

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

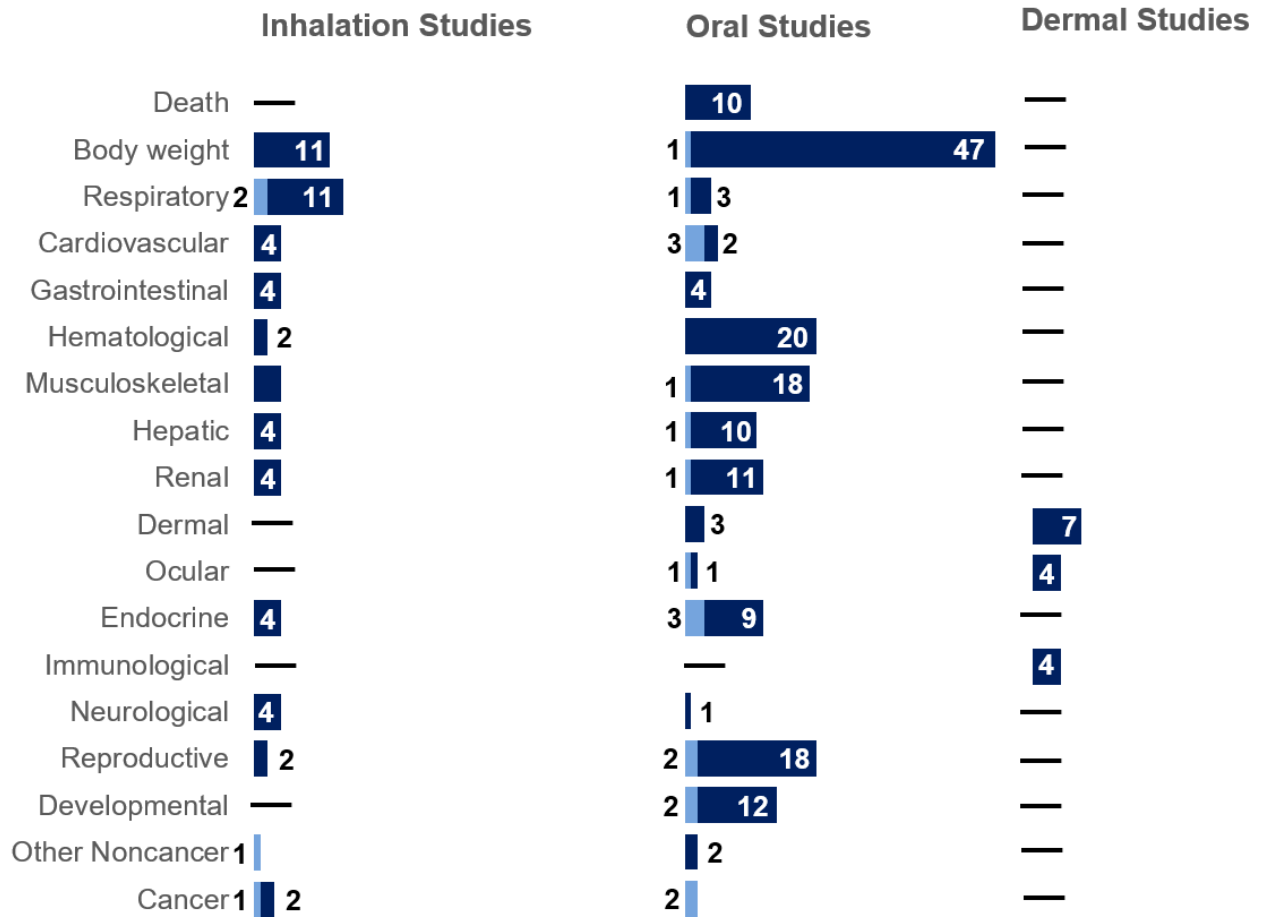
Missing information in Figure 6-1 should not be interpreted as a “data need.” A data need, as defined in ATSDR’s *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health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

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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.

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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

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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

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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.

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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 ($\text{Mo}^{\text{VI}}\text{O}_4^{2-}$) 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

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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.

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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.

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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.