BMCL_{HEC} \div UFs = MRL$$
$$0.071 \text{ mg molybdenum/m}^3 \div 30 = 0.002 \text{ mg molybdenum/m}^3$$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: This MRL is specific to molybdenum trioxide; there are insufficient data to evaluate the health effects associated with inhalation exposure to other molybdenum compounds.

Benchmark Dose Modeling: The incidence data (Table A-1) for respiratory tract lesions, which had significant increases in incidence at ≥6.7 mg/m^3 (squamous metaplasia of the epiglottis in male and

female rats and mice, hyaline degeneration of the nasal respiratory and olfactory epithelium in female rats, histiocyte infiltration in the lungs in male mice, and alveolar epithelial metaplasia in male and female mice), were fit to all available dichotomous models in EPA's Benchmark Dose Software (BMDS, version 3.1) using the extra risk option. Adequate model fit was judged by three criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined benchmark response (BMR). Among all of the models providing adequate fit to the data, the lowest BMCL was selected as the POD when the difference between the BMCLs estimated from these models was >3-fold; otherwise, the BMCL from the model with the lowest Akaike's Information Criterion (AIC) was chosen. For all lesion types, a BMR of 10% was used. Since the incidence of hyaline degeneration in the olfactory epithelium of female rats was essentially the same response level across groups, the data were not modeled since they provide limited information on the dose-response relationship. The incidence data for histiocyte infiltration in the lungs in male mice, alveolar epithelial metaplasia in male mice, squamous metaplasia in female mice, and alveolar epithelial metaplasia in female mice did not fit any of the available dichotomous models. The model predictions for the other endpoints are presented in Tables A-4, A-5, A-6, and A-7 and the fits of the selected models are presented in Figures A-1, A-2, A-3, and A-4.

Table A-4. Model Predictions for Squamous Metaplasia of the Epiglottis in Male Rats Exposed to Molybdenum Trioxide (NTP 1997)

Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Scaled residuals[b]: Dose below BMC	Scaled residuals[b]: Dose above BMC	Scaled residuals[b]: Overall largest	AIC	BMC_{10} (mg/m^3)	$BMCL_{10}$ (mg/m^3)
Gamma[c]	2	3.07	0.22	0.00	1.55	1.55	169.98	4.36	3.53
Logistic	2	9.45	0.01	1.50	0.93	-2.47	181.70	ND	ND
LogLogistic[d]	2	3.56	0.17	0.00	0.98	-1.42	170.75	3.80	2.23
LogProbit[d]	2	3.74	0.15	-0.00	0.93	-1.51	170.95	ND	ND
Multistage (1-degree)[e]	3	3.07	0.38	0.00	1.55	1.55	167.98	4.36	3.53
Multistage (2-degree)[e,f]	***3***	***3.07***	***0.38***	***0.00***	***1.55***	***1.55***	***167.98***	***4.36***	***3.53***
Multistage (3-degree)[e]	3	3.07	0.38	0.00	1.55	1.55	167.98	4.36	3.53
Probit	2	9.17	0.01	1.60	0.90	-2.37	181.01	ND	ND
Weibull[c]	2	3.07	0.22	0.00	1.55	1.55	169.98	4.36	3.53

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMC; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Betas restricted to ≥0.
[f]Selected model. BMCLs for models providing adequate fit were sufficiently close (differed by <3-fold). Therefore, the model with the lowest AIC was selected.

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); DF = degrees of freedom; ND = not determined, goodness-of-fit criteria, p<0.10

Figure A-1. Fit of 2-Degree Multistage Model to Data on Incidence of Squamous Metaplasia of the Epiglottis in Male Rats Exposed to Molybdenum Trioxide

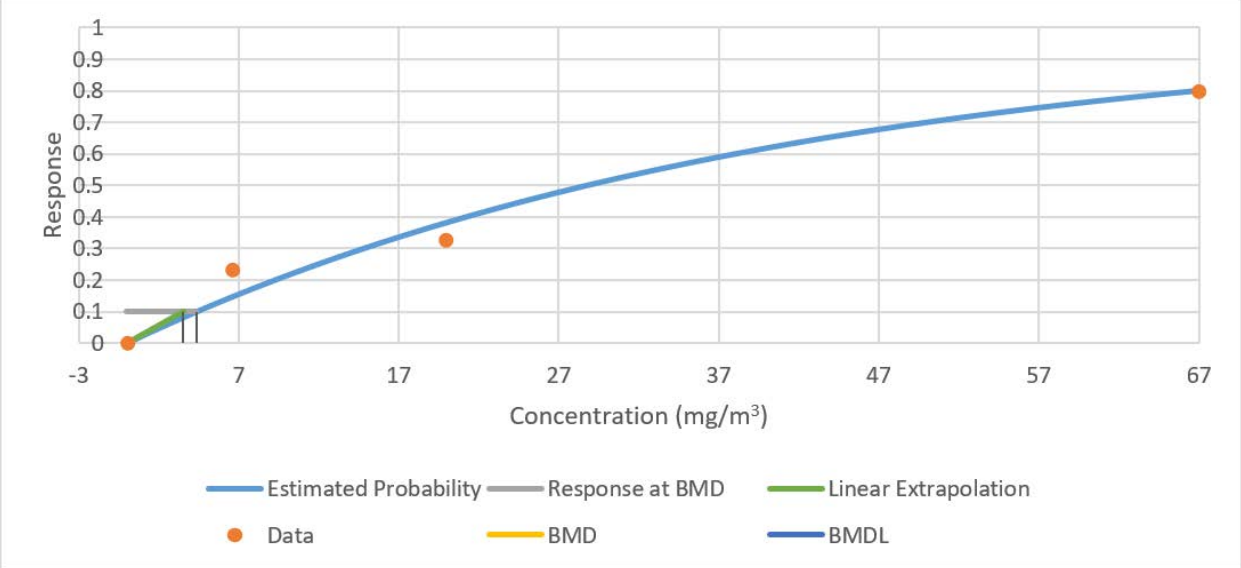


Table A-5. Model Predictions for Hyaline Degeneration of the Nasal Respiratory Epithelium in Female Rats Exposed to Molybdenum Trioxide (NTP 1997)

Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Scaled residuals[b] Dose below BMC	Dose above BMC	Overall largest	AIC	BMC_{10} (mg/m³)	$BMCL_{10}$ (mg/m³)
Gamma[c]	2	4.41	0.11	0.14	-1.03	1.82	77.98	3.69	2.85
Logistic	3	5.04	0.17	-1.20	-0.37	1.86	77.15	3.78	2.95
LogLogistic[d,e]	***2***	***0.02***	***0.99***	***0.00***	***-0.00***	***0.13***	***70.45***	***5.87***	***4.82***
LogProbit[d]	1	0.00	0.99	-0.00	-0.00	-0.00	72.42	5.92	4.73
Multistage (1-degree)[f]	2	18.41	0.00	0.28	-3.28	-3.28	95.80	ND	ND
Multistage (2-degree)[f]	2	2.81	0.24	0.20	-1.21	-1.21	74.57	3.40	2.54
Multistage (3-degree)[f]	2	0.02	0.99	0.01	-0.05	0.15	70.46	4.77	2.39
Probit	2	0.48	0.79	0.49	-0.28	0.49	71.03	4.09	3.12

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMC; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Selected model. BMCLs for models providing adequate fit were sufficiently close (differed by <3-fold). Therefore, the model with the lowest AIC was selected.
[f]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); DF = degrees of freedom; ND = not determined, goodness-of-fit criteria, p<0.10

Figure A-2. Fit of Log-logistic Model to Data on Incidence of Hyaline Degeneration of the Nasal Respiratory Epithelium in Female Rats Exposed to Molybdenum Trioxide

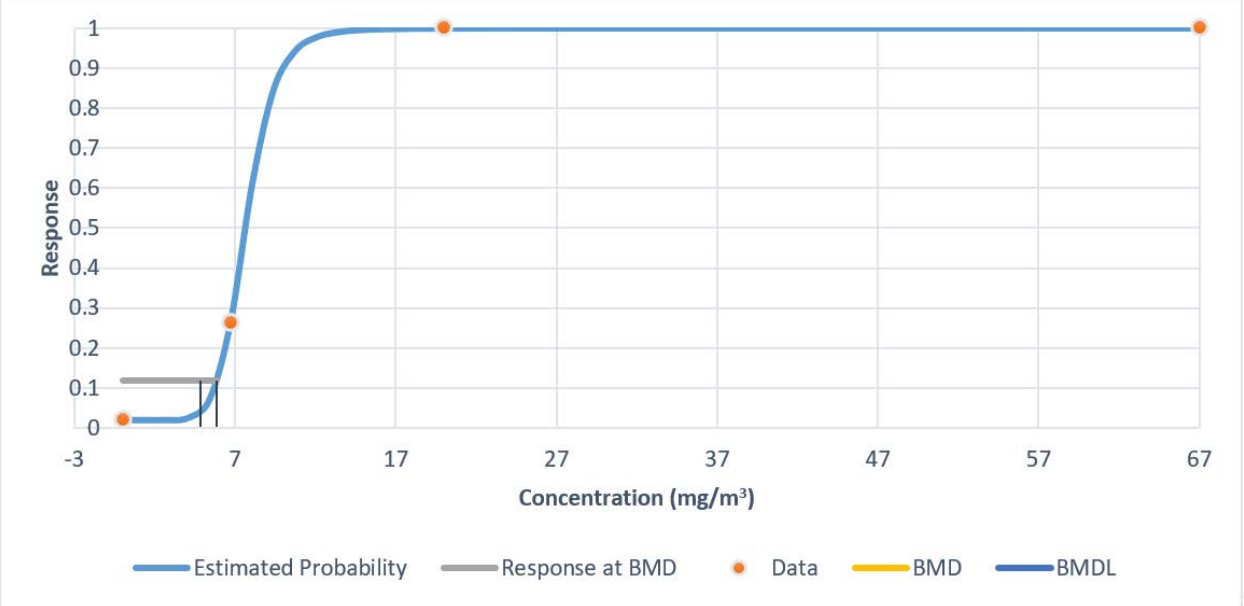


Table A-6. Model Predictions for Squamous Metaplasia of the Epiglottis in Female Rats Exposed to Molybdenum Trioxide (NTP 1997)

Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Scaled residuals[b] Dose below BMC	Scaled residuals[b] Dose above BMC	Scaled residuals[b] Overall largest	AIC	BMC_{10} (mg/m^3)	$BMCL_{10}$ (mg/m^3)
Gamma[c]	2	2.05	0.36	0.00	1.00	1.00	146.51	1.97	1.60
Logistic	2	15.55	0.00	-2.67	2.17	-2.67	163.85	ND	ND
LogLogistic[d]	1	5.02	0.03	-0.00	0.82	-1.58	152.04	ND	ND
LogProbit[e]	2	4.16	0.12	-0.00	0.79	-1.51	148.92	2.76	1.41
Multistage (1-degree)[e]	3	2.05	0.56	-0.00	1.00	1.00	144.51	1.97	1.60
Multistage (2-degree)[e]	1	2.05	0.15	-0.00	1.04	1.04	148.50	1.99	1.60
Multistage (3-degree)[e]	1	1.98	0.16	-0.00	1.11	1.11	148.42	2.02	1.61
Probit	2	17.51	0.00	-2.85	2.00	-2.13	166.05	ND	ND
Weibull[f]	***3***	***2.05***	***0.56***	***-0.00***	***1.00***	***1.00***	***144.51***	***1.97***	***1.60***

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMC; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Betas restricted to ≥0.
[f]Selected model. BMCLs for models providing adequate fit were sufficiently close (differed by <3-fold). Therefore, the model with the lowest AIC was selected.

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); DF = degrees of freedom; ND = not determined, goodness-of-fit criteria, p<0.10

Figure A-3. Fit of Weibull Model to Data on Incidence of Squamous Metaplasia of the Epiglottis in Female Rats Exposed to Molybdenum Trioxide

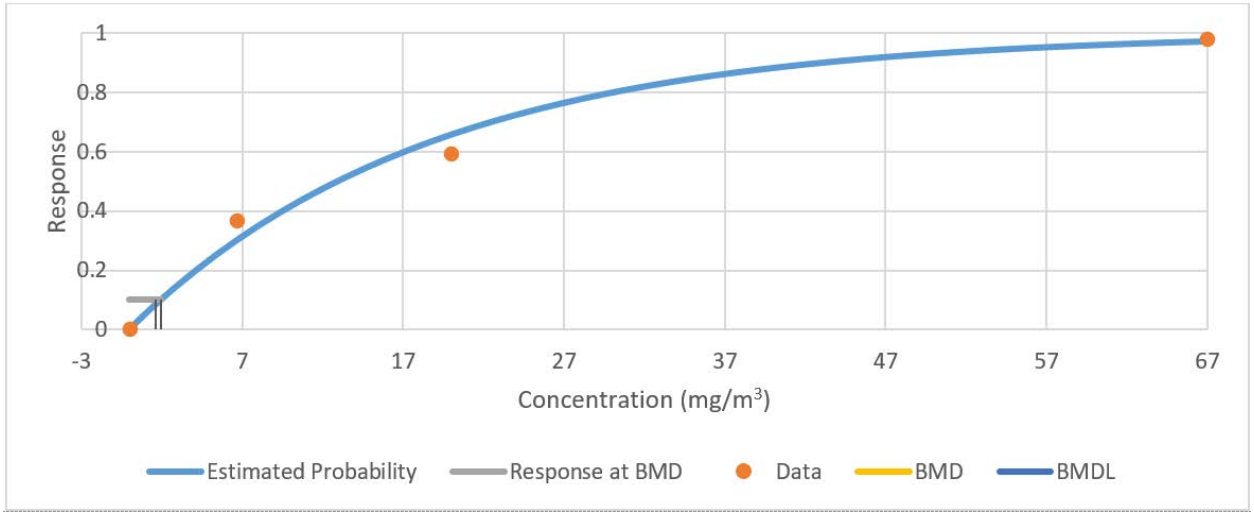


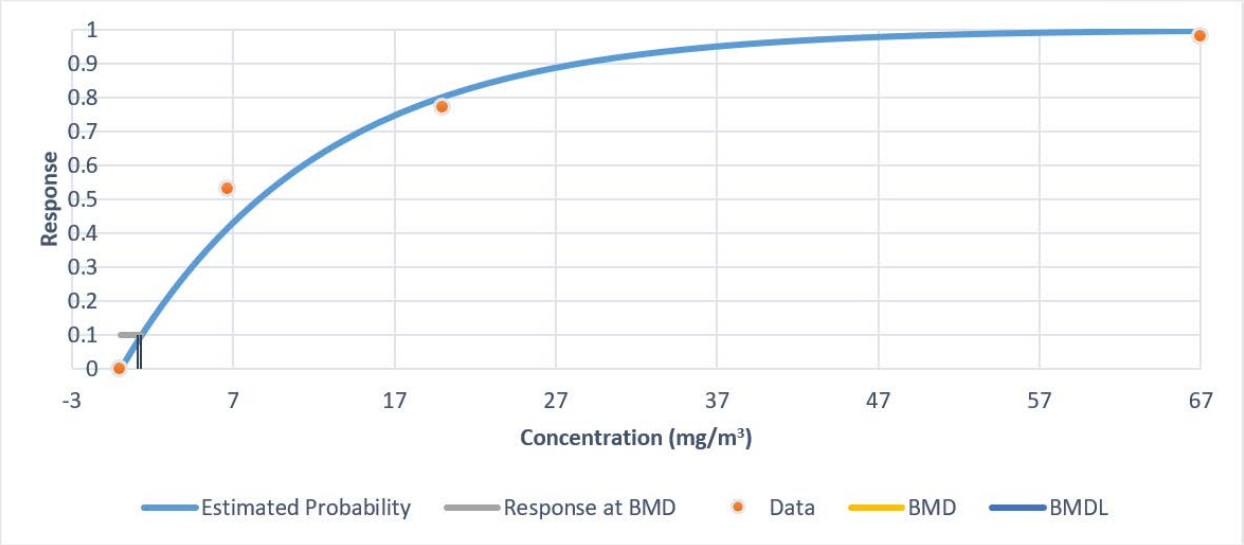
Table A-7. Model Predictions for Squamous Metaplasia of the Epiglottis in Male Mice Exposed to Molybdenum Trioxide (NTP 1997)

Model	DF	χ^2	χ^2 Goodness of fit p-value[a]	Scaled residuals[b] Dose below BMC	Dose above BMC	Overall largest	AIC	BMC_{10} (mg/m^3)	$BMCL_{10}$ (mg/m^3)
Gamma[c,d]	***3***	***5.55***	***0.14***	***-0.00***	***1.60***	***-1.65***	***135.46***	***1.30***	***1.06***
Logistic	2	61.77	0.00	-3.19	2.80	-6.62	164.85	ND-1	ND-1
LogLogistic[e]	1	1.42	0.23	-0.00	0.34	-0.85	134.73	ND-2	ND-2
LogProbit[d]	1	0.88	0.35	-0.00	0.31	-0.70	136.12	ND-2	ND-2
Multistage (1-degree)[f]	2	5.55	0.06	-0.00	1.60	-1.65	137.46	ND-1	ND-1
Multistage (2-degree)[f]	3	5.55	0.14	-0.00	1.60	-1.65	135.46	1.30	1.06
Multistage (3-degree)[f]	3	5.55	0.14	-0.00	1.60	-1.65	135.46	1.30	1.06
Probit	2	90.03	0.00	-3.63	2.65	-8.24	171.89	ND-1	ND-1
Weibull[c]	3	5.55	0.14	-0.00	1.60	-1.65	135.46	1.30	1.06

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMC; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Selected model. BMCLs for models providing adequate fit were sufficiently close (differed by <3-fold). Therefore, the model with the lowest AIC was selected.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); DF = degrees of freedom; ND-1 = not determined, goodness-of-fit criteria, p<0.10; ND-2 = not determined, BMCL was 10 times lower than lowest non-zero dose

Figure A-4. Fit of Gamma Model to Data on Incidence of Squamous Metaplasia of the Epiglottis in Male Mice Exposed to Molybdenum Trioxide



Agency Contacts (Chemical Managers): G. Daniel Todd

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Molybdenum
CAS Numbers: 7439-98-7
Date: May 2020
Profile Status: Final
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration oral MRL for molybdenum due inadequate information on the molybdenum and copper intake in the acute-duration studies reporting adverse reproductive effects and the conflicting results between the acute-duration studies and high-quality, intermediate-duration studies.

Rationale for Not Deriving an MRL: A small number of studies have evaluated the acute toxicity of molybdenum. One human study (Deosthale and Gopalan 1974) examining a limited number of potential endpoints did not find alterations in urinary uric acid levels in subjects exposed to doses as high as 0.022 mg molybdenum/kg/day for 10 days. In rabbits, exposure to 1.2 mg molybdenum/kg/day as ammonium heptamolybdate in the diet for 14 days resulted in a 60% increase in serum triglyceride levels (Bersenyi et al. 2008); no histological alterations were observed in the liver or kidneys. The toxicological significance of this finding is not known and has not been reported in a study of male rabbits exposed to 0.58 mg molybdenum/kg/day as ammonium heptamolybdate (Bersenyi et al. 2008) or rats exposed to 60 mg molybdenum/kg/day as sodium molybdate for 90 days (Murray et al. 2014a).

Reproductive effects have been observed in male and female mice and rabbits. In female mice, an increased rate of abnormal MII oocytes was observed at 11 mg molybdenum/kg/day (Zhang et al. 2013). A second acute-exposure study in rabbits exposed to 1.2 mg molybdenum/kg/day as ammonium heptamolybdate for 14 days (Bersenyi et al. 2008) and an intermediate-duration oral study in rats exposed to 60 mg molybdenum/kg/day as sodium molybdate for 90 days (Murray et al. 2014a) did not find histological alterations in the ovaries. In males, a significant decrease in sperm concentration and motility and an increase in sperm abnormalities were observed at 25 mg molybdenum/kg/day in mice (Zhai et al. 2013). A rabbit study reported a reduction in mature spermatocytes in rabbits exposed to 0.58 mg molybdenum/kg/day, but did not report the incidence or statistical significance (Bersenyi et al. 2008). Intermediate-duration studies in rats did not find significant alterations in sperm parameters in rats exposed to 60 mg molybdenum/kg/day as sodium molybdate for 90 days (Murray et al. 2014a) or in rats exposed to 40 mg molybdenum/kg/day as sodium molybdate in a 2-generation study (Murray et al. 2019). Interpretation of the Zhang et al. (2013) and Zhai et al. (2013) studies is limited by the lack of information on the copper content of the “commercial standard pellet” diet used in these studies and the lack of information on molybdenum doses. ATSDR estimated doses using the reported molybdenum concentration in the drinking water and reference values for water consumption and body weight (Zhang et al. 2013) or the midpoint of the reported body weights and an estimated water consumption based on this body weight (Zhai et al. 2013).

The acute-duration oral database was not considered suitable for derivation of an MRL due to the limited information on the molybdenum and copper intake and the conflicting results between the findings of the Zhang et al. (2013) and Zhai et al. (2013) studies with the intermediate-duration Murray et al. (2014a, 2019) studies.

Agency Contacts (Chemical Managers): G. Daniel Todd

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:**	Molybdenum
CAS Numbers:	7439-98-7
Date:	May 2020
Profile Status:	Final
Route:	Oral
Duration:	Intermediate
MRL	0.06 mg molybdenum/kg/day
Critical Effect:	Renal effect, proximal tubule hyperplasia
Reference:	Murray et al. 2014a
Point of Departure:	NOAEL of 17 mg molybdenum/kg/day
Uncertainty Factor:	100
Modifying Factor:	3
LSE Graph Key:	14
Species:	Rat

MRL Summary: An intermediate-duration oral MRL of 0.06 mg molybdenum/kg/day was derived for molybdenum based on an increased incidence of renal proximal tubule hyperplasia in rats exposed to sodium molybdate in the diet for 90 days (Murray et al. 2014a). The MRL is based on a NOAEL of 17 mg molybdenum/kg/day, a total uncertainty factor of 100 (10 for extrapolation from animals to humans, and 10 for human variability), and a modifying factor of 3 (to address concern that reproductive/developmental alterations may be sensitive outcomes in populations with marginal copper intakes). The MRL is calculated based on the assumption of healthy dietary levels of molybdenum and copper and represents the level of exposure above and beyond the normal diet.

Selection of the Critical Effect: Several adverse effects have been reported in intermediate-duration oral studies in laboratory animals. Observed effects include kidney damage (Bompart et al. 1990; Murray et al. 2014a, 2019), decreased body weight gain (Bompart et al. 1990; Lyubimov et al. 2004; Mills et al. 1958; Murray et al. 2014a; Van Reen and Williams 1956; Williams and Van Reen 1956), hematological effects (Arrington and Davis 1953; Lyubimov et al. 2004), reproductive effects (Fungwe et al. 1990; Jeter and Davis 1954; Lyubimov et al. 2004; Murray et al. 2014a; Pandey and Singh 2002; Wang et al. 2016), and developmental effects (Pandey and Singh 2002).

The toxicity of molybdenum can be influenced by several factors including animal species; previous dietary history; relative amounts of dietary molybdenum, copper, and sulfur; and the form of molybdenum. Copper nutritional status is particularly important in evaluating the relevance of animal toxicity studies for establishing an MRL. Marked differences in the distribution of molybdenum and copper and the toxicity of molybdenum have been observed in rats exposed to high doses of molybdenum and maintained on a copper-deficient diet compared to those maintained on a copper-adequate diet (Brinkman and Miller 1961; Johnson et al. 1969; Nederbragt 1980, 1982; Sasmal et al. 1968). Since the average copper intake of the U.S. population exceeds the dietary requirements (NAS 2001), studies in which animals were fed inadequate levels of copper were not considered relevant for MRL derivation and were excluded from further consideration. Similarly, studies in which the molybdenum was administered as ammonium tetrathiomolybdate were also excluded since administration of tetrathiomolybdate compounds can result in shifts in the copper levels in rats fed copper-adequate diets (increases in serum and kidney copper levels and decreases in liver copper levels) (Mills et al. 1981a), and copper supplementation of rats exposed to ammonium tetrathiomolybdate resulted in a reversal of adverse effects (Lyubimov et al. 2004). A summary of the NOAEL and LOAEL values for studies with adequate copper in the diet is presented in Table A-8.

Table A-8. Summary of Health Effects Following Intermediate-Duration Oral Exposure to Molybdenum

Species, duration (route)	NOAEL	LOAEL	Effect	Reference (compound)
Body weight				
Rat 147–158 days (diet)		40	22% decrease in maternal body weight gain on GDs 0–7; <10% decrease over entire study	Murray et al. 2019 (sodium molybdate)
Rat 90 days (diet)	17	60	Decrease in body weight gain in males; terminal weights 15.2% less than controls	Murray et al. 2014a (sodium molybdate)
Rat 5 weeks (diet)		74	36% decrease in body weight gain	Mills et al. 1958 (sodium molybdate)
Rat 8 weeks (gavage)	40	80	Decrease in body weight gain; terminal body weight was 26% lower than in controls	Bompart et al. 1990 (ammonium heptamolybdate)
Rat 6 weeks (diet)	85			Williams and Van Reen 1956 (sodium molybdate)
Rat 6 weeks (diet)		90	22% decrease in body weight gain	Williams and Van Reen 1956 (sodium molybdate)
Rat 4–5 weeks (diet)		110	46–48% decrease in body weight gain	Van Reen and Williams 1956 (sodium molybdate)
Rat 147–158 days (drinking water)	40			Murray et al. 2019 (sodium molybdate)
Hematological effects				
Rabbit 30–84 days (diet)	25	54	Anemia	Arrington and Davis 1953 (sodium molybdate)
Rabbit ≥8 weeks (diet)	7			Jeter and Davis 1954 (sodium molybdate)
Rat 90 days (diet)	60			Murray et al. 2014a (sodium molybdate)
Rat 6 weeks (diet)	70			Gray and Daniel 1954 (sodium molybdate)
Kidney effects				
Rat 90 days (diet)	17	60	Slight diffuse hyperplasia in proximal tubules	Murray et al. 2014a (sodium molybdate)
Rat 8 weeks (gavage)	40	80	Diuresis and creatinuria and decreases in creatinine clearance	Bompart et al. 1990 (ammonium heptamolybdate)
Rat 147–158 days (diet)	40			Murray et al. 2019 (sodium molybdate)
Rats 147–158 days (drinking water)	40			Murray et al. 2019 (sodium molybdate)

Table A-8. Summary of Health Effects Following Intermediate-Duration Oral Exposure to Molybdenum

Species, duration (route)	NOAEL	LOAEL	Effect	Reference (compound)
Reproductive effects				
Rat 8 weeks (drinking water)	0.76	1.5	Prolonged estrus phase; no effect on female fertility	Fungwe et al. 1990 (sodium molybdate)
Rat 60 days (gavage)	3.4[a]	10[a]	Decreases in sperm count and motility; increases in sperm abnormalities	Pandey and Singh 2002 (sodium molybdate)
Rat 60 days (gavage)		10[a]	Decreases in male fertility	Pandey and Singh 2002 (sodium molybdate)
Mouse 100 days (drinking water)		100	Decreased sperm density and motility	Wang et al. 2016 (unspecified molybdenum compound)
Rat 90 days (diet)	60		No treatment-related alterations in sperm parameters; no alterations in vaginal cytology, estrus cycle, or histology of male or female reproductive tissues	Murray et al. 2014a (sodium molybdate)
Rat ≥8 weeks (diet)	7		No effect on fertility	Jeter and Davis 1954 (sodium molybdate)
Rat 2 generations (diet)	40		No effects on sperm parameters, estrous cycling, or fertility	Murray et al. 2019 (sodium molybdate)
Rat 2 generations (drinking water)	40		No effects on sperm parameters, estrous cycling, or fertility	Murray et al. 2019 (sodium molybdate)
Developmental effects[b]				
Rat (males only) 60 days (gavage)		10[a]	Increased post-implantation losses, increased resorptions, decreased number of live fetuses, and decreases in fetal weight and crown-rump length	Pandey and Singh 2002 (sodium molybdate)
Rat ≥8 weeks (diet)	7			Jeter and Davis 1954 (sodium molybdate)
Rat GDs 6–20 (diet)	37.5			Murray et al. 2014b (sodium molybdate)
Rat 2 generations (diet)	40			Murray et al. 2019 (sodium molybdate)
Rat 2 generations (drinking water)	40			Murray et al. 2019 (sodium molybdate)

[a]Adjusted for intermittent exposure (5 days/week).
[b]The copper content of the basal diet (6 g/kg diet) in the Fungwe et al. (1990) study is below the recommended level of 8 g/kg required for pregnancy and lactation. Thus, the observed developmental effects are not included in this table.

GD = gestation day; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

The Fungwe et al. (1990) study identified the lowest LOAEL value: prolonged estrus phase without an effect on fertility in rats exposed to 1.5 mg molybdenum/kg/day as sodium molybdate in drinking water for 8 weeks (Fungwe et al. 1990). However, this finding was not selected as the critical effect because other high-quality studies have not reported estrus cycle alterations in a 90-day (Murray et al. 2014a) study or 2-generation study (Murray et al. 2019). Additionally, confidence in this study is decreased by the limited information on doses. The study reported molybdenum drinking water concentrations but did not calculate doses. ATSDR estimated doses using reference values for body weight and drinking water consumption. As presented in Table A-9, a comparison with the molybdenum liver concentrations in this study with levels reported in the Murray et al. (2014a, 2019) studies suggested that these estimated doses may have underestimated the actual doses. In the Fungwe et al. (1989) study, the average liver molybdenum level was 10.76 µg/g in the 15 mg/kg/day group; in the Murray et al. (2014a, 2014b) studies, the liver molybdenum level was 4.10–4.92 µg/g in the 17 mg/kg/day groups.

Table A-9. Comparison of Molybdenum Liver Concentrations in Female Rats

Study	Dose Liver molybdenum concentration				
Murray et al. 2019[a] (water exposure, unless noted)	0 mg/kg/day	5 mg/kg/day	17 mg/kg/day	40 mg/kg/day	40 mg/kg/day (dietary exposure)
	2.96 µg/g	3.18 µg/g	4.10 µg/g	6.48 µg/g	7.23 µg/g
Murray et al. 2014a[b] (dietary exposure)	0 mg/kg/day	5 mg/kg/day	17 mg/kg/day	60 mg/kg/day	
	2.46 µg/g	3.51 µg/g	4.92 µg/g	13.0 µg/g	
Fungwe et al. 1989[c] (water exposure)	0 mg/kg/day	0.76 mg/kg/day	1.5 mg/kg/day	7.6 mg/kg/day	15 mg/kg/day
	2.63 µg/g	5.01 µg/g	5.03 µg/g	7.77 µg/g	10.76 µg/g

[a]Parental generation.
[b]Liver concentrations reported in Murray et al. (2019).
[c]Liver concentrations from a study by Fungwe et al. (1990) utilizing the same water concentrations as Fungwe et al. (1989).

The next highest LOAEL is 14 mg molybdenum/kg for decreases in sperm count and motility, increased sperm abnormalities, decreased male fertility, increased post-implantation losses, decreased number of live fetuses, and decreased fetal weight in a study of male rats receiving gavage doses of sodium molybdate 5 days/week during a 60-day period (Pandey and Singh 2002). The reliability of this LOAEL is uncertain due to the lack of information on the copper content of the diet and because decreases in fertility and alterations in sperm parameters have not been observed in other high-quality studies involving exposure to 40 mg molybdenum/kg/day via the diet or drinking water in a 2-generation study (Murray et al. 2019) or 60 mg molybdenum/kg/day via the diet in a 90-day study (Murray et al. 2014a). Additionally, no developmental effects were observed in single-generation (Murray et al. 2014b) or 2-generation (Murray et al. 2019) studies in rats exposed to 37.5–40 mg/kg/day.

As with the reproductive and developmental effects, only one study reported hematological effects. Anemia was reported in rabbits exposed to 54 mg molybdenum/kg/day as sodium molybdate in the diet for 30–84 days (Arrington and Davis 1953). This is considered a low-quality study because the molybdenum was sprayed on the food pellets but there was no measurement of actual dietary

concentrations, only 2–5 animals per group were tested, and no information was provided on which hematological parameters were altered. Additionally, the diet may not have provided adequate copper levels since copper supplementation was administered to the 54 mg/kg/day group to prevent deaths in the 3/5 animals that exhibited "severe toxic symptoms" characteristic of copper deficiency.

If the reproductive, developmental, and hematological effects are excluded because they were reported in lesser-quality studies and were not confirmed in higher-quality studies, then the lowest LOAEL is 60 mg/kg/day for body weight and renal effects (Murray et al. 2014a). A 15% decrease in body weight gain was observed in male rats; no significant alterations were observed in females. Although a decrease in food consumption was also observed at this dose level, decreases in food efficiency observed at this dose suggest that the decrease in body weight was not solely related to the decreased food intake. The renal effects consisted of slight diffuse hyperplasia in the renal proximal tubules of 2/10 female rats. The investigators (Murray et al. 2014a) noted that this effect is an uncommon background finding in rats of this age and considered it to be treatment related; they also suggested that the effect may be due to the high levels of copper in the kidneys. Kidney effects (degeneration followed by regeneration) have been observed in rats exposed to high levels of copper in the diet (Haywood 1985). A second molybdenum study (Bompart et al. 1990) reported diuresis, creatinuria, decreases in creatinine clearance, and increases in daily excretion of immunoreactive kallikrein in rats administered 80 mg molybdenum/kg/day via gavage for 8 weeks. These alterations are suggestive of decreased glomerular function and distal tubule damage; the absence of changes in the brush border enzymes alanine aminopeptidase and γ-glutamyl transpeptidase suggests no damage to the proximal tubule functional capacity. The study did not include histopathological examination of the kidneys. Although the incidence of proximal tubular hyperplasia was not statistically significant in the high-dose females in the Murray et al. (2014a) study, support for identifying this as the critical effect comes from the Bompart et al. (1990) study, which found evidence of impaired renal function in rats exposed to a slightly higher dose.

Several studies have reported decreases in body weight gain; the lowest LOAEL for this effect was 40 mg molybdenum/kg/day as sodium molybdate in the diet in a 2-generation study (Murray et al. 2019). This study reported a 22% decrease in body weight gain on GDs 0–7 in the parental-generation females. The difference in body weight gain over the length of the study was <10% lower than the controls. This was not observed in the F1 generation and was not observed in P or F1 generation rats similarly exposed to 40 mg molybdenum/kg/day as sodium molybdate in the drinking water (Murray et al. 2019). Decreases in body weight have also been observed at higher molybdenum doses (Bompart et al. 1990; Mills et al. 1958; Murray et al. 2014a; Van Reem and Williams 1956). The decrease in body weight gain observed in the Murray et al. (2019) study was not selected as the basis of the MRL because it was not replicated in the F1 generation or in rats exposed via drinking water (Murray et al. 2019).

Selection of the Principal Study: The Murray et al. (2014a) study was selected as the principal study because it identified the lowest LOAEL for renal effects.

Summary of the Principal Study:

Murray FJ, Sullivan FM, Tiwary AK, et al. 2014a. 90-Day subchronic toxicity study of sodium molybdate dihydrate in rats. Regul Toxicol Pharmacol 79:579-588.

Groups of 10 male and 10 female Sprague-Dawley rats were exposed to 0, 5, 17, or 60 mg molybdenum/kg/day (actual concentrations were 0, 4.5, 15.1, and 54.8 mg/kg/day, respectively, in males and 0, 5.4, 19.0, and 65.2 mg/kg/day, respectively, in females and the average overall intakes were 0, 5.0, 17.1, and 60.0 mg/kg/day, respectively) as sodium molybdate dihydrate in the diet for 91 and 92 days; additional groups of rats (10/sex/group) were similarly exposed to 0 or 60 mg/kg/day for 91–92 days and then continued on the basal diet for 60 days. The basal diet contained 906.5 µg/kg molybdenum and

14.23 mg/kg copper; the investigators estimated that the control group received 0.08 mg molybdenum/kg/day. The following parameters were used to assess toxicity: cage-side observations, weekly clinical examinations, ophthalmic examination, weekly body weight measurements, measurement of hematological (hemoglobin, hematocrit, erythrocyte, platelet, mean corpuscular hemoglobin concentration, mean corpuscular volume, red cell distribution width, total and differential leukocyte, reticulocyte, and prothrombin time) and serum chemistry (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, blood urea nitrogen, creatinine, glucose, cholesterol, triglycerides, total protein, albumin, uric acid, total bilirubin, sodium, potassium, chloride, calcium, and inorganic phosphorus) parameters, organ weights (adrenal glands, brain, epididymides, heart, kidneys, liver, ovaries, pituitary gland, prostate gland and seminal vesicles, spleen, testes, thymus, thyroid/ parathyroid glands, and uterus with cervix), and histopathology examination of major tissues and organs in control and 60 mg/kg/day groups (primary and recovery groups) and the adrenal glands from males and kidneys from females in the 5 and 17 mg/kg/day groups. Additionally, sperm counts and sperm mobility and vaginal cytology and estrus cycles were evaluated.

Significant decreases in body weight gain were observed at 60 mg/kg/day in males starting at week 1 and in females starting at week 6. Terminal body weights were 15.2 and 5.6% less than controls, with only the males being significantly different from controls. At the end of the recovery period, the 60 mg/kg/day males weighed significantly less (9.5%) than controls. Decreases in food consumption were observed on numerous occasions in the males exposed to 60 mg/kg/day; a decrease in food conversion efficiency was also observed in this group. No significant or treatment-related alterations in hematological or serum chemistry parameters were observed. Significant decreases in absolute brain, liver, heart, spleen, and pituitary weights were observed in males exposed to 60 mg/kg/day; however, there were no significant alterations in relative organ weights. Treatment-related histopathological alterations were limited to a slight diffuse hyperplasia in the renal proximal tubules in 2/10 females in the 60 mg/kg/day group; the investigators considered it to be treatment-related because it is an uncommon finding at this age. No significant alterations in vaginal cytology or estrus cycles were observed. Similarly, no significant alterations in spermatid or sperm counts or sperm morphology were observed in males. A slight decrease in sperm motility was observed at 60 mg/kg/day; however, this was likely attributable to the control group having a value that approached the upper limit among historical controls and was not considered treatment related. No alterations in reproductive organ weights or histological alterations were observed.

Selection of the Point of Departure for the MRL: The NOAEL of 17 mg molybdenum/kg/day was selected as the POD for the MRL. BMD modeling was not considered because a response was only observed at the highest dose tested. A dataset exhibiting a response only at the highest dose level would likely provide limited information regarding the shape of a dose-response curve.

Calculations: The investigators estimated doses using body weight and food consumption data.

Intermittent Exposure: Not applicable.

Uncertainty Factor and Modifying Factor: The NOAEL is divided by a total uncertainty factor (UF) of 100 and a modifying factor (MF) of 3

- 10 UF for extrapolation from animals to humans
- 10 UF for human variability
- 3 MF for concern that reproductive and/or developmental effects may be a more sensitive endpoint than kidney effects in populations with marginal copper intakes. The copper content of the Murray et al. (2014b, 2019) reproductive/developmental studies used a commercial diet with a fairly high copper content. In contrast, the Fungwe et al. (1990) study, which reported

reproductive effects, utilized a diet that was slightly higher than the dietary requirement. The differences in the copper contents of the diet may explain differences between the study results.

MRL = NOAEL ÷ (UFs x MF)
0.06 mg molybdenum/kg/day = 17 mg molybdenum/kg/day ÷ ((10 x 10) x 3)

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Selection of the POD is supported by the Bompart et al. (1990) study, which found decreases in kidney function in rats administered sodium molybdate.

The MRL is calculated based on the assumption of healthy dietary levels of molybdenum and copper and represents the level of exposure above and beyond the normal diet.

Agency Contacts (Chemical Managers): G. Daniel Todd

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Molybdenum
CAS Numbers: 7439-98-7
Date: May 2020
Profile Status: Final
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration oral MRL for molybdenum. The only available experimental study was considered a low-quality study that was not considered a suitable basis for an MRL.

Rationale for Not Deriving an MRL: Data on the chronic toxicity of molybdenum come from several population-based studies; most of these studies looked for associations between background exposure to molybdenum and adverse health outcomes. No laboratory animal studies were identified.

Koval'skiy et al. (1961) found increases in blood uric acid and symptoms of gout in residents living in Armenia with high levels of molybdenum in the soil and food; the investigators estimated that the residents were exposed to 10–15 mg/day (0.14–0.21 mg/kg/day). A series of small studies of residents living in areas of Colorado with high levels of molybdenum in the drinking water did not find significant increases in uric acid levels; one study estimated that molybdenum intake was 500 μg/day (0.007 mg/kg/day) (EPA 1979). Other studies have found significant associations between serum or urinary molybdenum levels and the severity of complications from diabetes (Rodriguez Flores et al. 2011), high blood pressure (Yorita Christensen 2013), semen quality (Meeker et al. 2008), testosterone levels (Meeker et al. 2010), and psychomotor index in infants (molybdenum levels were measured in the mothers) (Vazques-Salas et al. 2014). However, none of these studies established causality, and the molybdenum levels accounted for only a small percentage of the variance.

Although the Koval'sky et al. (1961) study provided an estimated dose, the study was not considered suitable for derivation of a chronic-duration oral MRL for molybdenum. The study has a number of deficiencies that limit the interpretation of the results: (1) the control group consisted of 5 individuals compared to 52 subjects in the exposed group; (2) no information was provided on the controls to assess whether they were matched to the exposed group; (3) it does not appear that the study controlled for potential confounders, such as diet and alcohol, which can increase uric acid levels; and (4) NAS (2001) noted that there were potential analytical problems with the measurement of serum and urine copper levels.

Agency Contacts (Chemical Managers): G. Daniel Todd

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR MOLYBDENUM

The objective of the toxicological profile is to evaluate the potential for human exposure and the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to molybdenum.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen was conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for molybdenum. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of molybdenum have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest. The inclusion criteria used to identify relevant studies examining the health effects of molybdenum are presented in Table B-1.

Table B-1. Inclusion Criteria for the Literature Search and Screen

- Health Effects
  - Species
    - Human
    - Laboratory mammals
  - Route of exposure
    - Inhalation
    - Oral
    - Dermal (or ocular)
    - Parenteral (these studies will be considered supporting data)
  - Health outcome
    - Death
    - Systemic effects
    - Body weight effects
    - Respiratory effects
    - Cardiovascular effects
    - Gastrointestinal effects
    - Hematological effects
    - Musculoskeletal effects
    - Hepatic effects
    - Renal effects
    - Dermal effects
    - Ocular effects
    - Endocrine effects
    - Immunological effects
    - Neurological effects
    - Reproductive effects
    - Developmental effects
    - Other noncancer effects

Table B-1. Inclusion Criteria for the Literature Search and Screen

Cancer
Toxicokinetics
Absorption
Distribution
Metabolism
Excretion
PBPK models
Biomarkers
Biomarkers of exposure
Biomarkers of effect
Interactions with other chemicals
Potential for human exposure
Releases to the environment
Air
Water
Soil
Environmental fate
Transport and partitioning
Transformation and degradation
Environmental monitoring
Air
Water
Sediment and soil
Other media
Biomonitoring
General populations
Occupation populations

B.1.1 Literature Search

The current literature search was intended to update the draft toxicological profile for molybdenum released for public comment in 2017. The following main databases were searched in January 2018:

- PubMed
- National Library of Medicine's TOXLINE
- Scientific and Technical Information Network's TOXCENTER

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for molybdenum. The query strings used for the literature search are presented in Table B-2.

The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures and Results (NIH RePORTER) databases using the queries presented in Table B-3. Additional databases

were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance Priority List (SPL) resource page, and other items as needed. Regulations applicable to molybdenum were identified by searching international and U.S. agency websites and documents.

Review articles were identified and used for the purpose of providing background information and identifying additional references. ATSDR also identified reports from the grey literature, which included unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations.

Table B-2. Database Query Strings

Database search date	Query string
PubMed	
01/2018	((("Molybdenum/toxicity"[mh] OR "Molybdenum/adverse effects"[mh] OR "Molybdenum/poisoning"[mh] OR "Molybdenum/pharmacokinetics"[mh]) OR ("Molybdenum"[mh] AND ("environmental exposure"[mh] OR ci[sh])) OR ("Molybdenum"[mh] AND toxicokinetics[mh:noexp]) OR ("Molybdenum/blood"[mh] OR "Molybdenum/cerebrospinal fluid"[mh] OR "Molybdenum/urine"[mh]) OR ("Molybdenum"[mh] AND ("endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR ("Molybdenum"[mh] AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR ("Molybdenum/antagonists and inhibitors"[mh]) OR ("Molybdenum/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("Molybdenum"[mh] AND cancer[sb]) OR ("Molybdenum/pharmacology"[majr])) AND (2013/12/01 : 3000[dp] OR 2014/12/01 : 3000[mhda])) OR (("1317-33-5"[rn] OR "12033-29-3"[rn] OR "12033-33-9"[rn] OR "11098-99-0"[rn] OR "18868-43-4"[rn] OR "1313-27-5"[rn] OR "1313-29-7"[rn] OR "11098-84-3"[rn] OR "27546-07-2"[rn] OR "12054-85-2"[rn] OR "15060-55-6"[rn] OR "7631-95-0"[rn] OR "10102-40-6"[rn] OR "7789-82-4"[rn] OR "12011-97-1"[rn] OR "11119-46-3"[rn] OR "11062-51-4"[rn] OR "10241-05-1"[rn] OR "1309-56-4"[rn] OR "7783-77-9"[rn] OR "13939-06-5"[rn] OR "14221-06-8"[rn] OR "13814-74-9"[rn] OR "12027-67-7"[rn] OR "13106-76-8"[rn]) AND (("Disulfides/toxicity"[mh] OR "Disulfides/adverse effects"[mh] OR "Disulfides/poisoning"[mh] OR "Disulfides/pharmacokinetics"[mh]) OR ("Disulfides/blood"[mh] OR "Disulfides/cerebrospinal fluid"[mh] OR "Disulfides/urine"[mh]) OR ("Disulfides/antagonists and inhibitors"[mh]) OR ("Disulfides/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("Disulfides/pharmacology"[majr]) OR ("Chlorides/toxicity"[mh] OR "Chlorides/adverse effects"[mh] OR "Chlorides/poisoning"[mh] OR "Chlorides/pharmacokinetics"[mh]) OR ("Chlorides/blood"[mh] OR "Chlorides/cerebrospinal fluid"[mh] OR "Chlorides/urine"[mh]) OR ("Chlorides/antagonists and inhibitors"[mh]) OR ("Chlorides/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("Chlorides/pharmacology"[majr]) OR ("Oxides/toxicity"[mh] OR "Oxides/adverse effects"[mh] OR "Oxides/poisoning"[mh] OR "Oxides/pharmacokinetics"[mh]) OR ("Oxides/blood"[mh] OR "Oxides/cerebrospinal fluid"[mh] OR "Oxides/urine"[mh]) OR

Table B-2. Database Query Strings

Database search date	Query string
	("Oxides/antagonists and inhibitors"[mh]) OR ("Oxides/metabolism"[mh] AND ("humans"[mh] OR "animals"[mh])) OR ("Oxides/pharmacology"[majr]) OR (("disulfides"[mh] OR "chlorides"[mh] OR "oxides"[mh]) AND ("environmental exposure"[mh] OR ci[sh])) OR (("disulfides"[mh] OR "chlorides"[mh] OR "oxides"[mh]) AND toxicokinetics[mh:noexp]) OR (("disulfides"[mh] OR "chlorides"[mh] OR "oxides"[mh]) AND ("endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh])) OR (("disulfides"[mh] OR "chlorides"[mh] OR "oxides"[mh]) AND ("computational biology"[mh] OR "medical informatics"[mh] OR genomics[mh] OR genome[mh] OR proteomics[mh] OR proteome[mh] OR metabolomics[mh] OR metabolome[mh] OR genes[mh] OR "gene expression"[mh] OR phenotype[mh] OR genetics[mh] OR genotype[mh] OR transcriptome[mh] OR ("systems biology"[mh] AND ("environmental exposure"[mh] OR "epidemiological monitoring"[mh] OR analysis[sh])) OR "transcription, genetic "[mh] OR "reverse transcription"[mh] OR "transcriptional activation"[mh] OR "transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, messenger"[mh] OR "RNA, transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "reverse transcriptase polymerase chain reaction"[mh] OR "base sequence"[mh] OR "trans-activators"[mh] OR "gene expression profiling"[mh])) OR (("disulfides"[mh] OR "chlorides"[mh] OR "oxides"[mh]) AND cancer[sb])) AND (2013/12/01 : 3000[dp] OR 2014/12/01 : 3000[mhda])) OR "12027-67-7"[rn] OR ((("7439-98-7"[rn] OR "1317-33-5"[rn] OR "12033-29-3"[rn] OR "12033-33-9"[rn] OR "11098-99-0"[rn] OR "18868-43-4"[rn] OR "1313-27-5"[rn] OR "1313-29-7"[rn] OR "11098-84-3"[rn] OR "27546-07-2"[rn] OR "12054-85-2"[rn] OR "15060-55-6"[rn] OR "7631-95-0"[rn] OR "10102-40-6"[rn] OR "7789-82-4"[rn] OR "12011-97-1"[rn] OR "11119-46-3"[rn] OR "11062-51-4"[rn] OR "10241-05-1"[rn] OR "1309-56-4"[rn] OR "7783-77-9"[rn] OR "13939-06-5"[rn] OR "14221-06-8"[rn] OR "13814-74-9"[rn] OR "12027-67-7"[rn] OR "13106-76-8"[rn]) NOT ("molybdenum"[mh] OR "disulfides"[mh] OR "chlorides"[mh] OR "oxides"[mh])) AND (2013/12/01 : 3000[dp] OR 2014/12/01 : 3000[mhda])) OR (("Ammonium molybdenum sulfide"[tw] OR "Ammonium tetrasulfidomolybdate(2-)"[tw] OR "Ammonium tetrathiomolybdate"[tw] OR "Ammonium thiomolybdate(VI)"[tw] OR "ATTM"[tw] OR "Bis(ammonium)tetrathiomolybdate(2-)"[tw] OR "Calcium molybdate"[tw] OR "Calcium molybdate(VI)"[tw] OR "Calcium molybdenate"[tw] OR "Calcium molybdenum oxide"[tw] OR "Coprexa"[tw] OR "Diammonium tetrakis(sulfido)molybdate(2-)"[tw] OR "Diammonium tetrakis(thioxo)molybdate"[tw] OR "Diammonium tetrasulfidomolybdate"[tw] OR "Diammonium tetrathiomolybdate"[tw] OR "Diammonium tetrathiomolybdate(2-)"[tw] OR "Diammonium tetrathiooxomolybdate(2-)"[tw] OR "Diammonium tetrathioxomolybdate(2-)"[tw] OR "Diammonium thiomolybdate"[tw] OR "Dimolybdenum tetraacetate"[tw] OR "Dimolybdenum trioxide"[tw] OR "Dodecachlorohexamolybdenum"[tw] OR "Hexafluoromolybdenum"[tw] OR "Hexamolybdenum dodecachloride"[tw] OR "MC 400WR"[tw] OR "Molybdate, calcium"[tw] OR "Molybdenite"[tw] OR "Molybdenum anhydride"[tw] OR "Molybdenum carbide"[tw] OR "Molybdenum chloride"[tw] OR "Molybdenum chloride oxide"[tw] OR "Molybdenum dioxide"[tw] OR "Molybdenum fluoride"[tw] OR "Molybdenum hexafluoride"[tw] OR "Molybdenum monocarbide"[tw] OR "Molybdenum oxide"[tw] OR "Molybdenum oxychloride"[tw] OR "Molybdenum oxytrichloride"[tw] OR "Molybdenum sesquioxide"[tw] OR "Molybdenum sulfide"[tw] OR "Molybdenum trichloride monoxide"[tw] OR "Molybdenum trichloride oxide"[tw] OR "Molybdenum trisulfide"[tw] OR "Molybdenum(6+) fluoride"[tw] OR "Molybdenum(II) acetate"[tw] OR "Molybdenum(IV) oxide"[tw] OR "Molybdic acid, calcium salt"[tw] OR "Octachlorohexamolybdenum(4+) tetrachloride"[tw] OR "Tetraacetatodimolybdenum"[tw] OR "tetrakis(acetato)di-Molybdenum"[tw] OR "Tetrakis(acetato)dimolybdenum"[tw] OR "Tetrakis(acetato)molybdenum"[tw] OR "Tetrakis(mu-(acetato-O:O'))dimolybdenum"[tw]

Table B-2. Database Query Strings

Database search date	Query string
	OR "tetrakis(mu-acetato)di-Molybdenum"[tw] OR "Tetrakis(mu-acetato)dimolybdenum"[tw] OR "tetrakis[mu-(acetato-O:O')]di-Molybdenum"[tw] OR "Thiomolybdic acid (H2MoS4), diammonium salt"[tw] OR "Thiomolybdic acid, diammonium salt"[tw] OR "Tiomolibdate diammonium"[tw] OR "Trichlorooxomolybdenum"[tw] OR "Trichlorooxomolybdenum(V)"[tw]) AND (2013/12/01 : 3000[dp] OR 2014/12/01 : 3000[crdat] OR 2014/12/01 : 3000[edat])) OR ((("3N5"[tw] OR "A Powder"[tw] OR "Ammonium dimolybdate"[tw] OR "Ammonium heptamolybdate"[tw] OR "Ammonium heptamolybdate tetrahydrate"[tw] OR "Ammonium molibdate"[tw] OR "Ammonium molibdenum oxide"[tw] OR "Ammonium molybdate"[tw] OR "Ammonium molybdate hydrate"[tw] OR "Ammonium molybdate tetrahydrate"[tw] OR "Ammonium molybdate(VI)"[tw] OR "Ammonium molybdenum oxide"[tw] OR "Ammonium molybdenum sulfide"[tw] OR "ammonium paramolybdate"[tw] OR "Ammonium paramolybdate tetrahydrate"[tw] OR "Ammonium tetrasulfidomolybdate(2-)"[tw] OR "Ammonium tetrathiomolybdate"[tw] OR "Ammonium thiomolybdate(VI)"[tw] OR "Amperit 105.054"[tw] OR "Amperit 106.2"[tw] OR "ATTM"[tw] OR "Bis(ammonium)tetrathiomolybdate(2-)"[tw] OR "Bouen SKN 301"[tw] OR "C-Powder"[tw] OR "Calcium molybdate"[tw] OR "Calcium molybdate(VI)"[tw] OR "Calcium molybdenate"[tw] OR "Calcium molybdenum oxide"[tw] OR "Coprexa"[tw] OR "DAG 206"[tw] OR "DAG 325"[tw] OR "DAG-V 657"[tw] OR "Defric coat HMB 2"[tw] OR "Diammonium dimolybdate"[tw] OR "Diammonium tetrakis(sulfido)molybdate(2-)"[tw] OR "Diammonium tetrakis(thioxo)molybdate"[tw] OR "Diammonium tetrasulfidomolybdate"[tw] OR "Diammonium tetrathiomolybdate"[tw] OR "Diammonium tetrathiomolybdate(2-)"[tw] OR "Diammonium tetrathiooxomolybdate(2-)"[tw] OR "Diammonium tetrathioxomolybdate(2-)"[tw] OR "Diammonium thiomolybdate"[tw] OR "Dimolybdenum tetraacetate"[tw] OR "Dimolybdenum trioxide"[tw] OR "dimolybdenum trisulfide "[tw] OR "Disodium molybdate"[tw] OR "Disodium molybdate dihydrate"[tw] OR "Disodium tetraoxomolybdate"[tw] OR "DM 1 (sulfide)"[tw] OR "DMI 7"[tw] OR "Dodecachlorohexamolybdenum"[tw] OR "Hexaammonium heptamolybdate tetrahydrate"[tw] OR "Hexaammonium molybdate tetrahydrate"[tw] OR "Hexacarbonylmolybdenum"[tw] OR "Hexafluoromolybdenum"[tw] OR "Hexamolybdenum dodecachloride"[tw] OR "JCPDS 35-0609"[tw] OR "Liqui-Moly LM 11"[tw] OR "Liqui-Moly LM 2"[tw] OR "Liqui-Moly Z Powder"[tw] OR "LM 13"[tw] OR "MC 400WR"[tw] OR "MChVL"[tw] OR "MD 40"[tw] OR "Metco 63"[tw] OR "MF 000"[tw] OR "MIPO-M 15"[tw] OR "Mo 1202T"[tw] OR "Mo-1202T"[tw] OR "Moly Fine Powder Y"[tw] OR "Moly Powder B"[tw] OR "Moly Powder C"[tw] OR "Moly Powder PA"[tw] OR "Moly Powder PB"[tw] OR "Moly Powder PS"[tw] OR "Molybdate (Mo2O72-), diammonium"[tw] OR "Molybdate (MoO42-), disodium, dihydrate, (T-4)-"[tw] OR "Molybdate, calcium"[tw] OR "Molybdena"[tw] OR "Molybdenite"[tw] OR "Molybdenum"[tw] OR "Molybdenum anhydride"[tw] OR "Molybdenum bisulfide"[tw] OR "Molybdenum carbide"[tw] OR "Molybdenum carbonyl"[tw] OR "Molybdenum chloride"[tw] OR "Molybdenum chloride oxide"[tw] OR "Molybdenum dioxide"[tw] OR "Molybdenum disulfide"[tw] OR "Molybdenum disulphide"[tw] OR "Molybdenum fluoride"[tw] OR "Molybdenum hexacarbonyl"[tw] OR "Molybdenum hexafluoride"[tw] OR "Molybdenum metallicum"[tw] OR "Molybdenum monocarbide"[tw] OR "Molybdenum oxide"[tw] OR "Molybdenum oxychloride"[tw] OR "Molybdenum oxytrichloride"[tw] OR "Molybdenum pentachloride"[tw] OR "Molybdenum peroxide"[tw] OR "Molybdenum sesquioxide"[tw] OR "Molybdenum sesquisulfide"[tw] OR "Molybdenum sodium oxide"[tw] OR "Molybdenum sulfide"[tw] OR "Molybdenum sulphide"[tw] OR "Molybdenum trichloride monoxide"[tw] OR "Molybdenum trichloride oxide"[tw] OR "Molybdenum trioxide"[tw] OR "Molybdenum trioxide pentamer"[tw] OR "Molybdenum trioxide tetramer"[tw] OR "Molybdenum trisulfide"[tw] OR "Molybdenum(6+) fluoride"[tw] OR "Molybdenum(II) acetate"[tw] OR "Molybdenum(II) chloride"[tw] OR "molybdenum(III)

Table B-2. Database Query Strings

Database search date	Query string
	sulfide"[tw] OR "molybdenum(IV) oxide"[tw] OR "Molybdenum(IV) sulfide"[tw] OR "Molybdenum(V) chloride"[tw] OR "Molybdenum(VI) oxide"[tw] OR "Molybdenum(VI) trioxide"[tw] OR "Molybdenumperoxide"[tw] OR "Molybdic acid (H2Mo2O7), diammonium salt"[tw] OR "Molybdic acid (H2MoO4), calcium salt (1:1)"[tw] OR "Molybdic acid anhydride"[tw] OR "Molybdic acid, ammonium salt"[tw] OR "Molybdic acid, calcium salt"[tw] OR "Molybdic acid, disodium salt"[tw] OR "Molybdic acid, disodium salt, dihydrate"[tw] OR "Molybdic anhydride"[tw] OR "Molybdic oxide"[tw] OR "Molybdic trioxide"[tw] OR "Molycolloid CF 626"[tw] OR "Molyform 15"[tw] OR "Molyhibit 100"[tw] OR "Molyka R"[tw] OR "Molyka R-L 3"[tw] OR "Molyke R"[tw] OR "Molykote"[tw] OR "Molykote Microsize Powder"[tw] OR "Molykote Z"[tw] OR "Molykote Z Powder"[tw] OR "Molysulfide"[tw] OR "MOP-P 100"[tw] OR "Mopol M"[tw] OR "Mopol S"[tw] OR "Motimol"[tw] OR "MVCh 1"[tw] OR "Natural molybdenite"[tw] OR "Natural molybdite"[tw] OR "NeoZ"[tw] OR "Nichimoly C"[tw] OR "Octachlorohexamolybdenum(4+) tetrachloride"[tw] OR "OKS 110"[tw] OR "PA Powder"[tw] OR "Pentachloromolybdenum Molybdenite"[tw] OR "Pigment Black 34"[tw] OR "Pol-U"[tw] OR "Powder PA"[tw] OR "RAC 01"[tw] OR "SGC 15"[tw] OR "Sodium molybdate"[tw] OR "Sodium molybdate dihydrate"[tw] OR "Sodium molybdate(VI)"[tw] OR "Sodium molybdate(VI) dihydrate"[tw] OR "Sodium molybdenate"[tw] OR "Sodium molybdenum oxide"[tw] OR "Sodium tetraoxomolybdate(2-)"[tw] OR "Solvest 390A"[tw] OR "Sumipowder PA"[tw] OR "T-Powder"[tw] OR "Tetraacetatodimolybdenum"[tw] OR "tetrakis(acetato)di-Molybdenum"[tw] OR "Tetrakis(acetato)dimolybdenum"[tw] OR "Tetrakis(acetato)molybdenum"[tw] OR "Tetrakis(mu-(acetato-O:O'))dimolybdenum"[tw] OR "tetrakis(mu-acetato)di-Molybdenum"[tw] OR "Tetrakis(mu-acetato)dimolybdenum"[tw] OR "tetrakis[mu-(acetato-O:O')]di-Molybdenum"[tw] OR "Thiomolybdic acid, diammonium salt"[tw] OR "Tiomolibdate diammonium"[tw] OR "TMOIO"[tw] OR "Trichlorooxomolybdenum"[tw] OR "Trichlorooxomolybdenum(V)"[tw] OR "TsM1"[tw] OR "UP 10"[tw] OR "UP 50"[tw] OR ("Hexaammonium heptamolybdate"[tw] OR "Hexammonium heptamolybdat"[tw] OR "Hexammonium tetracosaoxoheptamolybdate"[tw] OR "Molybdate (Mo7O24), hexammonium"[tw] OR "Molybdate (Mo7O246-), ammonium (1:6)"[tw] OR "Molybdate (Mo7O246-), hexaammonium"[tw] OR "Molybdate, hexaammonium"[tw] OR "Molybdic acid (H6Mo7O24), hexaammonium salt"[tw] OR "Molybdic acid, hexaammonium salt"[tw] OR "Diammonium molybdate"[tw] OR "Diammonium tetraoxomolybdate(2-)"[tw] OR "Molybdate (MoO42-), ammonium (1:2), (T-4)-"[tw] OR "Molybdate (MoO42-), diammonium, (beta-4)-"[tw] OR "Molybdate (MoO42-), diammonium, (T-4)-"[tw] OR "Molybdic acid (H2MoO4), diammonium salt"[tw] OR "Molybdic acid, diammonium salt"[tw])) NOT medline[sb]) AND (2013/12/01 : 3000[dp] OR 2014/12/01 : 3000[crdat] OR 2014/12/01 : 3000[edat]))
Toxline	
01/2018	**Date limit 2013 to present:**
	7439-98-7[rn] OR 1317-33-5[rn] OR 12033-29-3[rn] OR 12033-33-9[rn] OR 11098-99-0[rn] OR 18868-43-4[rn] OR 1313-27-5[rn] OR 1313-29-7[rn] OR 11098-84-3[rn] OR 27546-07-2[rn] OR 12054-85-2[rn] OR 15060-55-6[rn] OR 7631-95-0[rn] OR 10102-40-6[rn] OR 7789-82-4[rn] OR 12011-97-1[rn] OR 11119-46-3[rn] OR 11062-51-4[rn] OR 10241-05-1[rn] OR 1309-56-4[rn] OR 7783-77-9[rn] OR 13939-06-5[rn] OR 14221-06-8[rn] OR 13814-74-9[rn]
	"3N5" OR "Ammonium dimolybdate" OR "Ammonium heptamolybdate" OR "Ammonium heptamolybdate tetrahydrate" OR "Ammonium molibdate" OR "Ammonium molibdenum oxide" OR "Ammonium molybdate" OR "Ammonium molybdate hydrate" OR "Ammonium molybdate tetrahydrate" OR "Ammonium molybdate(VI)" OR "Ammonium molybdenum oxide"

Table B-2. Database Query Strings

Database search date	Query string
	"Ammonium molybdenum sulfide" OR "ammonium paramolybdate" OR "Ammonium paramolybdate tetrahydrate" OR "Ammonium tetrasulfidomolybdate(2-)" OR "Ammonium tetrathiomolybdate" OR "Ammonium thiomolybdate(VI)" OR "Amperit 105.054" OR "Amperit 106.2" OR "ATTM" OR "Bis(ammonium)tetrathiomolybdate(2-)" OR "Bouen SKN 301" OR "C-Powder" OR "Calcium molybdate"
	"Calcium molybdate(VI)" OR "Calcium molybdenate" OR "Calcium molybdenum oxide" OR "Coprexa" OR "DAG 206" OR "DAG 325" OR "DAG-V 657" OR "Defric coat HMB 2" OR "Diammonium dimolybdate" OR "Diammonium tetrakis(sulfido)molybdate(2-)" OR "Diammonium tetrakis(thioxo)molybdate" OR "Diammonium tetrasulfidomolybdate" OR "Diammonium tetrathiomolybdate"
	"Diammonium tetrathiomolybdate(2-)" OR "Diammonium tetrathiooxomolybdate(2-)" OR "Diammonium tetrathioxomolybdate(2-)" OR "Diammonium thiomolybdate" OR "Dimolybdenum tetraacetate" OR "Dimolybdenum trioxide" OR "dimolybdenum trisulfide " OR "Disodium molybdate" OR "Disodium molybdate dihydrate" OR "Disodium tetraoxomolybdate" OR "DM 1 (sulfide)" OR "DMI 7"
	"Dodecachlorohexamolybdenum" OR "Hexaammonium heptamolybdate tetrahydrate" OR "Hexaammonium molybdate tetrahydrate" OR "Hexacarbonylmolybdenum" OR "Hexafluoromolybdenum" OR "Hexamolybdenum dodecachloride" OR "JCPDS 35-0609" OR "Liqui-Moly LM 11" OR "Liqui-Moly LM 2" OR "Liqui-Moly Z Powder" OR "LM 13" OR "M 5" OR "MC 400WR"
	"MChVL" OR "MD 40" OR "Metco 63" OR "MF 000" OR "MFR" OR "MIPO-M 15" OR "Mo 1202T" OR "Mo-1202T" OR "Moly Fine Powder Y" OR "Moly Powder B" OR "Moly Powder C" OR "Moly Powder PA" OR "Moly Powder PB" OR "Moly Powder PS" OR "Molybdate (Mo2O72-), diammonium" OR "Molybdate (MoO42-), disodium, dihydrate, (T-4)-" OR "Molybdate, calcium" OR "Molybdena" OR "Molybdenite"
	"Molybdenum" OR "Molybdenum anhydride" OR "Molybdenum bisulfide" OR "Molybdenum carbide" OR "Molybdenum carbonyl" OR "Molybdenum chloride" OR "Molybdenum chloride oxide" OR "Molybdenum dioxide" OR "Molybdenum disulfide" OR "Molybdenum disulphide" OR "Molybdenum fluoride" OR "Molybdenum hexacarbonyl" OR "Molybdenum hexafluoride"
	"Molybdenum metallicum" OR "Molybdenum monocarbide" OR "Molybdenum oxide" OR "Molybdenum oxychloride" OR "Molybdenum oxytrichloride" OR "Molybdenum pentachloride" OR "Molybdenum peroxide" OR "Molybdenum sesquioxide" OR "Molybdenum sesquisulfide" OR "Molybdenum sodium oxide" OR "Molybdenum sulfide" OR "Molybdenum sulphide" OR "Molybdenum trichloride monoxide"
	"Molybdenum trichloride oxide" OR "Molybdenum trioxide" OR "Molybdenum trioxide pentamer" OR "Molybdenum trioxide tetramer" OR "Molybdenum trisulfide" OR "Molybdenum(6+) fluoride" OR "Molybdenum(II) acetate" OR "Molybdenum(II) chloride" OR "molybdenum(III) sulfide" OR "molybdenum(IV) oxide" OR "Molybdenum(IV) sulfide" OR "Molybdenum(V) chloride"
	"Molybdenum(VI) oxide" OR "Molybdenum(VI) trioxide" OR "Molybdenumperoxide" OR "Molybdic acid (H2Mo2O7), diammonium salt" OR "Molybdic acid (H2MoO4), calcium salt (1:1)" OR "Molybdic acid anhydride" OR "Molybdic acid, ammonium salt" OR "Molybdic acid, calcium salt" OR "Molybdic acid, disodium salt" OR "Molybdic acid, disodium salt, dihydrate" OR "Molybdic anhydride"
	"Molybdic oxide" OR "Molybdic trioxide" OR "Molycolloid CF 626" OR "Molyform 15" OR "Molyhibit 100" OR "Molyka R" OR "Molyka R-L 3" OR "Molyke R" OR "Molykote" OR "Molykote Microsize Powder" OR "Molykote Z" OR "Molykote Z Powder" OR "Molysulfide"

Table B-2. Database Query Strings

Database search date	Query string
	OR "MOP-P 100" OR "Mopol M" OR "Mopol S" OR "Motimol" OR "MVCh 1" OR "Natural molybdenite" OR "Natural molybdite" OR "NeoZ"
	"Nichimoly C" OR "Octachlorohexamolybdenum(4+) tetrachloride" OR "OKS 110" OR "PA Powder" OR "Pentachloromolybdenum Molybdenite" OR "Pigment Black 34" OR "Pol-U" OR "Powder PA" OR "RAC 01" OR "SGC 15" OR "Sodium molybdate" OR "Sodium molybdate dihydrate" OR "Sodium molybdate(VI)" OR "Sodium molybdate(VI) dihydrate" OR "Sodium molybdenate"
	"Sodium molybdenum oxide" OR "Sodium tetraoxomolybdate(2-)" OR "Solvest 390A" OR "Sumipowder PA" OR "T-Powder" OR "Tetraacetatodimolybdenum" OR "tetrakis(acetato)di-Molybdenum" OR "Tetrakis(acetato)dimolybdenum" OR "Tetrakis(acetato)molybdenum" OR "Tetrakis(mu-(acetato-O:O'))dimolybdenum" OR "tetrakis(μ-acetato)di-Molybdenum" OR "Tetrakis(μ-acetato)dimolybdenum"
	"tetrakis[μ-(acetato-O:O')]di-Molybdenum" OR "Thiomolybdic acid, diammonium salt" OR "Tiomolibdate diammonium" OR "TMOIO" OR "Trichlorooxomolybdenum" OR "Trichlorooxomolybdenum(V)" OR "TsM1"
	No date limit:
	"Hexaammonium heptamolybdate" OR "Hexammonium heptamolybdat" OR "Hexammonium tetracosaoxoheptamolybdate" OR "Molybdate (Mo7O24), hexammonium" OR "Molybdate (Mo7O246-), ammonium (1:6)" OR "Molybdate (Mo7O246-), hexaammonium" OR "Molybdate, hexaammonium" OR "Molybdic acid (H6Mo7O24), hexaammonium salt" OR "Molybdic acid, hexaammonium salt" OR 12027-67-7[rn]
	"Diammonium molybdate" OR "Diammonium tetraoxomolybdate(2-)" OR "Molybdate (MoO42-), ammonium (1:2), (T-4)-" OR "Molybdate (MoO42-), diammonium, (beta-4)-" OR "Molybdate (MoO42-), diammonium, (T-4)-" OR "Molybdic acid (H2MoO4), diammonium salt" OR "Molybdic acid, diammonium salt" OR 13106-76-8[rn]
Toxcenter	
01/2018	(FILE 'HOME' ENTERED AT 14:16:56 ON 12 JAN 2018) FILE 'TOXCENTER' ENTERED AT 14:17:07 ON 12 JAN 2018 CHARGED TO COST=EH011.05.LB.02.05 L1 34132 SEA FILE=TOXCENTER 7439-98-7 OR 1317-33-5 OR 12033-29-3 OR 12033-33-9 OR 11098-99-0 OR 18868-43-4 OR 1313-27-5 OR 1313-29-7 OR 11098-84-3 OR 27546-07-2 OR 12054-85-2 OR 15060-55-6 OR 7631-95-0 OR 10102-40-6 L2 523 SEA FILE=TOXCENTER 7789-82-4 OR 12011-97-1 OR 11119-46-3 OR 11062-51-4 OR 10241-05-1 OR 1309-56-4 OR 7783-77-9 OR 13939-06-5 OR 14221-06-8 OR 13814-74-9 L3 1148 SEA FILE=TOXCENTER 12027-67-7 OR 13106-76-8 L4 34486 SEA FILE=TOXCENTER L1 OR L2 L5 636 SEA FILE=TOXCENTER L3 NOT L4 L6 35122 SEA FILE=TOXCENTER L1 OR L2 OR L3 L7 22953 SEA FILE=TOXCENTER L6 NOT PATENT/DT L8 22927 SEA FILE=TOXCENTER L7 NOT TSCATS/FS ACT TOXQUERY/Q --------- L9 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L10 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT,

Table B-2. Database Query Strings

Database search date	Query string
	IT)
	L11 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50)
	L12 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT
	L13 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?)
	L14 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?)
	L15 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?)
	L16 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE))
	L17 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)
	L18 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?)
	L19 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)
	L20 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)
	L21 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L22 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L23 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L24 QUE (ENDOCRIN? AND DISRUPT?)
	L25 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L26 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L27 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L28 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L29 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L30 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L31 QUE (NEPHROTOX? OR HEPATOTOX?)
	L32 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L33 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L34 QUE L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 OR L30 OR L31 OR L32 OR L33
	L35 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?)

Table B-2. Database Query Strings

Database search date	Query string
	L36 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L37 QUE L34 OR L35 OR L36
	L38 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?)
	L39 QUE L37 OR L38

	L40 8795 SEA FILE=TOXCENTER L8 AND L39
	L41 1436 SEA FILE=TOXCENTER L40 AND ED>=20141201
	L42 1422 SEA FILE=TOXCENTER L41 AND PY>2012
	L43 184 SEA FILE=TOXCENTER L40 AND L3
	L44 1597 SEA FILE=TOXCENTER L41 OR L43
	L45 0 SEA FILE=TOXCENTER L44 AND MEDLINE/SB
	L46 269 SEA FILE=TOXCENTER L44 AND MEDLINE/FS
	L47 263 SEA FILE=TOXCENTER L44 AND BIOSIS/FS
	L48 1050 SEA FILE=TOXCENTER L44 AND CAPLUS/FS
	L49 15 SEA FILE=TOXCENTER L44 NOT (L46 OR L47 OR L48)
	L50 1425 DUP REM L46 L47 L49 L48 (172 DUPLICATES REMOVED) ANSWERS '1-1425' FROM FILE TOXCENTER
	L*** DEL 269 S L44 AND MEDLINE/FS
	L*** DEL 269 S L44 AND MEDLINE/FS
	L51 269 SEA FILE=TOXCENTER L50
	L*** DEL 263 S L44 AND BIOSIS/FS
	L*** DEL 263 S L44 AND BIOSIS/FS
	L52 234 SEA FILE=TOXCENTER L50
	L*** DEL 1050 S L44 AND CAPLUS/FS
	L*** DEL 1050 S L44 AND CAPLUS/FS
	L53 908 SEA FILE=TOXCENTER L50
	L*** DEL 15 S L44 NOT (L46 OR L47 OR L48)
	L*** DEL 15 S L44 NOT (L46 OR L47 OR L48)
	L54 14 SEA FILE=TOXCENTER L50
	L55 211 SEA FILE=TOXCENTER (L51 OR L52 OR L53 OR L54) AND BIOSIS/FS AND ED>=20141201
	L*** DEL 269 S L44 AND MEDLINE/FS
	L*** DEL 269 S L44 AND MEDLINE/FS
	L56 269 SEA FILE=TOXCENTER L50
	L*** DEL 263 S L44 AND BIOSIS/FS
	L*** DEL 263 S L44 AND BIOSIS/FS
	L57 234 SEA FILE=TOXCENTER L50
	L*** DEL 1050 S L44 AND CAPLUS/FS
	L*** DEL 1050 S L44 AND CAPLUS/FS
	L58 908 SEA FILE=TOXCENTER L50
	L*** DEL 15 S L44 NOT (L46 OR L47 OR L48)
	L*** DEL 15 S L44 NOT (L46 OR L47 OR L48)
	L59 14 SEA FILE=TOXCENTER L50
	L60 826 SEA FILE=TOXCENTER (L56 OR L57 OR L58 OR L59) AND CAPLUS/FS AND ED>=20141201
	L*** DEL 269 S L44 AND MEDLINE/FS

Table B-2. Database Query Strings

Database search date	Query string
	L*** DEL 269 S L44 AND MEDLINE/FS L61 269 SEA FILE=TOXCENTER L50 L*** DEL 263 S L44 AND BIOSIS/FS L*** DEL 263 S L44 AND BIOSIS/FS L62 234 SEA FILE=TOXCENTER L50 L*** DEL 1050 S L44 AND CAPLUS/FS L*** DEL 1050 S L44 AND CAPLUS/FS L63 908 SEA FILE=TOXCENTER L50 L*** DEL 15 S L44 NOT (L46 OR L47 OR L48) L*** DEL 15 S L44 NOT (L46 OR L47 OR L48) L64 14 SEA FILE=TOXCENTER L50 L65 0 SEA FILE=TOXCENTER (L61 OR L62 OR L63 OR L64) NOT (CAPLUS/FS OR MEDLINE/FS OR BIOSIS/FS) AND ED>=20141201 L*** DEL 269 S L44 AND MEDLINE/FS L*** DEL 269 S L44 AND MEDLINE/FS L66 269 SEA FILE=TOXCENTER L50 L*** DEL 263 S L44 AND BIOSIS/FS L*** DEL 263 S L44 AND BIOSIS/FS L67 234 SEA FILE=TOXCENTER L50 L*** DEL 1050 S L44 AND CAPLUS/FS L*** DEL 1050 S L44 AND CAPLUS/FS L68 908 SEA FILE=TOXCENTER L50 L*** DEL 15 S L44 NOT (L46 OR L47 OR L48) L*** DEL 15 S L44 NOT (L46 OR L47 OR L48) L69 14 SEA FILE=TOXCENTER L50 L70 150 SEA FILE=TOXCENTER (L66 OR L67 OR L68 OR L69) NOT ED>=20141201 L71 23 SEA FILE=TOXCENTER L70 AND BIOSIS/FS L72 14 SEA FILE=TOXCENTER L70 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L73 82 SEA FILE=TOXCENTER L70 AND CAPLUS/FS L74 52 SEA FILE=TOXCENTER L60 AND ?MOLYB?/TI L75 29 SEA FILE=TOXCENTER L73 AND ?MOLYB?/TI D SCAN L55 L76 37 SEA FILE=TOXCENTER L71 OR L72 D SCAN L76 D SCAN L74 D SCAN L75 L*** DEL 269 S L44 AND MEDLINE/FS L*** DEL 269 S L44 AND MEDLINE/FS L77 269 SEA FILE=TOXCENTER L50 L*** DEL 263 S L44 AND BIOSIS/FS L*** DEL 263 S L44 AND BIOSIS/FS L78 234 SEA FILE=TOXCENTER L50 L*** DEL 1050 S L44 AND CAPLUS/FS L*** DEL 1050 S L44 AND CAPLUS/FS L79 908 SEA FILE=TOXCENTER L50 L*** DEL 15 S L44 NOT (L46 OR L47 OR L48) L*** DEL 15 S L44 NOT (L46 OR L47 OR L48) L80 14 SEA FILE=TOXCENTER L50

Table B-2. Database Query Strings

Database search date	Query string
	L81 1275 SEA FILE=TOXCENTER (L77 OR L78 OR L79 OR L80) AND ED>=20141201 L82 1265 SEA FILE=TOXCENTER L81 AND (L1 OR L2) L83 1012 SEA FILE=TOXCENTER L81 NOT (L55 OR L74) L84 84 SEA FILE=TOXCENTER L70 NOT (L76 OR L75) D SCAN L84 D SCAN L83 (FILE 'HOME' ENTERED AT 20:36:59 ON 14 JAN 2018) FILE 'TOXCENTER' ENTERED AT 20:37:09 ON 14 JAN 2018 CHARGED TO COST=EH011.05.LB.02.05 ACT MOLY1/A --------- L1 (34132)SEA FILE=TOXCENTER 7439-98-7 OR 1317-33-5 OR 12033-29-3 OR 12033-33-9 OR 11098-99-0 OR 18868-43-4 OR 1313-27-5 OR 1313-29-7 OR 11098-84-3 OR 27546-07-2 OR 12054-85-2 OR 15060-55-6 OR 7631-95-0 OR 10102-40-6 L2 (523)SEA FILE=TOXCENTER 7789-82-4 OR 12011-97-1 OR 11119-46-3 OR 11062-51-4 OR 10241-05-1 OR 1309-56-4 OR 7783-77-9 OR 13939-06-5 OR 14221-06-8 OR 13814-74-9 L3 (1148)SEA FILE=TOXCENTER 12027-67-7 OR 13106-76-8 L4 (35122)SEA FILE=TOXCENTER L1 OR L2 OR L3 L5 (22953)SEA FILE=TOXCENTER L4 NOT PATENT/DT L6 (22927)SEA FILE=TOXCENTER L5 NOT TSCATS/FS L7 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L8 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L9 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L10 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L11 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L12 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L13 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L14 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L15 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L16 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L17 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L18 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) L19 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?) L20 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR

Table B-2. Database Query Strings

Database search date	Query string
	SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L21 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L22 QUE (ENDOCRIN? AND DISRUPT?)
	L23 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L24 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L25 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L26 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR
	NEOPLAS?)
	L27 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L28 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L29 QUE (NEPHROTOX? OR HEPATOTOX?)
	L30 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L31 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L32 QUE L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 OR L30 OR L31
	L33 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE
	OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE
	OR PORCINE OR MONKEY? OR MACAQUE?)
	L34 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA
	OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L35 QUE L32 OR L33 OR L34
	L36 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR
	PRIMATES OR PRIMATE?)
	L37 QUE L35 OR L36
	L38 (8795)SEA FILE=TOXCENTER L6 AND L37
	L39 (1436)SEA FILE=TOXCENTER L38 AND ED>=20141201
	L40 (184)SEA FILE=TOXCENTER L38 AND L3
	L41 (1597)SEA FILE=TOXCENTER L39 OR L40
	L42 (269)SEA FILE=TOXCENTER L41 AND MEDLINE/FS
	L43 (263)SEA FILE=TOXCENTER L41 AND BIOSIS/FS
	L44 (1050)SEA FILE=TOXCENTER L41 AND CAPLUS/FS
	L45 (15)SEA FILE=TOXCENTER L41 NOT (L42 OR L43 OR L44)
	L46 (1425)DUP REM L42 L43 L45 L44 (172 DUPLICATES REMOVED)
	L47 (269)SEA FILE=TOXCENTER L46
	L48 (234)SEA FILE=TOXCENTER L46
	L49 (908)SEA FILE=TOXCENTER L46
	L50 (14)SEA FILE=TOXCENTER L46
	L51 (211)SEA FILE=TOXCENTER (L47 OR L48 OR L49 OR L50) AND BIOSIS/FS AND ED>=20141201
	L52 (269)SEA FILE=TOXCENTER L46

Table B-2. Database Query Strings

Database search date	Query string
	L53 (234)SEA FILE=TOXCENTER L46 L54 (908)SEA FILE=TOXCENTER L46 L55 (14)SEA FILE=TOXCENTER L46 L56 (826)SEA FILE=TOXCENTER (L52 OR L53 OR L54 OR L55) AND CAPLUS/FS AND ED>=20141201 L57 (52)SEA FILE=TOXCENTER L56 AND ?MOLYB?/TI L58 (269)SEA FILE=TOXCENTER L46 L59 (234)SEA FILE=TOXCENTER L46 L60 (908)SEA FILE=TOXCENTER L46 L61 (14)SEA FILE=TOXCENTER L46 L62 (1275)SEA FILE=TOXCENTER (L58 OR L59 OR L60 OR L61) AND ED>=20141201 L63 1012 SEA FILE=TOXCENTER L62 NOT (L51 OR L57) --------- L64 97 SEA FILE=TOXCENTER L63 AND (MOLYB?/TI OR DIMOLYB?/TI OR DODECACHLOROHEXAMOLYB?/TI OR HEPTAMOLYB?/TI OR HEXACARBONYLMOLY B?/TI OR HEXAFLUOROMOLYB?/TI OR HEXAMOLYB?/TI OR OCTACHLOROHEXA MOLYB?/TI OR PARAMOLYB?/TI) L65 5 SEA FILE=TOXCENTER L63 AND (PENTACHLOROMOLYB?/TI OR TETRAACETAT ODIMOLYB?/TI OR TETRAOXOMOLYB?/TI OR TETRASULFIDOMOLYB?/TI OR TETRATHIOMOLYB?/TI OR TETRATHIOOXOMOLYB?/TI OR THIOMOLYB?/TI OR TRICHLOROOXOMOLYB?/TI) L66 1 SEA FILE=TOXCENTER L63 AND ("3N5"/TI OR "AMMONIUM MOLIBDATE"/TI OR "AMMONIUM MOLIBDENUM OXIDE"/TI OR "AMPERIT 105.054"/TI OR "AMPERIT 106.2"/TI OR "ATTM"/TI OR "BIS(AMMONIUM)TETRATHIOMOLYB DATE(2-)"/TI OR "BOUEN SKN 301"/TI) L67 0 SEA FILE=TOXCENTER L63 AND ("C-POWDER"/TI OR "COPREXA"/TI OR "DAG 206"/TI OR "DAG 325"/TI OR "DAG-V 657"/TI OR "DEFRIC COAT HMB 2"/TI OR "DM 1 (SULFIDE)"/TI OR "DMI 7"/TI OR "JCPDS 35-0609"/TI OR "LIQUI-MOLY LM 11"/TI OR "LIQUI-MOLY LM 2"/TI) L68 0 SEA FILE=TOXCENTER L63 AND ("LIQUI-MOLY Z POWDER"/TI OR "LM 13"/TI OR "MC 400WR"/TI OR "MCHVL"/TI OR "MD 40"/TI OR "METCO 63"/TI OR "MF 000"/TI OR "MIPO-M 15"/TI OR "MO 1202T"/TI OR "MO-1202T"/TI OR "MOLY FINE POWDER Y"/TI) L69 0 SEA FILE=TOXCENTER L63 AND ("MOLY POWDER B"/TI OR "MOLY POWDER C"/TI OR "MOLY POWDER PA"/TI OR "MOLY POWDER PB"/TI OR "MOLY POWDER PS"/TI OR "MOLYCOLLOID CF 626"/TI OR "MOLYFORM 15"/TI OR "MOLYHIBIT 100"/TI OR "MOLYKA R"/TI OR "MOLYKA R-L 3"/TI) L70 0 SEA FILE=TOXCENTER L63 AND ("MOLYKE R"/TI OR "MOLYKOTE"/TI OR "MOLYKOTE MICROSIZE POWDER"/TI OR "MOLYKOTE Z"/TI OR "MOLYKOTE Z POWDER"/TI OR "MOLYSULFIDE"/TI OR "MOP-P 100"/TI OR "MOPOL M"/TI OR "MOPOL S"/TI OR "MOTIMOL"/TI OR "MVCH 1"/TI) L71 0 SEA FILE=TOXCENTER L63 AND ("NEOZ"/TI OR "NICHIMOLY C"/TI OR

Table B-2. Database Query Strings

Database search date	Query string
	"OKS 110"/TI OR "PA POWDER"/TI OR "PIGMENT BLACK 34"/TI OR "POL-U"/TI OR "POWDER PA"/TI OR "RAC 01"/TI OR "SGC 15"/TI OR "SOLVEST 390A"/TI OR "SUMIPOWDER PA"/TI OR "T-POWDER"/TI OR "TIOMOLIBDATE DIAMMONIUM"/TI OR "TMOIO"/TI OR "TSM1"/TI)
	L72 103 SEA FILE=TOXCENTER L64 OR L65 OR L66
	D SCAN L72
	ACT MOLY2/A

	L76 (34132)SEA FILE=TOXCENTER 7439-98-7 OR 1317-33-5 OR 12033-29-3 OR 12033-33-9 OR 11098-99-0 OR 18868-43-4 OR 1313-27-5 OR 1313-29-7 OR 11098-84-3 OR 27546-07-2 OR 12054-85-2 OR 15060-55-6 OR 7631-95-0 OR 10102-40-6
	L77 (523)SEA FILE=TOXCENTER 7789-82-4 OR 12011-97-1 OR 11119-46-3 OR 11062-51-4 OR 10241-05-1 OR 1309-56-4 OR 7783-77-9 OR 13939-06-5 OR 14221-06-8 OR 13814-74-9
	L78 (1148)SEA FILE=TOXCENTER 12027-67-7 OR 13106-76-8
	L79 (35122)SEA FILE=TOXCENTER L76 OR L77 OR L78
	L80 (22953)SEA FILE=TOXCENTER L79 NOT PATENT/DT
	L81 (22927)SEA FILE=TOXCENTER L80 NOT TSCATS/FS
	L82 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?)
	L83 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT)
	L84 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50)
	L85 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT
	L86 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?)
	L87 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?)
	L88 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?)
	L89 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE))
	L90 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)
	L91 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?)
	L92 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)
	L93 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)
	L94 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L95 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L96 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L97 QUE (ENDOCRIN? AND DISRUPT?)

Table B-2. Database Query Strings

Database search date	Query string
	L98 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L99 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L100 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L101 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L102 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L103 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L104 QUE (NEPHROTOX? OR HEPATOTOX?)
	L105 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L106 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L107 QUE L82 OR L83 OR L84 OR L85 OR L86 OR L87 OR L88 OR L89 OR L90 OR L91 OR L92 OR L93 OR L94 OR L95 OR L96 OR L97 OR L98 OR L99 OR L100 OR L101 OR L102 OR L103 OR L104 OR L105 OR L106
	L108 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?)
	L109 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L110 QUE L107 OR L108 OR L109
	L111 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?)
	L112 QUE L110 OR L111
	L113(8795)SEA FILE=TOXCENTER L81 AND L112
	L114(1436)SEA FILE=TOXCENTER L113 AND ED>=20141201
	L115(184)SEA FILE=TOXCENTER L113 AND L78
	L116(1597)SEA FILE=TOXCENTER L114 OR L115
	L117(269)SEA FILE=TOXCENTER L116 AND MEDLINE/FS
	L118(263)SEA FILE=TOXCENTER L116 AND BIOSIS/FS
	L119(1050)SEA FILE=TOXCENTER L116 AND CAPLUS/FS
	L120(15)SEA FILE=TOXCENTER L116 NOT (L117 OR L118 OR L119)
	L121(1425)DUP REM L117 L118 L120 L119 (172 DUPLICATES REMOVED)
	L122(269)SEA FILE=TOXCENTER L121
	L123(234)SEA FILE=TOXCENTER L121
	L124(908)SEA FILE=TOXCENTER L121
	L125(14)SEA FILE=TOXCENTER L121
	L126(150)SEA FILE=TOXCENTER (L122 OR L123 OR L124 OR L125) NOT ED>=20141
	L127(23)SEA FILE=TOXCENTER L126 AND BIOSIS/FS
	L128(14)SEA FILE=TOXCENTER L126 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/
	L129(82)SEA FILE=TOXCENTER L126 AND CAPLUS/FS
	L130(29)SEA FILE=TOXCENTER L129 AND ?MOLYB?/TI

Table B-2. Database Query Strings

Database search date	Query string
	L131(37)SEA FILE=TOXCENTER L127 OR L128 L132 84 SEA FILE=TOXCENTER L126 NOT (L131 OR L130) --------- L133 15 SEA FILE=TOXCENTER L132 AND (MOLYB?/TI OR DIMOLYB?/TI OR DODECACHLOROHEXAMOLYB?/TI OR HEPTAMOLYB?/TI OR HEXACARBONYLMOLYB?/TI OR HEXAFLUOROMOLYB?/TI OR HEXAMOLYB?/TI OR OCTACHLOROHEXAMOLYB?/TI OR PARAMOLYB?/TI) L134 0 SEA FILE=TOXCENTER L1L32 AND (PENTACHLOROMOLYB?/TI OR TETRAACETATODIMOLYB?/TI OR TETRAOXOMOLYB?/TI OR TETRASULFIDOMOLYB?/TI OR TETRATHIOMOLYB?/TI OR TETRATHIOOXOMOLYB?/TI OR THIOMOLYB?/TI OR TRICHLOROOXOMOLYB?/TI) L135 0 SEA FILE=TOXCENTER L132 AND ("3N5"/TI OR "AMMONIUM MOLIBDATE"/TI OR "AMMONIUM MOLIBDENUM OXIDE"/TI OR "AMPERIT 105.054"/TI OR "AMPERIT 106.2"/TI OR "ATTM"/TI OR "BIS(AMMONIUM)TETRATHIOMOLYBDATE(2-)"/TI OR "BOUEN SKN 301"/TI) L136 0 SEA FILE=TOXCENTER L132 AND ("C-POWDER"/TI OR "COPREXA"/TI OR "DAG 206"/TI OR "DAG 325"/TI OR "DAG-V 657"/TI OR "DEFRIC COAT HMB 2"/TI OR "DM 1 (SULFIDE)"/TI OR "DMI 7"/TI OR "JCPDS 35-0609"/TI OR "LIQUI-MOLY LM 11"/TI OR "LIQUI-MOLY LM 2"/TI) L137 0 SEA FILE=TOXCENTER L132 AND ("LIQUI-MOLY Z POWDER"/TI OR "LM 13"/TI OR "MC 400WR"/TI OR "MCHVL"/TI OR "MD 40"/TI OR "METCO 63"/TI OR "MF 000"/TI OR "MIPO-M 15"/TI OR "MO 1202T"/TI OR "MO-1202T"/TI OR "MOLY FINE POWDER Y"/TI) L138 0 SEA FILE=TOXCENTER L132 AND ("MOLY POWDER B"/TI OR "MOLY POWDER C"/TI OR "MOLY POWDER PA"/TI OR "MOLY POWDER PB"/TI OR "MOLY POWDER PS"/TI OR "MOLYCOLLOID CF 626"/TI OR "MOLYFORM 15"/TI OR "MOLYHIBIT 100"/TI OR "MOLYKA R"/TI OR "MOLYKA R-L 3"/TI) L139 0 SEA FILE=TOXCENTER L132 AND ("MOLYKE R"/TI OR "MOLYKOTE"/TI OR "MOLYKOTE MICROSIZE POWDER"/TI OR "MOLYKOTE Z"/TI OR "MOLYKOTE Z POWDER"/TI OR "MOLYSULFIDE"/TI OR "MOP-P 100"/TI OR "MOPOL M"/TI OR "MOPOL S"/TI OR "MOTIMOL"/TI OR "MVCH 1"/TI) L140 0 SEA FILE=TOXCENTER L132 AND ("NEOZ"/TI OR "NICHIMOLY C"/TI OR "OKS 110"/TI OR "PA POWDER"/TI OR "PIGMENT BLACK 34"/TI OR "POL-U"/TI OR "POWDER PA"/TI OR "RAC 01"/TI OR "SGC 15"/TI OR "SOLVEST 390A"/TI OR "SUMIPOWDER PA"/TI OR "T-POWDER"/TI OR "TIOMOLIBDATE DIAMMONIUM"/TI OR "TMOIO"/TI OR "TSM1"/TI) D SCAN L133

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS[a]	
01/2018	Compounds searched: 7439-98-7, 1317-33-5, 12033-29-3, 12033-33-9, 11098-99-0, 18868-43-4, 1313-27-5, 1313-29-7, 11098-84-3, 27546-07-2, 12054-85-2, 15060-55-6, 7631-95-0, 10102-40-6, 7789-82-4, 12011-97-1, 11119-46-3, 11062-51-4, 10241-05-1, 1309-56-4, 7783-77-9, 13939-06-5, 14221-06-8, 13814-74-9, 12027-67-7, 13106-76-8
NTP	
01/2018	**14th ROC (https://ntp.niehs.nih.gov/pubhealth/roc/index-1.html):** 7439-98-7 OR 1317-33-5 OR 12033-29-3 OR 12033-33-9 OR 11098-99-0 OR 18868-43-4 OR 1313-27-5 OR 1313-29-7 OR 11098-84-3 OR 27546-07-2 OR 12054-85-2 OR 15060-55-6 OR 7631-95-0 OR 10102-40-6 OR 7789-82-4 OR 12011-97-1 OR 11119-46-3 OR 11062-51-4 OR 10241-05-1 OR 1309-56-4 OR 7783-77-9 OR 13939-06-5 OR 14221-06-8 OR 13814-74-9 OR 12027-67-7 OR 13106-76-8 molybdenum OR molybdate OR molybdic OR dimolybdate OR dimolybdenum OR dodecachlorohexamolybdenum OR heptamolybdate OR hexacarbonylmolybdenum OR hexafluoromolybdenum OR hexamolybdenum OR molibdate OR molibdenum OR octachlorohexamolybdenum OR paramolybdate OR pentachloromolybdenum OR tetraacetatodimolybdenum OR tetraoxomolybdate OR tetrasulfidomolybdate OR tetrathiomolybdate OR tetrathiooxomolybdate OR thiomolybdate OR thiomolybdic OR tiomolibdate OR trichlorooxomolybdenum OR pigment black 34 **NTP Site Search (http://ntpsearch.niehs.nih.gov/home) with Content Types "Reports & Publications", "Systematic Review" or "Testing Status":** 7439-98-7 OR 1317-33-5 OR 12033-29-3 OR 12033-33-9 OR 11098-99-0 OR 18868-43-4 OR 1313-27-5 OR 1313-29-7 OR 11098-84-3 OR 27546-07-2 OR 12054-85-2 OR 15060-55-6 OR 7631-95-0 OR 10102-40-6 OR 7789-82-4 OR 12011-97-1 OR 11119-46-3 OR 11062-51-4 OR 10241-05-1 OR 1309-56-4 OR 7783-77-9 OR 13939-06-5 OR 14221-06-8 OR 13814-74-9 OR 12027-67-7 OR 13106-76-8 molybdenum OR molybdate OR molybdic OR dimolybdate OR dimolybdenum OR dodecachlorohexamolybdenum OR heptamolybdate OR hexacarbonylmolybdenum OR hexafluoromolybdenum OR hexamolybdenum OR molibdate OR molibdenum OR octachlorohexamolybdenum OR paramolybdate OR pentachloromolybdenum OR tetraacetatodimolybdenum OR tetraoxomolybdate OR tetrasulfidomolybdate OR tetrathiomolybdate OR tetrathiooxomolybdate OR thiomolybdate OR thiomolybdic OR tiomolibdate OR trichlorooxomolybdenum OR pigment black 34
Regulations.gov	
01/2018	**Notices or rules:** 7439-98-7, 1317-33-5, 12033-29-3, 12033-33-9, 11098-99-0, 18868-43-4, 1313-27-5, 1313-29-7, 11098-84-3, 27546-07-2, 12054-85-2, 15060-55-6, 7631-95-0, 10102-40-6, 7789-82-4, 12011-97-1, 11119-46-3, 11062-51-4, 10241-05-1, 1309-56-4, 7783-77-9, 13939-06-5, 14221-06-8, 13814-74-9, 12027-67-7, 13106-76-8
NIH RePORTER	
04/2019	**Text Search:** "3N5" OR "Ammonium dimolybdate" OR "Ammonium heptamolybdate" OR "Ammonium heptamolybdate tetrahydrate" OR "Ammonium molibdate" OR "Ammonium molibdenum oxide" OR "Ammonium molybdate" OR "Ammonium molybdate hydrate" OR "Ammonium molybdate tetrahydrate" OR "Ammonium molybdate(VI)" OR "Ammonium molybdenum oxide" OR "Ammonium molybdenum sulfide" OR "ammonium paramolybdate" OR "Ammonium paramolybdate tetrahydrate" OR "Ammonium tetrasulfidomolybdate(2-)" OR "Ammonium tetrathiomolybdate" OR "Ammonium thiomolybdate(VI)" OR "Amperit 105.054" OR "Amperit 106.2" OR

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	"ATTM" OR "Bis(ammonium)tetrathiomolybdate(2-)" OR "Bouen SKN 301" OR "C-Powder" OR "Calcium molybdate" OR "Calcium molybdate(VI)" OR "Calcium molybdenate" OR "Calcium molybdenum oxide" OR "Coprexa" OR "DAG 206" OR "DAG 325" OR "DAG-V 657" OR "Defric coat HMB 2" OR "Diammonium dimolybdate" OR "Diammonium tetrakis(sulfido)molybdate(2-)" OR "Diammonium tetrakis(thioxo)molybdate" OR "Diammonium tetrasulfidomolybdate" OR "Diammonium tetrathiomolybdate" OR "Diammonium tetrathiomolybdate(2-)" OR "Diammonium tetrathiooxomolybdate(2-)" OR "Diammonium tetrathioxomolybdate(2-)" OR "Diammonium thiomolybdate" OR "Dimolybdenum tetraacetate" OR "Dimolybdenum trioxide" OR "dimolybdenum trisulfide " OR "Disodium molybdate" OR "Disodium molybdate dihydrate" OR "Disodium tetraoxomolybdate" OR "DM 1 (sulfide)" OR "DMI 7" OR "Dodecachlorohexamolybdenum" OR "Hexaammonium heptamolybdate tetrahydrate" OR "Hexaammonium molybdate tetrahydrate" OR "Hexacarbonylmolybdenum" OR "Hexafluoromolybdenum" OR "Hexamolybdenum dodecachloride" OR "JCPDS 35-0609" OR "Liqui-Moly LM 11" OR "Liqui-Moly LM 2" OR "Liqui-Moly Z Powder" OR "LM 13" OR "MC 400WR" OR "MChVL" OR "MD 40" OR "Metco 63" OR "MF 000" OR "MIPO-M 15" OR "Mo 1202T" OR "Mo-1202T" OR "Moly Fine Powder Y" OR "Moly Powder B" OR "Moly Powder C" OR "Moly Powder PA" OR "Moly Powder PB" OR "Moly Powder PS" OR "Molybdate (Mo2O72-), diammonium" OR "Molybdate (MoO42-), disodium, dihydrate, (T-4)-" OR "Molybdate, calcium" OR "Molybdena" OR "Molybdenite" OR "Molybdenum" OR "Molybdenum anhydride" OR "Molybdenum bisulfide" OR "Molybdenum carbide" OR "Molybdenum carbonyl" OR "Molybdenum chloride" OR "Molybdenum chloride oxide" OR "Molybdenum dioxide" OR "Molybdenum disulfide" OR "Molybdenum disulphide" OR "Molybdenum fluoride" OR "Molybdenum hexacarbonyl" OR "Molybdenum hexafluoride" OR "Molybdenum metallicum" OR "Molybdenum monocarbide" OR "Molybdenum oxide" OR "Molybdenum oxychloride" **(Advanced), Search in: Projects AdminIC: All, Fiscal Year: Active Projects** **Text Search:** "Molybdenum oxytrichloride" OR "Molybdenum pentachloride" OR "Molybdenum peroxide" OR "Molybdenum sesquioxide" OR "Molybdenum sesquisulfide" OR "Molybdenum sodium oxide" OR "Molybdenum sulfide" OR "Molybdenum sulphide" OR "Molybdenum trichloride monoxide" OR "Molybdenum trichloride oxide" OR "Molybdenum trioxide" OR "Molybdenum trioxide pentamer" OR "Molybdenum trioxide tetramer" OR "Molybdenum trisulfide" OR "Molybdenum(6) fluoride" OR "Molybdenum(II) acetate" OR "Molybdenum(II) chloride" OR "molybdenum(III) sulfide" OR "molybdenum(IV) oxide" OR "Molybdenum(IV) sulfide" OR "Molybdenum(V) chloride" OR "Molybdenum(VI) oxide" OR "Molybdenum(VI) trioxide" OR "Molybdenumperoxide" OR "Molybdic acid (H2Mo2O7), diammonium salt" OR "Molybdic acid (H2MoO4), calcium salt (1:1)" OR "Molybdic acid anhydride" OR "Molybdic acid, ammonium salt" OR "Molybdic acid, calcium salt" OR "Molybdic acid, disodium salt" OR "Molybdic acid, disodium salt, dihydrate" OR "Molybdic anhydride" OR "Molybdic oxide" OR "Molybdic trioxide" OR "Molycolloid CF 626" OR "Molyform 15" OR "Molyhibit 100" OR "Molyka R" OR "Molyka R-L 3" OR "Molyke R" OR "Molykote" OR "Molykote Microsize Powder" OR "Molykote Z" OR "Molykote Z Powder" OR "Molysulfide" OR "MOP-P 100" OR "Mopol M" OR "Mopol S" OR "Motimol" OR "MVCh 1" OR "Natural molybdenite" OR "Natural molybdite" OR "NeoZ" OR "Nichimoly C" OR "Octachlorohexamolybdenum(4) tetrachloride" OR "OKS 110" OR "PA Powder" OR "Pentachloromolybdenum Molybdenite" OR "Pigment Black 34" OR "Pol-U" OR "Powder PA" OR "RAC 01" OR "SGC 15" OR "Sodium molybdate" OR "Sodium molybdate dihydrate" OR "Sodium molybdate(VI)" OR "Sodium molybdate(VI) dihydrate" OR "Sodium molybdenate" OR "Sodium molybdenum oxide" OR "Sodium tetraoxomolybdate(2-)" OR "Solvest 390A" OR "Sumipowder PA" OR

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	"Tetraacetatodimolybdenum" OR "tetrakis(acetato)di-Molybdenum" OR "Tetrakis(acetato)dimolybdenum" OR "Tetrakis(acetato)molybdenum" OR "Tetrakis(mu-(acetato-O:O'))dimolybdenum" OR "tetrakis(mu-acetato)di-Molybdenum" OR "Tetrakis(mu-acetato)dimolybdenum" OR "tetrakis[mu-(acetato-O:O')]di-Molybdenum" OR "Thiomolybdic acid, diammonium salt" OR "Tiomolibdate diammonium" OR "TMOIO" OR "Trichlorooxomolybdenum" OR "Trichlorooxomolybdenum(V)" OR "TsM1" OR "Hexaammonium heptamolybdate" OR "Hexammonium heptamolybdat" OR "Hexammonium tetracosaoxoheptamolybdate" OR "Molybdate (Mo7O24), hexammonium" OR "Molybdate (Mo7O246-), ammonium (1:6)" OR "Molybdate (Mo7O246-), hexaammonium" **(Advanced), Search in: Projects Admin IC: All, Fiscal Year: Active Projects** **Text Search:** "Molybdate, hexaammonium" OR "Molybdic acid (H6Mo7O24), hexaammonium salt" OR "Molybdic acid, hexaammonium salt" OR "Diammonium molybdate" OR "Diammonium tetraoxomolybdate(2-)" OR "Molybdate (MoO42-), ammonium (1:2), (T-4)-" OR "Molybdate (MoO42-), diammonium, (beta-4)-" OR "Molybdate (MoO42-), diammonium, (T-4)-" OR "Molybdic acid (H2MoO4), diammonium salt" OR "Molybdic acid, diammonium salt" (Advanced), Search in: Projects Admin IC: All, Fiscal Year: Active Projects Text Search: molybdenum OR molybdate OR molybdic OR dimolybdate OR dimolybdenum OR dodecachlorohexamolybdenum OR heptamolybdate OR hexacarbonylmolybdenum OR hexafluoromolybdenum OR hexamolybdenum OR molibdate OR molibdenum OR octachlorohexamolybdenum OR paramolybdate OR pentachloromolybdenum OR tetraacetatodimolybdenum OR tetraoxomolybdate OR tetrasulfidomolybdate OR tetrathiomolybdate OR tetrathiooxomolybdate OR thiomolybdate OR thiomolybdic OR tiomolibdate OR trichlorooxomolybdenum OR pigment black 34 **(Advanced), Search in: Projects AdminIC: All, Fiscal Year: Active Projects**
Other	Identified throughout the assessment process

[a]Several versions of the TSCATS database were searched, as needed, by CASRN including TSCATS1 via Toxline (no date limit), TSCATS2 via https://yosemite.epa.gov/oppts/epatscat8.nsf/ReportSearch?OpenForm (date restricted by EPA receipt date), and TSCATS via CDAT (date restricted by 'Mail Received Date Range'), as well as google for recent TSCA submissions.

The 2018 results were:

- Number of records identified from PubMed, TOXLINE, and TOXCENTER (after duplicate removal): 2,394
- Number of records identified from other strategies: 114
- Total number of records to undergo literature screening: 2,508

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on molybdenum:

- Title and abstract screen
- Full text screen

Title and Abstract Screen. Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered relevant (see Table B-1 for inclusion criteria) were moved to the

second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study was not relevant to the toxicological profile.

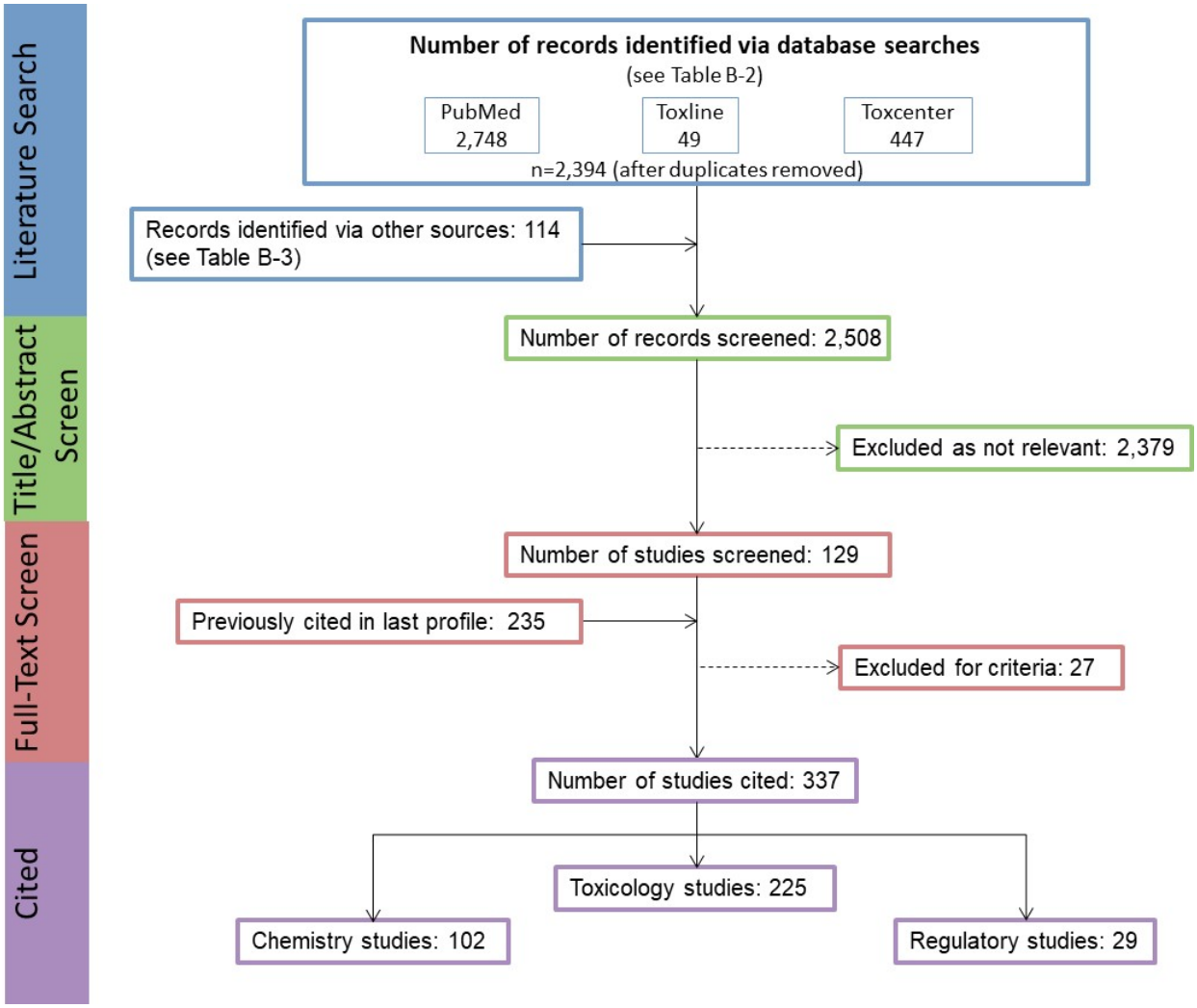
- Number of titles and abstracts screened: 2,508
- Number of studies considered relevant and moved to the next step: 129

Full Text Screen. The second step in the literature screening process was a full text review of individual studies considered relevant in the title and abstract screen step. Each study was reviewed to determine whether it was relevant for inclusion in the toxicological profile.

- Number of studies undergoing full text review: 129
- Number of studies cited in the pre-public draft of the toxicological profile: 235
- Total number of studies cited in the profile: 337

A summary of the results of the literature search and screening is presented in Figure B-1.

Figure B-1. January 2018 Literature Search Results and Screen for Molybdenum



APPENDIX C. FRAMEWORK FOR ATSDR'S SYSTEMATIC REVIEW OF HEALTH EFFECTS DATA FOR MOLYBDENUM

To increase the transparency of ATSDR's process of identifying, evaluating, synthesizing, and interpreting the scientific evidence on the health effects associated with exposure to molybdenum, ATSDR utilized a slight modification of NTP's Office of Health Assessment and Translation (OHAT) systematic review methodology (NTP 2013, 2015; Rooney et al. 2014). ATSDR's framework is an eight-step process for systematic review with the goal of identifying the potential health hazards of exposure to molybdenum:

- Step 1. Problem Formulation
- Step 2. Literature Search and Screen for Health Effects Studies
- Step 3. Extract Data from Health Effects Studies
- Step 4. Identify Potential Health Effect Outcomes of Concern
- Step 5. Assess the Risk of Bias for Individual Studies
- Step 6. Rate the Confidence in the Body of Evidence for Each Relevant Outcome
- Step 7. Translate Confidence Rating into Level of Evidence of Health Effects
- Step 8. Integrate Evidence to Develop Hazard Identification Conclusions

C.1 PROBLEM FORMULATION

The objective of the toxicological profile and this systematic review was to identify the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to molybdenum. The inclusion criteria used to identify relevant studies examining the health effects of molybdenum are presented in Table C-1.

Table C-1. Inclusion Criteria for Identifying Health Effects Studies

Species
Human
Laboratory mammals
Route of exposure
Inhalation
Oral
Dermal (or ocular)
Parenteral (these studies will be considered supporting data)
Health outcome
Death
Systemic effects
Body weight effects
Respiratory effects
Cardiovascular effects
Gastrointestinal effects
Hematological effects
Musculoskeletal effects
Hepatic effects
Renal effects

Table C-1. Inclusion Criteria for Identifying Health Effects Studies

Dermal effects
Ocular effects
Endocrine effects
Immunological effects
Neurological effects
Reproductive effects
Developmental effects
Other noncancer effects
Cancer

Data from human and laboratory animal studies were considered relevant for addressing this objective. Human studies were divided into two broad categories: observational epidemiology studies and controlled exposure studies. The observational epidemiology studies were further divided: cohort studies (retrospective and prospective studies), population studies (with individual data or aggregate data), and case-control studies.

C.2 LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

A literature search and screen was conducted to identify studies examining the health effects of molybdenum. The literature search framework for the toxicological profile is discussed in detail in Appendix B.

C.2.1 Literature Search

As noted in Appendix B, the current literature search was intended to update the draft toxicological profile for molybdenum released for public comment in 2017. See Appendix B for the databases searched and the search strategy.

A total of 2,508 records relevant to all sections of the toxicological profile were identified (after duplicate removal).

C.2.2 Literature Screening

As described in Appendix B, a two-step process was used to screen the literature search to identify relevant studies examining the health effects of molybdenum.

Title and Abstract Screen. In the Title and Abstract Screen step, 2,508 records were reviewed; 71 documents were considered to meet the health effects inclusion criteria in Table C-1 and were moved to the next step in the process.

Full Text Screen. In the second step in the literature screening process for the systematic review, a full text review of 92 health effects documents (documents identified in the update literature search and documents cited in older versions of the profile) was performed. From those 92 documents, 115 studies were included in the qualitative review.

C.3 EXTRACT DATA FROM HEALTH EFFECTS STUDIES

Relevant data extracted from the individual studies selected for inclusion in the systematic review were collected in customized data forms. A summary of the type of data extracted from each study is presented in Table C-2. For references that included more than one experiment or species, data extraction records were created for each experiment or species.

Table C-2. Data Extracted From Individual Studies

Citation
Chemical form
Route of exposure (e.g., inhalation, oral, dermal)
Specific route (e.g., gavage in oil, drinking water)
Species
Strain
Exposure duration category (e.g., acute, intermediate, chronic)
Exposure duration
Frequency of exposure (e.g., 6 hours/day, 5 days/week)
Exposure length
Number of animals or subjects per sex per group
Dose/exposure levels
Parameters monitored
Description of the study design and method
Summary of calculations used to estimate doses (if applicable)
Summary of the study results
Reviewer's comments on the study
Outcome summary (one entry for each examined outcome)
No-observed-adverse-effect level (NOAEL) value
Lowest-observed-adverse-effect level (LOAEL) value
Effect observed at the LOAEL value

A summary of the extracted data for each study is presented in the Supplemental Document for Molybdenum and overviews of the results of the studies are presented in Sections 2.2–2.18 of the profile and in the Levels of Significant Exposures tables in Section 2.1 of the profile (Tables 2-1–2-3).

C.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN

Overviews of the potential health effect outcomes for molybdenum identified in human and animal studies are presented in Tables C-3 and C-4, respectively. The available human studies examined a limited number of endpoints and reported respiratory, hepatic, endocrine, other systemic (alterations in uric acid levels), reproductive, and developmental effects. Animal studies examined a number of endpoints following inhalation and oral exposure; no dermal exposure studies were identified. These studies examined most systemic endpoints and reported respiratory, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, dermal, and body weight effects. Additionally, animal studies

Table C-3. Overview of the Health Outcomes for Molybdenum Evaluated In Human Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological	Neurological	Reproductive	Developmental	Other Noncancer	Caner
Inhalation studies																	
Cohort		2 1														1 1	1 1
Case control																	
Population																	
Case series																	
Oral studies																	
Cohort														2 2	2 1	1 0	
Case control																	
Population	1 0	1 0	3 2			1 0	1 1			1 1	3 2						2 0
Case series																1 0	
Dermal studies																	
Cohort																	
Case control																	
Population																	
Case series																	

Number of studies examining endpoint	0	1	2	3	4	5-9	≥10	
Number of studies reporting outcome	0	1	2	3	4	5-9	≥10	

APPENDIX C

Table C-4. Overview of the Health Outcomes for Molybdenum Evaluated in Experimental Animal Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological[a]	Neurological[a]	Reproductive[a]	Developmental	Other Noncancer	Caner
Inhalation studies																	
Acute-duration	5 5	5 0															
Intermediate-duration		2 0	2 0	2 0	2 0	2 0	2 0	2 0			2 0		2 0	2 0			
Chronic-duration	2 0	2 2	2 0	2 0		2 0	2 0	2 0			2 0		2 0	2 0			2 2
Oral studies																	
Acute-duration	6 2			1 1	1 0	5 4	2 1	2 0						4 3			
Intermediate-duration	41 28	3 0	2 0	3 1	19 6	13 10	8 6	9 6	3 3		8 5		1 0	12 8	12 5	2 0	
Chronic-duration																	
Dermal studies																	
Acute-duration									7 0	4 4		4 0					
Intermediate-duration																	
Chronic-duration																	

Number of studies examining endpoint	0	1	2	3	4	5-9	≥10
Number of studies reporting outcome	0	1	2	3	4	5-9	≥10

[a]Number of studies examining endpoint includes study evaluating histopathology, but not evaluating function.

have reported neurological, reproductive, and developmental effects. Although animal studies have identified a number of affected tissues and systems, interpretation of much of the data is limited by an inadequate amount of copper in the diet. Studies in which the diet did not contain adequate levels of copper or administered ammonium tetrathiomolybdate were carried through Step 3 of the systematic review, but were not considered in the identification of potential health effect outcomes of concern. Additionally, body weight effects were not considered a primary effect especially since most studies did not provide data on food intake; thus, this endpoint was not considered in the assessment of potential human hazards. Studies examining the respiratory, hepatic, renal, uric acid, reproductive, and developmental outcomes were carried through to Steps 4–8 of the systematic review. There were 115 studies (published in 92 documents) examining these potential outcomes were carried through to Steps 4–8 of the systematic review.

C.5 ASSESS THE RISK OF BIAS FOR INDIVIDUAL STUDIES

C.5.1 Risk of Bias Assessment

The risk of bias of individual studies was assessed using OHAT's Risk of Bias Tool (NTP 2015). The risk of bias questions for observational epidemiology studies, human-controlled exposure studies, and animal experimental studies are presented in Tables C-5, C-6, and C-7, respectively. Each risk of bias question was answered on a four-point scale:

- **Definitely low risk of bias (++)**
- **Probably low risk of bias (+)**
- **Probably high risk of bias (-)**
- **Definitely high risk of bias (– –)**

Table C-5. Risk of Bias Questionnaire for Observational Epidemiology Studies

Selection bias
Were the comparison groups appropriate?
Confounding bias
Did the study design or analysis account for important confounding and modifying variables?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

Table C-6. Risk of Bias Questionnaire for Human-Controlled Exposure Studies

Selection bias
Was administered dose or exposure level adequately randomized?
Was the allocation to study groups adequately concealed?
Performance bias
Were the research personnel and human subjects blinded to the study group during the study?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

Table C-7. Risk of Bias Questionnaire for Experimental Animal Studies

Selection bias
Was administered dose or exposure level adequately randomized?
Was the allocation to study groups adequately concealed?
Performance bias
Were experimental conditions identical across study groups?
Were the research personnel blinded to the study group during the study?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

In general, “definitely low risk of bias” or “definitely high risk of bias” were used if the question could be answered with information explicitly stated in the study report. If the response to the question could be inferred, then “probably low risk of bias” or “probably high risk of bias” responses were typically used.

After the risk of bias questionnaires were completed for the health effects studies, the studies were assigned to one of three risk of bias tiers based on the responses to the key questions listed below and the responses to the remaining questions.

- Is there confidence in the exposure characterization? (only relevant for observational studies)
- Is there confidence in the outcome assessment?
- Does the study design or analysis account for important confounding and modifying variables? (only relevant for observational studies)

First Tier. Studies placed in the first tier received ratings of "definitely low" or "probably low" risk of bias on the key questions **AND** received a rating of "definitely low" or "probably low" risk of bias on the responses to at least 50% of the other applicable questions.

Second Tier. A study was placed in the second tier if it did not meet the criteria for the first or third tiers.

Third Tier. Studies placed in the third tier received ratings of "definitely high" or "probably high" risk of bias for the key questions **AND** received a rating of "definitely high" or "probably high" risk of bias on the response to at least 50% of the other applicable questions.

The results of the risk of bias assessment for the different types of molybdenum health effects studies (observational epidemiology, human-controlled exposure studies, and animal experimental studies) are presented in Tables C-8, C-9, and C-10, respectively.

C.6 RATE THE CONFIDENCE IN THE BODY OF EVIDENCE FOR EACH RELEVANT OUTCOME

Confidences in the bodies of human and animal evidence were evaluated independently for each potential outcome. ATSDR did not evaluate the confidence in the body of evidence for carcinogenicity; rather, the Agency defaulted to the cancer weight-of-evidence assessment of other agencies including DHHS, EPA, and IARC. The confidence in the body of evidence for an association or no association between exposure to molybdenum and a particular outcome was based on the strengths and weaknesses of individual studies. Four descriptors were used to describe the confidence in the body of evidence for effects or when no effect was found:

- **High confidence:** the true effect is highly likely to be reflected in the apparent relationship
- **Moderate confidence:** the true effect may be reflected in the apparent relationship
- **Low confidence:** the true effect may be different from the apparent relationship
- **Very low confidence:** the true effect is highly likely to be different from the apparent relationship

Confidence in the body of evidence for a particular outcome was rated for each type of study: case-control, case series, cohort, population, human-controlled exposure, and experimental animal. In the absence of data to the contrary, data for a particular outcome were collapsed across animal species, routes of exposure, and exposure durations. If species (or strain), route, or exposure duration differences were noted, then the data were treated as separate outcomes.

Table C-8. Summary of Risk of Bias Assessment for Molybdenum—Observational Epidemiological Studies

Reference	Risk of bias criteria and ratings: Selection bias — Were the comparison groups appropriate?	Confounding bias — Did the study design or analysis account for important confounding and modifying variables?*	Attrition / exclusion bias — Were outcome data complete without attrition or exclusion from analysis?	Detection bias — Is there confidence in the exposure characterization?*	Detection bias — Is there confidence in the outcome assessment?*	Selective reporting bias — Were all measured outcomes reported?	Risk of bias tier
Outcome: Respiratory effects							
Cohort studies							
Ott et al. 2004	–	–	+	na	+	++	Second
Walravens et al. 1979	–	–	+	+	–	+	Second
Outcome: Hepatic effects							
Cross-sectional studies							
Mendy et al. 2012	+	+	+	+	–	+	Second
Outcome: Alterations in uric acid levels							
Cross-sectional studies							
Koval'sky et al. 1961	–	–	+	–	+	+	Second
Cohort studies							
Walravens et al. 1979	–	–	+	+	–	+	Second
Outcome: Reproductive effects							
Cross-sectional studies							
Lewis and Meeker 2015	na	-	+	+	+	+	First
Meeker et al. 2008	+	+	+	++	++	++	First
Meeker et al. 2010	+	+	++	+	++	++	First

Table C-8. Summary of Risk of Bias Assessment for Molybdenum—Observational Epidemiological Studies

Reference	Risk of bias criteria and ratings: Selection bias — Were the comparison groups appropriate?	Confounding bias — Did the study design or analysis account for important confounding and modifying variables?*	Attrition / exclusion bias — Were outcome data complete without attrition or exclusion from analysis?	Detection bias — Is there confidence in the exposure characterization?*	Detection bias — Is there confidence in the outcome assessment?*	Selective reporting bias — Were all measured outcomes reported?	Risk of bias tier
Outcome: Developmental effects							
Cross-sectional studies							
Vazquez-Salas et al. 2014	+	+	+	+	++	+	First
Shirai et al. 2010	na	–	+	+	+	+	Second

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; na = not applicable

*Key question used to assign risk of bias tier.

Table C-9. Summary of Risk of Bias Assessment for Molybdenum—Human-Controlled Exposure Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias: Were outcome data complete without attrition or exclusion from analysis?	Detection bias: Is there confidence in the exposure characterization?	Detection bias: Is there confidence in the outcome assessment?*	Selective reporting bias: Were all measured outcomes reported?	Risk of bias tier
Outcome: Alterations in uric acid levels								
Oral acute exposure								
Deosthale and Gopalan 1974	na	+	+	+	+	+	++	First

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; na = not applicable

*Key question used to assign risk of bias tier.

Table C-10. Summary of Risk of Bias Assessment for Molybdenum—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were experimental conditions identical across study groups?	Performance bias: Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias: Were outcome data complete without attrition or exclusion from analysis?	Detection bias: Is there confidence in the exposure characterization?	Detection bias: Is there confidence in the outcome assessment?*	Selective reporting bias: Were all measured outcomes reported?	Other bias: Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Outcome: Respiratory effects										
Inhalation acute exposure										
NTP 1997 (rat)	++	+	++	+	++	++	++	++	+	First
NTP 1997 (mouse)	++	+	++	+	++	++	++	++	+	First
Inhalation intermediate exposure										
NTP 1997 (rat)	++	+	++	+	++	++	++	++	+	First
NTP 1997 (mouse)	++	+	++	+	++	++	++	++	+	First
Inhalation chronic exposure										
NTP 1997 (rat)	++	+	++	+	++	++	++	++	+	First
NTP 1997 (mouse)	++	+	++	+	++	++	++	++	+	First
Outcome: Hepatic effects										
Inhalation intermediate exposure										
NTP 1997 (rat)	++	+	++	+	++	++	++	++	+	First
NTP 1997 (mouse)	++	+	++	+	++	++	++	++	+	First
Inhalation chronic exposure										
NTP 1997 (rat)	++	+	++	+	++	++	++	++	+	First
NTP 1997 (mouse)	++	+	++	+	++	++	++	++	+	First

Table C-10. Summary of Risk of Bias Assessment for Molybdenum—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were experimental conditions identical across study groups?	Performance bias: Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias: Were outcome data complete without attrition or exclusion from analysis?	Detection bias: Is there confidence in the exposure characterization?	Detection bias: Is there confidence in the outcome assessment?*	Selective reporting bias: Were all measured outcomes reported?	Other bias: Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Oral acute exposure										
Bersenyi et al. 2008 (rabbit)	–	+	+	–	++	–	+	+	+	First
Bersenyi et al. 2008 (rabbit)	–	+	+	–	++	–	+	+	+	First
Oral intermediate exposure										
Murray et al. 2014a (rat)	++	+	++	–	++	++	++	++	++	First
Rana and Chauhan 2000 (rat)	–	+	+	–	++	+	–	++	–	Second
Rana and Kumar 1980b (rat)	–	+	+	–	++	–	–	+	–	Third
Rana and Kumar 1980c (rat)	+	+	–	–	++	–	+	++	–	First
Rana and Kumar 1983 (rat)	+	+	–	–	++	+	+	++	–	First
Rana and Prakash 1986 (rat)	–	+	+	–	++	–	+	+	+	First
Rana et al. 1980 (rat)	–	+	+	–	+	–	+	+	+	First
Rana et al. 1985 (rat)	+	+	+	–	++	+	+	+	+	First
Outcome: Renal effects										
Inhalation intermediate exposure										
NTP 1997 (rat)	++	+	++	+	++	++	++	++	+	First
NTP 1997 (mouse)	++	+	++	+	++	++	++	++	+	First

Table C-10. Summary of Risk of Bias Assessment for Molybdenum—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were experimental conditions identical across study groups?	Performance bias: Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias: Were outcome data complete without attrition or exclusion from analysis?	Detection bias: Is there confidence in the exposure characterization?	Detection bias: Is there confidence in the outcome assessment?*	Selective reporting bias: Were all measured outcomes reported?	Other bias: Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Inhalation chronic exposure										
NTP 1997 (rat)	++	+	++	+	++	++	++	++	+	First
NTP 1997 (mouse)	++	+	++	+	++	++	++	++	+	First
Oral acute exposure										
Bersenyi et al. 2008 (rabbit, males)	–	+	+	–	++	–	+	+	+	First
Bersenyi et al. 2008 (rabbit, females)	–	+	+	–	++	–	+	+	+	First
Oral intermediate exposure										
Bandyopadhyay et al. 1981 (rat)	–	+	+	–	++	–	+	++	++	First
Bompart et al. 1990 (rat)	+	+	+	–	++	+	+	++	+	First
Murray et al. 2014a (rat)	++	+	++	–	++	++	++	++	++	First
Rana et al. 1980 (rat)	–	+	+	–	+	–	+	+	+	First
Rana and Kumar 1980c	+	+	–	–	++	–	+	++	–	First
Rana and Kumar 1983 (rat)	+	+	–	–	++	+	+	++	–	First

Table C-10. Summary of Risk of Bias Assessment for Molybdenum—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were experimental conditions identical across study groups?	Performance bias: Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias: Were outcome data complete without attrition or exclusion from analysis?	Detection bias: Is there confidence in the exposure characterization?	Detection bias: Is there confidence in the outcome assessment?*	Selective reporting bias: Were all measured outcomes reported?	Other bias: Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Outcome: Alterations in uric acid levels										
Oral intermediate exposure										
Murray et al. 2014a (rat)	++	+	++	-	++	++	++	++	++	First
Outcome: Reproductive effects										
Inhalation intermediate exposure										
NTP 1997 (rat)	++	+	++	+	++	++	++	++	+	First
NTP 1997 (mouse)	++	+	++	+	++	++	++	++	+	First
Oral acute exposure										
Zhang et al. 2013 (mouse)	–	+	++	–	++	– –	+	++	–	First
Zhai et al. 2013 (mouse)	–	+	++	–	++	– –	+	++	+	First
Bersenyi et al. 2008 (rabbit, males)	–	+	+	–	++	–	+	+	+	First
Bersenyi et al. 2008 (rabbit, females)	–	+	+	–	++	–	+	+	+	First
Oral intermediate exposure										
Fungwe et al. 1990 (rat)	+	+	+	–	++	–	+	+	– –	First
Jeter and Davis 1954 (rat, adults)	–	+	+	–	++	–	+	+	–	First

Table C-10. Summary of Risk of Bias Assessment for Molybdenum—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were experimental conditions identical across study groups?	Performance bias: Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias: Were outcome data complete without attrition or exclusion from analysis?	Detection bias: Is there confidence in the exposure characterization?	Detection bias: Is there confidence in the outcome assessment?*	Selective reporting bias: Were all measured outcomes reported?	Other bias: Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Jeter and Davis 1954 (rat, weanling)	–	+	+	–	++	–	+	+	– –	First
Murray et al. 2014a (rat)	++	+	++	–	++	++	++	++	++	First
Murray et al. 2019 (rat)	++	+	++	–	++	++	++	++	++	First
Pandey and Singh 2002 (rat)	–	+	++	–	++	+	+	++	–	First
Pandey and Singh 2002 (rat fertility study)	–	+	++	–	++	+	+	++	–	First
Outcome: Developmental effects										
Oral intermediate exposure										
Jeter and Davis 1954 (rat, weanling)	–	+	+	–	++	–	+	+	– –	First
Murray et al. 2014b (rat)	++	+	+	–	++	++	+	++	+	First
Pandey and Singh 2002 (rat)	–	+	++	–	++	+	+	++	–	First

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias

*Key question used to assign risk of bias tier.

C.6.1 Initial Confidence Rating

In ATSDR's modification to the OHAT approach, the body of evidence for an association (or no association) between exposure to molybdenum and a particular outcome was given an initial confidence rating based on the key features of the individual studies examining that outcome. The presence of these key features of study design was determined for individual studies using four "yes or no" questions, which were customized for epidemiology, human controlled exposure, or experimental animal study designs. Separate questionnaires were completed for each outcome assessed in a study. The key features for observational epidemiology (cohort, population, and case-control) studies, human controlled exposure, and experimental animal studies are presented in Tables C-11, C-12, and C-13, respectively. The initial confidence in the study was determined based on the number of key features present in the study design:

- **High Initial Confidence:** Studies in which the responses to the four questions were "yes".
- **Moderate Initial Confidence:** Studies in which the responses to only three of the questions were "yes".
- **Low Initial Confidence:** Studies in which the responses to only two of the questions were "yes".
- **Very Low Initial Confidence:** Studies in which the response to one or none of the questions was "yes".

Table C-11. Key Features of Study Design for Observational Epidemiology Studies

Exposure was experimentally controlled
Exposure occurred prior to the outcome
Outcome was assessed on individual level rather than at the population level
A comparison group was used

Table C-12. Key Features of Study Design for Human-Controlled Exposure Studies

A comparison group was used or the subjects served as their own control
A sufficient number of subjects were tested
Appropriate methods were used to measure outcomes (i.e., clinically-confirmed outcome versus self-reported)
Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis

Table C-13. Key Features of Study Design for Experimental Animal Studies

A concurrent control group was used
A sufficient number of animals per group were tested
Appropriate parameters were used to assess a potential adverse effect
Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis

The presence or absence of the key features and the initial confidence levels for studies examining The presence or absence of the key features and the initial confidence levels for studies examining respiratory, gastrointestinal, renal, dermal, and ocular effects observed in the observational epidemiology, human-controlled exposure, and animal experimental studies are presented in Tables C-14, C-15, and C-16, respectively.

Table C-14. Presence of Key Features of Study Design for Molybdenum—Observational Epidemiology Studies

Reference	Key features: Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	Initial study confidence
Outcome: Respiratory effects					
Cohort studies					
Ott et al. 2004	No	Yes	Yes	No	Low
Walravens et al. 1979	No	No	No	No	Very Low
Outcome: Hepatic effects					
Cross-sectional studies					
Mendy et al. 2012	No	No	Yes	Yes	Low
Outcome: Alterations in uric acid levels					
Cross-sectional studies					
Koval'sky et al. 1961	No	Yes	Yes	No	Low
Cohort studies					
Walravens et al. 1979	No	No	No	No	Very Low
Outcome: Reproductive effects					
Cross-sectional studies					
Lewis and Meeker 2015	No	No	Yes	Yes	Low
Meeker et al. 2008	No	No	Yes	Yes	Low
Meeker et al. 2010	No	No	Yes	Yes	Low

Table C-14. Presence of Key Features of Study Design for Molybdenum—Observational Epidemiology Studies

Reference	Key features: Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	Initial study confidence
Outcome: Developmental effects					
Cross-sectional studies					
Vazquez-Salas et al. 2014	No	No	Yes	Yes	Low
Shirai et al. 2010	No	No	Yes	Yes	Low

Table C-15. Presence of Key Features of Study Design for Molybdenum—Human-Controlled Exposure Studies

Reference	Key feature: Concurrent control group or self-control	Sufficient number of subjects tested	Appropriate methods to measure outcome	Adequate data for statistical analysis	Initial study confidence
Outcome: Alterations in uric acid levels					
Oral acute exposure					
Deosthale and Gopalan 1974	Yes	No	Yes	No	Low

Table C-16. Presence of Key Features of Study Design for Molybdenum—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Outcome: Respiratory effects					
Inhalation acute exposure					
NTP 1997 (rat)	Yes	Yes	Yes	Yes	High
NTP 1997 (mouse)	Yes	Yes	Yes	Yes	High
Inhalation intermediate exposure					
NTP 1997 (rat)	Yes	Yes	Yes	Yes	High
NTP 1997 (mouse)	Yes	Yes	Yes	Yes	High
Inhalation chronic exposure					
NTP 1997 (rat)	Yes	Yes	Yes	Yes	High
NTP 1997 (mouse)	Yes	Yes	Yes	Yes	High
Outcome: Hepatic effects					
Inhalation intermediate exposure					
NTP 1997 (rat)	Yes	Yes	Yes	Yes	High
NTP 1997 (mouse)	Yes	Yes	Yes	Yes	High
Inhalation chronic exposure					
NTP 1997 (rat)	Yes	Yes	Yes	Yes	High
NTP 1997 (mouse)	Yes	Yes	Yes	Yes	High
Oral acute exposure					
Bersenyi et al. 2008 (rabbit, males)	Yes	No	Yes	Yes	Moderate
Bersenyi et al. 2008 (rabbit, females)	Yes	No	Yes	Yes	Moderate
Oral intermediate exposure					
Murray et al. 2014a (rat)	Yes	Yes	Yes	Yes	High
Rana and Chauhan 2000 (rat)	Yes	Yes	No	Yes	Moderate
Rana and Kumar 1980b (rat)	Yes	Yes	No	Yes	Moderate
Rana and Kumar 1980c (rat)	Yes	Yes	No	Yes	Moderate
Rana and Kumar 1983 (rat)	Yes	Yes	No	Yes	Moderate
Rana and Prakash 1986 (rat)	Yes	Yes	No	Yes	Moderate
Rana et al. 1980 (rat)	Yes	Yes	No	No	Low
Rana et al. 1985 (rat)	Yes	Yes	No	Yes	Moderate
Outcome: Renal effects					
Inhalation intermediate exposure					
NTP 1997 (rat)	Yes	Yes	Yes	Yes	High
NTP 1997 (mouse)	Yes	Yes	Yes	Yes	High

Table C-16. Presence of Key Features of Study Design for Molybdenum—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Inhalation chronic exposure					
NTP 1997 (rat)	Yes	Yes	Yes	Yes	High
NTP 1997 (mouse)	Yes	Yes	Yes	Yes	High
Oral acute exposure					
Bersenyi et al. 2008 (rabbit, males)	Yes	No	Yes	Yes	Moderate
Bersenyi et al. 2008 (rabbit, females)	Yes	No	Yes	Yes	Moderate
Oral intermediate exposure					
Bandyopadhyay et al. 1981 (rat)	Yes	No	Yes	No	Low
Bompart et al. 1990 (rat)	Yes	No	Yes	Yes	Moderate
Murray et al. 2014a (rat)	Yes	Yes	Yes	Yes	High
Murray et al. 2019 (rat)	Yes	Yes	Yes	Yes	High
Rana et al. 1980 (rat)	Yes	Yes	No	No	Low
Rana and Kumar 1980c	Yes	Yes	No	Yes	Moderate
Rana and Kumar 1983 (rat)	Yes	Yes	No	Yes	Moderate
Outcome: Alterations in uric acid levels					
Oral intermediate exposure					
Murray et al. 2014a (rat)	Yes	Yes	Yes	Yes	High
Outcome: Reproductive effects					
Inhalation intermediate exposure					
NTP 1997 (rat)	Yes	Yes	Yes	Yes	High
NTP 1997 (mouse)	Yes	Yes	Yes	Yes	High
Oral acute exposure					
Zhang et al. 2013 (mouse)	Yes	Yes	No	Yes	Moderate
Zhai et al. 2013 (mouse)	Yes	Yes	No	Yes	Moderate
Bersenyi et al. 2008 (rabbit, males)	Yes	No	No	Yes	Low
Bersenyi et al. 2008 (rabbit, females)	Yes	No	No	No	Very Low
Oral intermediate exposure					
Fungwe et al. 1990 (rat)	Yes	No	Yes	Yes	Moderate
Jeter and Davis 1954 (rat, adult)	Yes	No	No	No	Very Low
Murray et al. 2014a (rat)	Yes	Yes	Yes	Yes	High
Murray et al. 2019 (rat)	Yes	Yes	Yes	Yes	High
Pandey and Singh 2002 (rat)	Yes	Yes	No	Yes	Moderate
Pandey and Singh 2002 (rat, fertility study)	Yes	Yes	Yes	Yes	High

Table C-16. Presence of Key Features of Study Design for Molybdenum—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Key feature: Sufficient number of animals per group	Key feature: Appropriate parameters to assess potential effect	Key feature: Adequate data for statistical analysis	Initial study confidence
Outcome: Developmental effects					
Oral intermediate exposure					
Jeter and Davis 1954 (rat, weanling)	Yes	No	No	No	Very Low
Murray et al. 2014b (rat)	Yes	Yes	Yes	Yes	High
Murray et al. 2019 (rat)	Yes	Yes	Yes	Yes	High
Pandey and Singh 2002 (rat)	Yes	Yes	Yes	Yes	High

A summary of the initial confidence ratings for each outcome is presented in Table C-17. If individual studies for a particular outcome and study type had different study quality ratings, then the highest confidence rating for the group of studies was used to determine the initial confidence rating for the body of evidence; any exceptions were noted in Table C-17.

Table C-17. Initial Confidence Rating for Molybdenum Health Effects Studies

	Finding	Initial study confidence	Initial confidence rating
Outcome: Respiratory effects (inhalation only)			
Inhalation acute exposure			
Animal studies			
NTP 1997 (rat)	No effect	High	High
NTP 1997 (mouse)	No effect	High	
Inhalation intermediate exposure			
Animal studies			
NTP 1997 (rat)	No effect	High	High
NTP 1997 (mouse)	No effect	High	
Inhalation chronic exposure			
Human studies			
Observational studies			
Ott et al. 2004	Effect	Low	Low
Walravens et al. 1979	Effect	Very Low	

Table C-17. Initial Confidence Rating for Molybdenum Health Effects Studies

	Finding	Initial study confidence	Initial confidence rating
Animal studies			
NTP 1997 (rat)	Effect	High	High
NTP 1997 (mouse)	Effect	High	
Outcome: Hepatic effects			
Inhalation intermediate exposure			
Animal studies			
NTP 1997 (rat)	No effect	High	High
NTP 1997 (mouse)	No effect	High	
Inhalation chronic exposure			
Animal studies			
NTP 1997 (rat)	No effect	High	High
NTP 1997 (mouse)	No effect	High	
Oral acute exposure			
Animal studies			
Bersenyi et al. 2008 (rabbit, males)	Effect	Moderate	Moderate
Bersenyi et al. 2008 (rabbit, females)	Effect	Moderate	
Oral intermediate exposure			
Animal studies			
Murray et al. 2014a (rat)	No effect	High	High
Rana and Chauhan 2000 (rat)	Effect	Moderate	
Rana and Kumar 1980b (rat)	Effect	Moderate	
Rana and Kumar 1980c (rat)	Effect	Moderate	
Rana and Kumar 1983 (rat)	Effect	Moderate	Low
Rana and Prakash 1986 (rat)	Effect	Moderate	
Rana et al. 1980 (rat)	Effect	Low	
Rana et al. 1985 (rat)	Effect	Moderate	
Oral chronic exposure			
Human studies			
Observational studies			
Mendy et al. 2012	Effect	Low	Low
Outcome: Renal effects			
Inhalation intermediate exposure			
Animal studies			
NTP 1997 (rat)	No effect	High	High
NTP 1997 (mouse)	No effect	High	
Inhalation chronic exposure			
Animal studies			
NTP 1997 (rat)	No effect	High	High
NTP 1997 (mouse)	No effect	High	
Oral acute exposure			
Animal studies			
Bersenyi et al. 2008 (rabbit, males)	No effect	Moderate	Moderate
Bersenyi et al. 2008 (rabbit, females)	No effect	Moderate	

Table C-17. Initial Confidence Rating for Molybdenum Health Effects Studies

	Finding	Initial study confidence	Initial confidence rating
Oral intermediate exposure			
Animal studies			
Bandyopadhyay et al. 1981 (rat)	Effect	Low	High
Bompart et al. 1990 (rat)	Effect	Moderate	
Murray et al. 2014a (rat)	Effect	High	
Rana et al. 1980 (rat)	Effect	Low	
Rana and Kumar 1980c	Effect	Moderate	
Rana and Kumar 1983 (rat)	Effect	Moderate	
Murray et al. 2019 (rat)	No effect	High	High
Outcome: Alterations in uric acid levels			
Inhalation chronic exposure			
Human studies			
Observational studies			
Walravens et al. 1979	Effect	Very Low	Very Low
Oral acute exposure			
Human studies			
Controlled exposure			
Deosthale and Gopalan 1974	No Effect	Low	Low
Oral intermediate exposure			
Animal studies			
Murray et al. 2014a (rat)	No effect	High	High
Oral chronic exposure			
Human studies			
Observational studies			
Koval'sky et al. 1961	Effect	Low	Low
Outcome: Reproductive effects			
Inhalation intermediate exposure			
Animal studies			
NTP 1997 (rat)	No effect	High	High
NTP 1997 (mouse)	No effect	High	
Oral acute exposure			
Animal studies			
Zhang et al. 2013 (mouse)	Effect	Moderate	Moderate
Zhai et al. 2013 (mouse)	Effect	Moderate	
Bersenyi et al. 2008 (male, rabbit)	Effect	Low	
Bersenyi et al. 2008 (female, rabbit)	No effect	Very Low	Very low
Oral intermediate exposure			
Animal studies			
Fungwe et al. 1990 (rat)	Effect	Moderate	High
Jeter and Davis 1954 (rat, adult)	Effect	Very Low	
Jeter and Davis 1954 (rat, weanling)	Effect	Very Low	
Pandey and Singh 2002 (rat)	Effect	Moderate	

Table C-17. Initial Confidence Rating for Molybdenum Health Effects Studies

	Finding	Initial study confidence	Initial confidence rating
Pandey and Singh 2002 (rat, fertility study)	Effect	High	
Murray et al. 2014a (rat)	No effect	High	High
Murray et al. 2019 (rat)	No effect	High	
Oral chronic exposure			
Human studies			
Observational studies			
Lewis and Meeker 2015	Effect	Low	
Meeker et al. 2008	Effect	Low	Low
Meeker et al. 2010	Effect	Low	
Outcome: Developmental effects			
Oral intermediate exposure			
Animal studies			
Pandey and Singh 2002 (rat)	Effect	High	High
Jeter and Davis 1954 (rat, weanling)	No effect	Very Low	
Murray et al. 2014b (rat)	No effect	High	High
Murray et al. 2019 (rat)	No effect	High	
Oral chronic exposure			
Human studies			
Observational studies			
Vazquez-Salas et al. 2014	Effect	Low	Low
Shirai et al. 2010	No effect	Low	Low

C.6.2 Adjustment of the Confidence Rating

The initial confidence rating was then downgraded or upgraded depending on whether there were substantial issues that would decrease or increase confidence in the body of evidence. The nine properties of the body of evidence that were considered are listed below. The summaries of the assessment of the confidence in the body of evidence for respiratory, hepatic, renal, alterations in uric acid levels, reproductive, and developmental effects are presented in Table C-18. If the confidence ratings for a particular outcome were based on more than one type of human study, then the highest confidence rating was used for subsequent analyses. An overview of the confidence in the body of evidence for all health effects associated with molybdenum exposure is presented in Table C-19.

Five properties of the body of evidence were considered to determine whether the confidence rating should be downgraded:

- **Risk of bias.** Evaluation of whether there is substantial risk of bias across most of the studies examining the outcome. This evaluation used the risk of bias tier groupings for individual studies examining a particular outcome (Tables C-14, C-15, and C-16). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for risk of bias:
    - No downgrade if most studies are in the risk of bias first tier
    - Downgrade one confidence level if most studies are in the risk of bias second tier
    - Downgrade two confidence levels if most studies are in the risk of bias third tier

Table C-18. Adjustments to the Initial Confidence in the Body of Evidence

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Outcome: Respiratory effects			
Observational studies (effect)	Low	-1 risk of bias; -1 imprecision	Very low
Animal studies (effect)	High	None	High
Animal studies (no effect)	High	+1 magnitude	High
Outcome: Hepatic effects			
Observational studies (effect)	Low	-1 risk of bias	Very low
Animal studies (effect)	Moderate	-1 indirectness (secondary outcomes);	Moderate
Animal studies (no effect)	High	None	High
Outcome: Renal effects			
Animal studies	High	None	High
Animal studies	High	None	High
Outcome: Alterations in uric acid levels			
Observational studies (effect)	Low	-1 risk of bias	Very low
Controlled exposure studies (no effect)	Low	None	Low
Animal studies (no effect)	High	None	High
Outcome: Reproductive effects			
Observational studies (effect)	Low	None	Low
Animal studies (effect)	High	-1 inconsistency	Moderate
Animal studies (no effect)	High	None	High
Outcome: Developmental effects			
Observational studies (effect)	Low	None	Low
Observational studies (no effect)	Low	None	Low
Animal studies	High	-1 inconsistency	Moderate
Animal studies	High	None	High

Table C-19. Confidence in the Body of Evidence for Molybdenum

	Confidence in body of evidence	
Outcome	Human studies	Animal studies
Respiratory effects	Very low (effect)	High (effect) High (no effect)
Hepatic effects	Very low (effect)	Moderate (effect) High (no effect)
Renal effects	No data	High (effect) High (no effect)
Alterations in uric acid levels	Very low (effect) Low (no effect)	High (effect)
Reproductive Effects	Low (effect)	Moderate (effect) High (no effect)
Developmental effects	Low (effect) Low (no effect)	Moderate (effect) High (no effect)

- **Unexplained inconsistency.** Evaluation of whether there is inconsistency or large variability in the magnitude or direction of estimates of effect across studies that cannot be explained. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for unexplained inconsistency:
    - No downgrade if there is little inconsistency across studies or if only one study evaluated the outcome
    - Downgrade one confidence level if there is variability across studies in the magnitude or direction of the effect
    - Downgrade two confidence levels if there is substantial variability across studies in the magnitude or direct of the effect

- **Indirectness.** Evaluation of four factors that can affect the applicability, generalizability, and relevance of the studies:
    - Relevance of the animal model to human health—unless otherwise indicated, studies in rats, mice, and other mammalian species are considered relevant to humans
    - Directness of the endpoints to the primary health outcome—examples of secondary outcomes or nonspecific outcomes include organ weight in the absence of histopathology or clinical chemistry findings in the absence of target tissue effects
    - Nature of the exposure in human studies and route of administration in animal studies—inhalation, oral, and dermal exposure routes are considered relevant unless there are compelling data to the contrary
    - Duration of treatment in animal studies and length of time between exposure and outcome assessment in animal and prospective human studies—this should be considered on an outcome-specific basis

  Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for indirectness:
    - No downgrade if none of the factors are considered indirect
    - Downgrade one confidence level if one of the factors is considered indirect
    - Downgrade two confidence levels if two or more of the factors are considered indirect

- **Imprecision.** Evaluation of the narrowness of the effect size estimates and whether the studies have adequate statistical power. Data are considered imprecise when the ratio of the upper to lower 95% CIs for most studies is ≥10 for tests of ratio measures (e.g., odds ratios) and ≥100 for absolute measures (e.g., percent control response). Adequate statistical power is determined if the study can detect a potentially biologically meaningful difference between groups (20% change from control response for categorical data or risk ratio of 1.5 for continuous data). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for imprecision:
    - No downgrade if there are no serious imprecisions
    - Downgrade one confidence level for serious imprecisions
    - Downgrade two confidence levels for very serious imprecisions

- **Publication bias.** Evaluation of the concern that studies with statistically significant results are more likely to be published than studies without statistically significant results.
    - Downgrade one level of confidence for cases where there is serious concern with publication bias

Four properties of the body of evidence were considered to determine whether the confidence rating should be upgraded:

- **Large magnitude of effect.** Evaluation of whether the magnitude of effect is sufficiently large so that it is unlikely to have occurred as a result of bias from potential confounding factors.
    - Upgrade one confidence level if there is evidence of a large magnitude of effect in a few studies, provided that the studies have an overall low risk of bias and there is no serious unexplained inconsistency among the studies of similar dose or exposure levels; confidence can also be upgraded if there is one study examining the outcome, provided that the study has an overall low risk of bias

- **Dose response.** Evaluation of the dose-response relationships measured within a study and across studies. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
    - Upgrade one confidence level for evidence of a monotonic dose-response gradient
    - Upgrade one confidence level for evidence of a non-monotonic dose-response gradient where there is prior knowledge that supports a non-monotonic dose-response and a non-monotonic dose-response gradient is observed across studies

- **Plausible confounding or other residual biases.** This factor primarily applies to human studies and is an evaluation of unmeasured determinants of an outcome such as residual bias towards the null (e.g., "healthy worker" effect) or residual bias suggesting a spurious effect (e.g., recall bias). Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
    - Upgrade one confidence level for evidence that residual confounding or bias would underestimate an apparent association or treatment effect (i.e., bias toward the null) or suggest a spurious effect when results suggest no effect

- **Consistency in the body of evidence.** Evaluation of consistency across animal models and species, consistency across independent studies of different human populations and exposure scenarios, and consistency across human study types. Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
    - Upgrade one confidence level if there is a high degree of consistency in the database

C.7 TRANSLATE CONFIDENCE RATING INTO LEVEL OF EVIDENCE OF HEALTH EFFECTS

In the seventh step of the systematic review of the health effects data for molybdenum, the confidence in the body of evidence for specific outcomes was translated to a level of evidence rating. The level of evidence rating reflected the confidence in the body of evidence and the direction of the effect (i.e., toxicity or no toxicity); route-specific differences were noted. The level of evidence for health effects was rated on a five-point scale:

- **High level of evidence:** High confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Moderate level of evidence:** Moderate confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Low level of evidence:** Low confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Evidence of no health effect:** High confidence in the body of evidence that exposure to the substance is not associated with the health outcome
- **Inadequate evidence:** Low or moderate confidence in the body of evidence that exposure to the substance is not associated with the health outcome OR very low confidence in the body of evidence for an association between exposure to the substance and the health outcome

A summary of the level of evidence of health effects for molybdenum is presented in Table C-20.

Table C-20. Level of Evidence of Health Effects for Molybdenum

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Human studies			
Respiratory effects (inhalation only)	Very low	Health effect	Inadequate
Hepatic effects	Very low	Health effect	Inadequate
Renal effects	No data	No data	No data
Alterations in uric acid levels	Low	Health effect	Inadequate
Reproductive effects	Low	Health effect	Low
Developmental effects	Low	Health effect	Low
Animal studies			
Respiratory effects (inhalation only)	High	Health effect No health effect	High High
Hepatic effects	Moderate	Health effect No health effect	Moderate High
Renal effects	High	Health effect	High
Alterations in uric acid levels	High	No effect	Evidence of no health effect

Table C-20. Level of Evidence of Health Effects for Molybdenum

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Reproductive effects	Moderate	Health effect No health effect	Moderate High
Developmental effects[a]	Moderate	Health effect No health effect	High Evidence of no health effect

C.8 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS

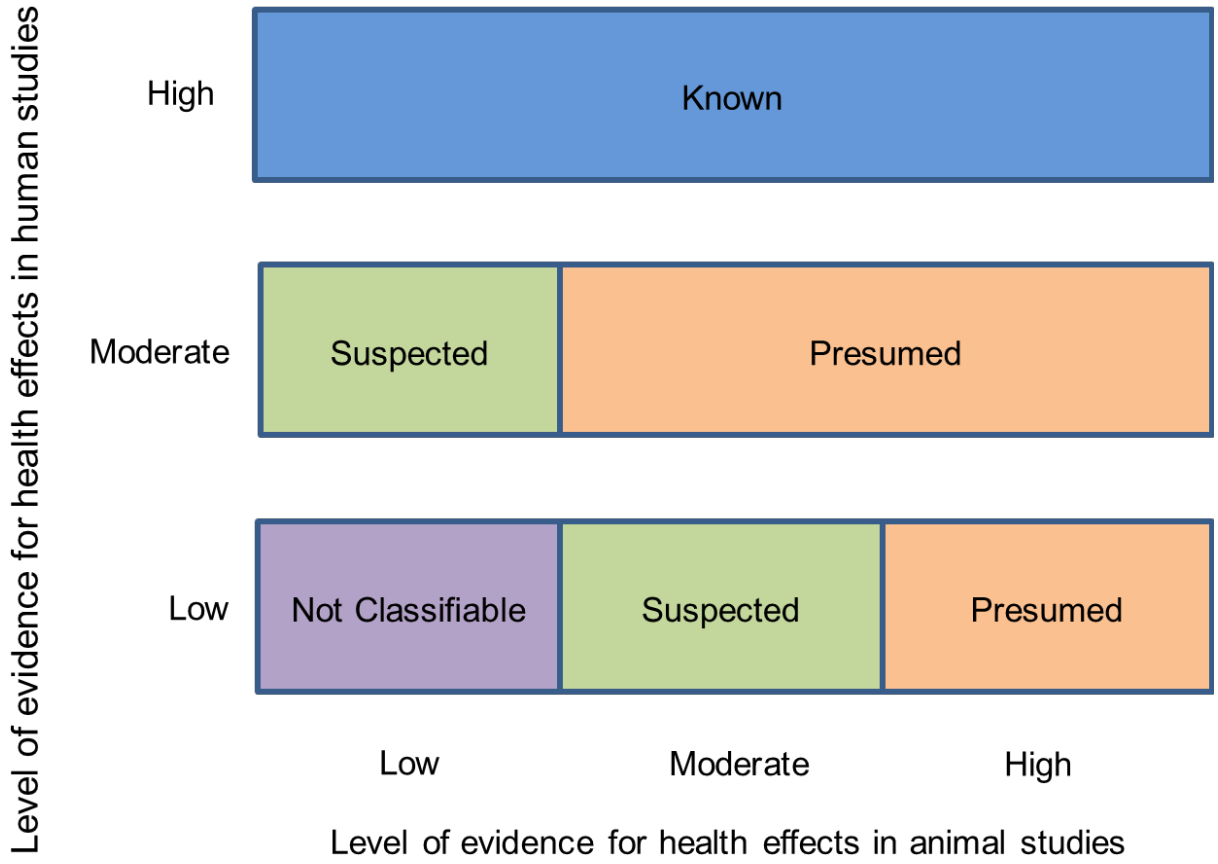
The final step involved the integration of the evidence streams for the human studies and animal studies to allow for a determination of hazard identification conclusions. For health effects, there were four hazard identification conclusion categories:

- **Known** to be a hazard to humans
- **Presumed** to be a hazard to humans
- **Suspected** to be a hazard to humans
- **Not classifiable** as to the hazard to humans

The initial hazard identification was based on the highest level of evidence in the human studies and the level of evidence in the animal studies; if there were no data for one evidence stream (human or animal), then the hazard identification was based on the one data stream (equivalent to treating the missing evidence stream as having low level of evidence). The hazard identification scheme is presented in and described below:

- **Known:** A health effect in this category would have:
  - High level of evidence for health effects in human studies **AND** a high, moderate, or low level of evidence in animal studies.
- **Presumed:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** high or moderate level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** high level of evidence in animal studies
- **Suspected:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** low level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** moderate level of evidence in animal studies
- **Not classifiable:** A health effect in this category would have:
  - Low level of evidence in human studies **AND** low level of evidence in animal studies

Figure C-1. Hazard Identification Scheme



Other relevant data such as mechanistic or mode-of-action data were considered to raise or lower the level of the hazard identification conclusion by providing information that supported or opposed biological plausibility.

Two hazard identification conclusion categories were used when the data indicated that there may be no health effect in humans:

- **Not identified** to be a hazard in humans
- **Inadequate** to determine hazard to humans

If the human level of evidence conclusion of no health effect was supported by the animal evidence of no health effect, then the hazard identification conclusion category of "not identified" was used. If the human or animal level of evidence was considered inadequate, then a hazard identification conclusion category of "inadequate" was used. As with the hazard identification for health effects, the impact of other relevant data was also considered for no health effect data.

The hazard identification conclusions for molybdenum are listed below and summarized in Table C-21.

Table C-21. Hazard Identification Conclusions for Molybdenum

Outcome	Hazard identification
Respiratory effects	Presumed health effect following long-term inhalation exposure
Hepatic effects	Not classifiable as a hazard to humans
Renal effects	Presumed health effect
Alterations in uric acid levels	Not classifiable as a hazard to humans
Reproductive effects	Suspected health effect
Developmental effects	Not classifiable as a hazard to humans

Presumed Health Effects

- Respiratory effects following long-term inhalation exposure to molybdenum oxides
  - Inadequate evidence from studies of molybdenum oxide workers (Ott et al. 2004; Walravens et al. 1979).
  - High level of evidence from chronic studies in rats and mice exposed to molybdenum trioxide (NTP 1997). Respiratory effects were not observed following acute- or intermediate-duration inhalation exposure.
- Renal effects
  - No data in humans.
  - High level of evidence of histological alterations in kidneys, alterations in renal function, and/or increased lipid levels in the kidneys in orally exposed rats (Bandyopadhyay et al. 1981; Bompart et al. 1990; Murray et al. 2014a; Rana and Kumar 1980c, 1983; Rana et al. 1980).

Not Classifiable as a Hazard to Humans

- Hepatic effects
  - Inadequate evidence of increased risk of self-reported liver conditions from a cross-sectional study (Mendy et al. 2012).
  - High evidence of no histological alterations following intermediate or chronic inhalation exposure of rats and mice to molybdenum trioxide (NTP 1997), acute oral exposure of rabbits to ammonium heptamolybdate (Bersenyi et al. 2008), or intermediate oral exposure of rats to sodium molybdate (Murray et al. 2014a;).
  - Moderate evidence of increases in clinical chemistry parameters and/or liver lipid levels in rabbits following acute oral exposure (Bersenyi et al. 2008) or rats exposed orally exposed to high doses (Rana and Chauhan 2000; Rana and Kumar 1980b, 1980c, 1983; Rana and Prakash 1986; Rana et al. 1980, 1985).
  - The hazard identification for hepatic effects was downgraded to Not Classifiable because the toxicological significance of the alterations in serum enzyme levels and lipid levels were not known and well-designed inhalation and oral laboratory animal studies have not reported histological alterations.
- Alterations in uric acid levels
  - Low evidence of an effect in cross-sectional studies (Koval'skiy et al. 1961; Walravens et al. 1979).
  - High confidence in an animal study not finding an effect (Murray et al. 2014a).
- Reproductive effects
  - Low level of evidence of male reproductive effects in cross-sectional studies (Lewis and Meeker 2015; Meeker et al. 2008, 2010).

  - Two high-quality, intermediate-duration (Murray et al. 2014a) and 2-generation (Murray et al. 2019) studies have not reported reproductive effects.
  - There is a moderate level of evidence of male and/or female reproductive effects in orally exposed rats (Fungwe et al. 1990; Pandey and Singh 2002), mice (Zhai et al. 2013; Zhang et al. 2013), and rabbits (Bersenyi et al. 2008).
- Developmental effects
  - Low evidence of an effect in a cross-sectional study. Two cross-sectional studies reported no alterations in newborn body weight (Shirai et al. 2010; Vazquez-Salas et al. 2014); one study reported decreases in psychomotor development indices (Vazquez-Salas et al. 2014).
  - Three studies in rats did not find alterations in resorptions, post-implantation losses, or fetal body weights (Jeter and Davis 1954; Murray et al. 2014b, 2019); the initial confidence levels for two of these studies were high and the third study was very low. A fourth study (initial high confidence level) involving male-only exposure found decreases in number of live fetuses and fetal body weights (Pandey and Singh 2002). The animal studies had different study designs (male only, female only, male and female exposure) making a comparison across studies difficult. Additionally, none of the animal studies evaluated potential neurodevelopmental effects, which were observed in an epidemiology study. Thus, the available data were not considered adequate for drawing a conclusion on the potential developmental toxicity of molybdenum in humans.

APPENDIX D. USER'S GUIDE

Chapter 1. Relevance to Public Health

This chapter provides an overview of U.S. exposures, a summary of health effects based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information, and an overview of the minimal risk levels. This is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

Minimal Risk Levels (MRLs)

Where sufficient toxicologic information is available, ATSDR derives MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Section 1.2, Summary of Health Effects, contains basic information known about the substance. Other sections, such as Section 3.2 Children and Other Populations that are Unusually Susceptible and Section 3.4 Interactions with Other Substances, provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a

substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables that are provided in Chapter 2. Detailed discussions of the MRLs are presented in Appendix A.

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species and MRLs to humans for noncancer endpoints. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE tables and figures follow. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

TABLE LEGEND

See Sample LSE Table (page D-5)

(1) Route of exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically, when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure (i.e., inhalation, oral, and dermal). LSE figures are limited to the inhalation and oral routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures. Profiles with more than one chemical may have more LSE tables and figures.

(2) Exposure period. Three exposure periods—acute (<15 days), intermediate (15–364 days), and chronic (≥365 days)—are presented within each relevant route of exposure. In this example, two oral studies of chronic-duration exposure are reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Figure key. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 51 identified NOAELs and less serious LOAELs (also see the three "51R" data points in sample LSE Figure 2-X).

(4) Species (strain) No./group. The test species (and strain), whether animal or human, are identified in this column. The column also contains information on the number of subjects and sex per group. Chapter 1, Relevance to Public Health, covers the relevance of animal data to human toxicity and Section 3.1, Toxicokinetics, contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(5) Exposure parameters/doses. The duration of the study and exposure regimens are provided in these columns. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 51), rats were orally exposed to “Chemical X” via feed for 2 years. For a

more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Aida et al. 1992).

(6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), behavioral (BH), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), enzyme activity (EA), food intake (FI), fetal toxicity (FX), gross necropsy (GN), hematology (HE), histopathology (HP), lethality (LE), maternal toxicity (MX), organ function (OF), ophthalmology (OP), organ weight (OW), teratogenicity (TG), urinalysis (UR), and water intake (WI).

(7) Endpoint. This column lists the endpoint examined. The major categories of health endpoints included in LSE tables and figures are death, body weight, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, endocrine, immunological, neurological, reproductive, developmental, other noncancer, and cancer. "Other noncancer" refers to any effect (e.g., alterations in blood glucose levels) not covered in these systems. In the example of key number 51, three endpoints (body weight, hematological, and hepatic) were investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. The body weight effect reported in key number 51 is a NOAEL at 25.5 mg/kg/day. NOAELs are not reported for cancer and death; with the exception of these two endpoints, this field is left blank if no NOAEL was identified in the study.

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. Key number 51 reports a less serious LOAEL of 6.1 mg/kg/day for the hepatic system, which was used to derive a chronic exposure, oral MRL of 0.008 mg/kg/day (see footnote "c"). MRLs are not derived from serious LOAELs. A cancer effect level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases. If no LOAEL/CEL values were identified in the study, this field is left blank.

(10) Reference. The complete reference citation is provided in Chapter 8 of the profile.

(11) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. For example, footnote "c" indicates that the LOAEL of 6.1 mg/kg/day in key number 51 was used to derive an oral MRL of 0.008 mg/kg/day.

FIGURE LEGEND

See Sample LSE Figure (page D-6)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the chronic exposure period are illustrated.

(14) Endpoint. These are the categories of health effects for which reliable quantitative data exist. The same health effect endpoints appear in the LSE table.

(15) Levels of exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) LOAEL. In this example, the half-shaded circle that is designated 51R identifies a LOAEL critical endpoint in the rat upon which a chronic oral exposure MRL is based. The key number 51 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 6.1 mg/kg/day (see entry 51 in the sample LSE table) to the MRL of 0.008 mg/kg/day (see footnote "c" in the sample LSE table).

(17) CEL. Key number 59R is one of studies for which CELs were derived. The diamond symbol refers to a CEL for the test species (rat). The number 59 corresponds to the entry in the LSE table.

(18) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral (1)

Figure key[a] (3)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
51	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 6.1, 25.5, 138.0 F: 0, 8.0, 31.7, 168.4	CS, WI, BW, OW, HE, BC, HP	Bd wt	25.5	138.0		Decreased body weight gain in males (23–25%) and females (31–39%)
					Hemato	138.0			
					Hepatic		6.1[c]		Increases in absolute and relative weights at ≥6.1/8.0 mg/kg/day after 12 months of exposure; fatty generation at ≥6.1 mg/kg/day in males and at ≥31.7 mg/kg/day in females, and granulomas in females at 31.7 and 168.4 mg/kg/day after 12, 18, or 24 months of exposure and in males at ≥6.1 mg/kg/day only after 24 months of exposure
Aida et al. 1992 (10)									
52	Rat (F344) 78 M	104 weeks (W)	0, 3.9, 20.6, 36.3	CS, BW, FI, BC, OW, HP	Hepatic	36.3			
					Renal	20.6	36.3		Increased incidence of renal tubular cell hyperplasia
					Endocr	36.3			
George et al. 2002									
59	Rat (Wistar) 58M, 58F	Lifetime (W)	M: 0, 90 F: 0, 190	BW, HP	Cancer		190 F		Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided
Tumasonis et al. 1985									

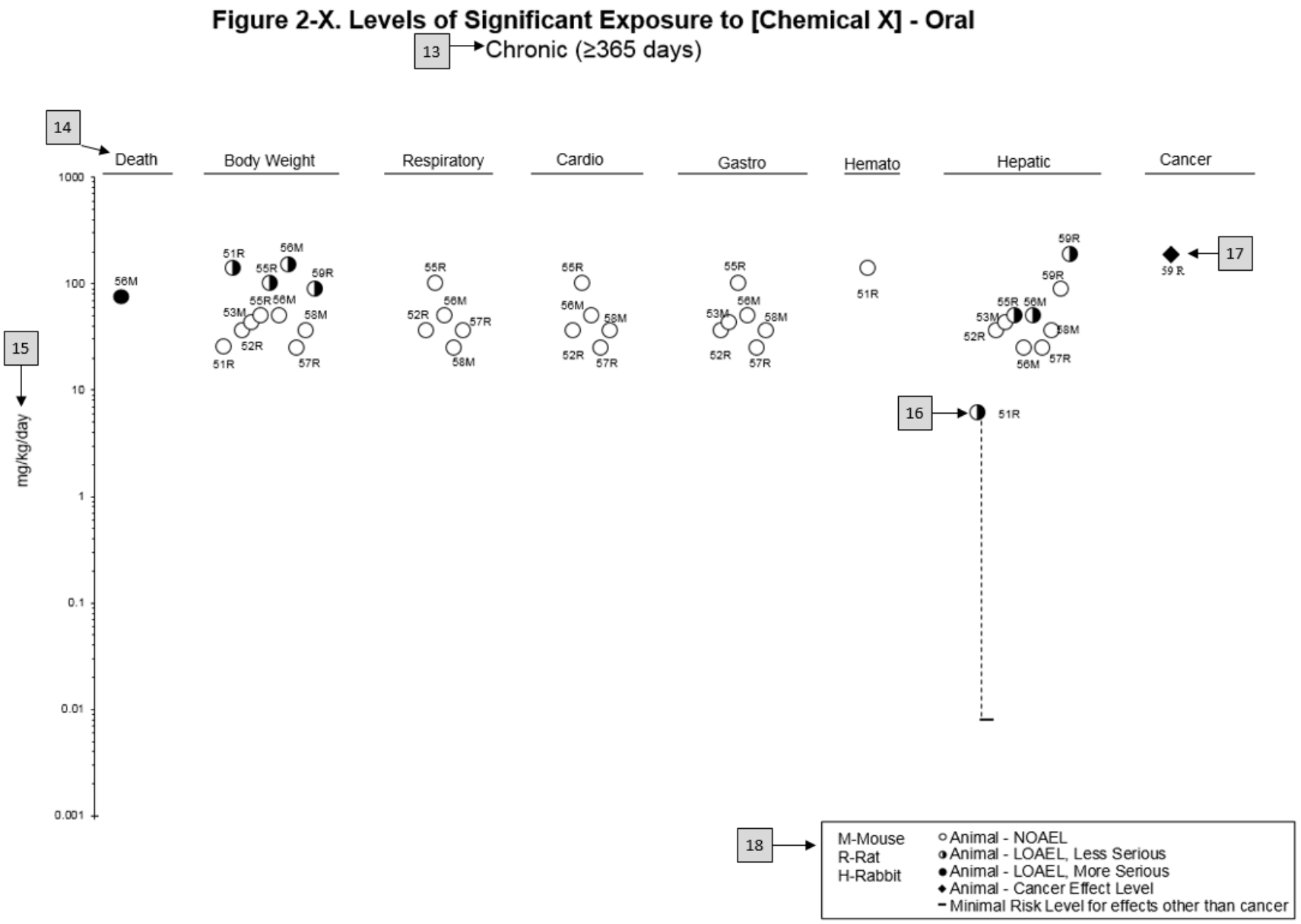
[a]The number corresponds to entries in Figure 2-x.

(11) [b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

[c]Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the $BMDL_{10}$ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

1

Figure 2-X. Levels of Significant Exposure to [Chemical X] - Oral



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APPENDIX E. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances may find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Relevance to Public Health: The Relevance to Public Health Section provides an overview of exposure and health effects and evaluates, interprets, and assesses the significance of toxicity data to human health. A table listing minimal risk levels (MRLs) is also included in this chapter.

Chapter 2: Health Effects: Specific health effects identified in both human and animal studies are reported by type of health effect (e.g., death, hepatic, renal, immune, reproductive), route of exposure (e.g., inhalation, oral, dermal), and length of exposure (e.g., acute, intermediate, and chronic).
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting.

Pediatrics:

Section 3.2 Children and Other Populations that are Unusually Susceptible
Section 3.3 Biomarkers of Exposure and Effect

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
Internet: http://www.atsdr.cdc.gov

The following additional materials are available online:

Case Studies in Environmental Medicine are self-instructional publications designed to increase primary health care providers' knowledge of a hazardous substance in the environment and to aid in the evaluation of potentially exposed patients (see https://www.atsdr.cdc.gov/csem/csem.html).

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see https://www.atsdr.cdc.gov/MHMI/index.asp). Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see https://www.atsdr.cdc.gov/toxfaqs/Index.asp).

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015 • Web Page: https://www.cdc.gov/nceh/.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212 • Web Page: https://www.niehs.nih.gov/.

Clinical Resources (Publicly Available Information)

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: http://www.acoem.org/.

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at http://pehsu.net/findhelp.html.

The American Association of Poison Control Centers (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: http://www.aapcc.org/.

APPENDIX F. GLOSSARY

Absorption—The process by which a substance crosses biological membranes and enters systemic circulation. Absorption can also refer to the taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of ≤14 days, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD) or Benchmark Concentration (BMC)—is the dose/concentration corresponding to a specific response level estimate using a statistical dose-response model applied to either experimental toxicology or epidemiology data. For example, a BMD_{10} would be the dose corresponding to a 10% benchmark response (BMR). The BMD is determined by modeling the dose-response curve in the region of the dose-response relationship where biologically observable data are feasible. The BMDL or BMCL is the 95% lower confidence limit on the BMD or BMC.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Indicators signaling events in biologic systems or samples, typically classified as markers of exposure, effect, and susceptibility.

Cancer Effect Level (CEL)—The lowest dose of a chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the outcome.

Case Report—A report that describes a single individual with a particular disease or exposure. These reports may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Reports that describe the experience of a small number of individuals with the same disease or exposure. These reports may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration that must not be exceeded.

Chronic Exposure—Exposure to a chemical for ≥365 days, as specified in the Toxicological Profiles.

Clastogen—A substance that causes breaks in chromosomes resulting in addition, deletion, or rearrangement of parts of the chromosome.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome, and who are disease-free at start of follow-up. Often, at least one exposed group is compared to one unexposed group, while in other cohorts, exposure is a continuous variable and analyses are directed towards analyzing an exposure-response coefficient.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at a specific point in time.

Data Needs—Substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the response or amount of the response.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the effect occurs. Effects include malformations and variations, altered growth, and *in utero* death.

Epidemiology—The investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Excretion—The process by which metabolic waste products are removed from the body.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one-half of a quantity of a chemical from the body or environmental media.

Health Advisory—An estimate of acceptable drinking water levels for a chemical substance derived by EPA and based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH)—A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

Immunotoxicity—Adverse effect on the functioning of the immune system that may result from exposure to chemical substances.

Incidence—The ratio of new cases of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Metabolism—Process in which chemical substances are biotransformed in the body that could result in less toxic and/or readily excreted compounds or produce a biologically active intermediate.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—The state of being diseased; the morbidity rate is the incidence or prevalence of a disease in a specific population.

Mortality—Death; the mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations, which are changes in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a hazardous substance.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Although effects may be produced at this dose, they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio that is greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests (insects or other organisms harmful to cultivated plants or animals).

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic endpoints. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—A type of physiologically based dose-response model that is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information, including tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which a group is followed over time and the pertinent observations are made on events occurring after the start of the study.

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation RfC is expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily oral exposure of the human population to a potential hazard that is likely to be without risk of deleterious noncancer health effects during a lifetime. The oral RfD is expressed in units of mg/kg/day.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). RQs are (1) ≥1 pound or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a hazardous substance. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a hazardous substance.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio/Relative Risk—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio that is greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time-Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

Time-Weighted Average (TWA)—An average exposure within a given time period.

Toxicokinetic—The absorption, distribution, metabolism, and elimination of toxic compounds in the living organism.

Toxics Release Inventory (TRI)—The TRI is an EPA program that tracks toxic chemical releases and pollution prevention activities reported by industrial and federal facilities.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL), Reference Dose (RfD), or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis (3 being the approximate logarithmic average of 10 and 1).

Xenobiotic—Any substance that is foreign to the biological system.

APPENDIX G. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AAPCC	American Association of Poison Control Centers
ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ACMT	American College of Medical Toxicology
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AEGL	Acute Exposure Guideline Level
AIC	Akaike's information criterion
AIHA	American Industrial Hygiene Association
ALT	alanine aminotransferase
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BCF	bioconcentration factor
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
C	Celsius
CAA	Clean Air Act
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
cm	centimeter
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DWEL	drinking water exposure level
EAFUS	Everything Added to Food in the United States
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
ERPG	emergency response planning guidelines
F	Fahrenheit
F1	first-filial generation
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act

FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GGT	γ-glutamyl transferase
GRAS	generally recognized as safe
HEC	human equivalent concentration
HED	human equivalent dose
HHS	Department of Health and Human Services
HPLC	high-performance liquid chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Level of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
MRL	Minimal Risk Level
MS	mass spectrometry
MSHA	Mine Safety and Health Administration
Mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NCEH	National Center for Environmental Health
ND	not detected
ng	nanogram

NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PEHSU	Pediatric Environmental Health Specialty Unit
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PND	postnatal day
POD	point of departure
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure level/limit
REL-C	recommended exposure level-ceiling value
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
SMR	standardized mortality ratio
sRBC	sheep red blood cell
STEL	short term exposure limit
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States

USDA	United States Department of Agriculture
USGS	United States Geological Survey
USNRC	U.S. Nuclear Regulatory Commission
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result