3. HEALTH EFFECTS

3.1 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.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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 first by route of exposure (inhalation, oral, and dermal) and then by health effect (e.g., death, systemic, immunological, neurological, reproductive, developmental, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure 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 end point 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 end points. 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.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

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

### 3.2.1 Inhalation Exposure

The highest NOAEL values and all LOAEL values from each reliable study for each end point in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

#### 3.2.1.1 Death

No deaths were reported in rats or mice exposed to ≤200 mg molybdenum/m³ for 14 days (NTP 1997) or ≤67 mg molybdenum/m³ for 90 days or 2 years (NTP 1997).

#### 3.2.1.2 Systemic Effects

No information was located regarding cardiovascular, gastrointestinal, hematological, muscular/skeletal, hepatic, renal, endocrine, dermal, ocular, or body weight effects in humans following inhalation exposure to molybdenum. No information was located regarding dermal or ocular effects in animals following inhalation exposure to molybdenum.

The highest NOAEL values and all LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

**Respiratory Effects.** Limited data are available on the toxicity of molybdenum to the respiratory tract of humans. A study of workers exposed to molybdenum trioxide and other oxides at a molybdenite
Table 3-1. Levels of Significant Exposure to Molybdenum – Inhalation

<table>
<thead>
<tr>
<th>Figure key*</th>
<th>Species (strain) No./group</th>
<th>Exposure duration/ concentrations</th>
<th>Parameters monitored</th>
<th>System</th>
<th>NOAEL (mg/m³)</th>
<th>Less serious LOAEL (mg/m³)</th>
<th>Serious LOAEL (mg/m³)</th>
<th>Results</th>
<th>Reference/comments</th>
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<tbody>
<tr>
<td><strong>ACUTE EXPOSURE</strong></td>
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<tr>
<td>1</td>
<td>Rat 5M, 5F (F344/N)</td>
<td>6 hours/day; 5 days/week; 14 days 0, 2, 6.7, 20, 67, 200 mg Mo/m³</td>
<td>CS, BW, HP</td>
<td>Resp Bd Wt</td>
<td>200</td>
<td>67</td>
<td>200</td>
<td>No histological alterations were observed in the nasal cavity. Decreased body weight gain in males exposed to 67 mg/m³ (10%) and females exposed to 200 mg/m³ (13%); weight loss was observed in males exposed to 200 mg/m³.</td>
<td>NTP 1997 (molybdenum trioxide)</td>
</tr>
<tr>
<td>2</td>
<td>Mouse 5M, 5F (B6C3F1)</td>
<td>6 hours/day; 5 days/week; 14 days 0, 2, 6.7, 20, 67, 200 mg Mo/m³</td>
<td>CS, BW, HP</td>
<td>Resp Bd Wt</td>
<td>200</td>
<td>200</td>
<td>No histological alterations were observed in the nasal cavity. Body weight loss in males and decrease in body weight gain in females.</td>
<td>NTP 1997 (molybdenum trioxide)</td>
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<tr>
<td><strong>INTERMEDIATE EXPOSURE</strong></td>
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<tr>
<td>3</td>
<td>Rat 10M, 10F (F344/N)</td>
<td>6.5 hours/day; 5 days/week; 13 weeks 0, 0.67, 2, 6.7, 20, 67mg Mo/m³</td>
<td>CS, BW,OW, HP</td>
<td>Resp Cardio Gastro Hemato Musc/skel Hepatic Renal Endocr Bd Wt</td>
<td>67</td>
<td>67</td>
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<tr>
<td>4</td>
<td>Mouse 10M, 10F (B6C3F1)</td>
<td>6.5 hours/day; 5 days/week; 13 weeks 0, 0.67, 2, 6.7, 20, 67mg Mo/m³</td>
<td>CS, BW,OW, HP</td>
<td>Resp Cardio Gastro Hemato Musc/skel Hepatic Renal Endocr Bd Wt</td>
<td>67</td>
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</tbody>
</table>
### Table 3-1. Levels of Significant Exposure to Molybdenum – Inhalation

<table>
<thead>
<tr>
<th>Figure keya</th>
<th>Species (strain)</th>
<th>Exposure duration/ concentrations</th>
<th>Parameters monitored</th>
<th>System</th>
<th>NOAEL (mg/m³)</th>
<th>Serious LOAEL (mg/m³)</th>
<th>LOAEL (mg/m³)</th>
<th>Results</th>
<th>Reference/comments</th>
</tr>
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<tbody>
<tr>
<td>Reproductive</td>
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<td>5</td>
<td>Rat 10M, 10F (F344/N)</td>
<td>6.5 hours/day; 5 days/week; 13 weeks 0, 0.67, 2, 6.7, 20, 67mg Mo/m³</td>
<td>CS, BW, OW, HP</td>
<td>67</td>
<td>No significant alterations in sperm counts or motility were found</td>
<td>NTP 1997 (molybdenum trioxide)</td>
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<tr>
<td>6</td>
<td>Mouse 10M, 10F (B6C3F1)</td>
<td>6.5 hours/day; 5 days/week; 13 weeks 0, 0.67, 2, 6.7, 20, 67mg Mo/m³</td>
<td>CS, BW, OW, HP</td>
<td>67</td>
<td>No significant alterations in sperm counts or motility were found</td>
<td>NTP 1997 (molybdenum trioxide)</td>
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<td>Systemic</td>
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<tr>
<td>7</td>
<td>Rat 50M, 50F (F344/N)</td>
<td>6 hours/day; 5 days/week; 105 weeks 0, 6.7, 20, 67mg Mo/m³</td>
<td>CS, BW, HP</td>
<td>Resp</td>
<td>Cardio 67 Gastro 67 Musc/skel 67 Hepatic 67 Renal 67 Endocr 67 Bd Wt 67</td>
<td>Concentration-related increasing incidence of 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/m³ concentrations)</td>
<td>NTP 1997 (molybdenum trioxide)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Mouse 50M, 50F (B6C3F1)</td>
<td>6 hours/day; 5 days/week; 105 weeks 0, 6.7, 20, 67mg Mo/m³</td>
<td>CS, BW, HP</td>
<td>Resp</td>
<td>Cardio 67 Gastro 67 Musc/skel 67 Hepatic 67 Renal 67 Endocr 67 Bd Wt 67</td>
<td>Concentration-related increasing incidence of squamous metaplasia of the epiglottis, histiocytic cellular infiltration in the lungs, and alveolar epithelial metaplasia were observed at 6.7, 20, and 67 mg/m³. Other respiratory effects were nasal suppurative inflammation in males at 20 or 67 mg/m³ and hyaline degeneration of nasal respiratory and olfactory epithelium (females only) at 67 mg/m³.</td>
<td>NTP 1997 (molybdenum trioxide)</td>
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</tbody>
</table>
### Table 3-1. Levels of Significant Exposure to Molybdenum – Inhalation

<table>
<thead>
<tr>
<th>Figure key&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Species (strain) No./group</th>
<th>Exposure duration/ concentrations</th>
<th>Parameters monitored</th>
<th>NOAEL (mg/m&lt;sup&gt;3&lt;/sup&gt;)</th>
<th>Serious NOAEL (mg/m&lt;sup&gt;3&lt;/sup&gt;)</th>
<th>Results</th>
<th>Reference/comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>Mouse 50M, 50F (B6C3F&lt;sub&gt;1&lt;/sub&gt;)</td>
<td>6 hours/day; 5 days/week; 105 weeks</td>
<td>CS, BW, HP</td>
<td>6.7</td>
<td>Increased incidences of alveolar/bronchiolar carcinoma in males (molybdenum trioxide) at ≥6.7 mg/m&lt;sup&gt;3&lt;/sup&gt;; increased incidence of alveolar/bronchiolar adenoma in females at ≥20 mg/m&lt;sup&gt;3&lt;/sup&gt;. An increase in alveolar/bronchiolar adenoma or carcinoma were also observed in male mice exposed to 6.7 or 20 mg/m&lt;sup&gt;3&lt;/sup&gt;.</td>
<td>NTP 1997 (molybdenum trioxide)</td>
<td></td>
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</tbody>
</table>

<sup>a</sup>The number corresponds to entries in Figure 3-1.

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**Abbreviations:**
- BC = biochemistry
- BW = body weight
- Cardio = cardiovascular
- CI = confidence interval
- CS = clinical signs
- d = day(s)
- Endocr = endocrine
- F = female(s)
- FI = food intake
- Gastro = gastrointestinal
- GC = gas chromatography
- GN = gross necropsy
- HE = hematology
- Hemato = hematology
- HP = histopathology
- hr = hour(s)
- LC<sub>50</sub> = lethal concentration, 50% kill
- LE = lethality
- M = male(s)
- min = minute(s)
- MRL = Minimal Risk Level
- NS = not specified
- OP = ophthalmology
- OW = organ weight
- RD<sub>50</sub> = concentration resulting in a 50% reduction in respiratory rate
- Resp = respiratory
- sec = second(s)
- UR = urinalysis
- WI = water intake
- wk = week(s)
Figure 3-1. Levels of Significant Exposure to Molybdenum - Inhalation
Acute (≤ 14 days)

Systemic

Respiratory  |  Body Weight
---|---

![Diagram showing levels of significant exposure to molybdenum via inhalation for different species and exposure levels.](image-url)
Figure 3-1. Levels of Significant Exposure to Molybdenum - Inhalation (Continued)
Intermediate (15-364 days)

Systemic

Respiratory  Cardio  Gastro  Hemato  Musc/Skeletal  Hepatic  Renal  Endocrine  Body Weight  Reproductive

1000 100 10 1 0.1 0.01 0.001

mg/m³

C-Cat  K-Monkey  J-Pigeon  O-Other  △ Human - NOAEL  △ Human - LOAEL, Less Serious  △ Human - LOAEL, More Serious  △ Human - Cancer Effect Level  △ Animal - LD50/LC50
D-Dog  M-Mouse  E-Gerbil  S-Hamster  △ Animal - NOAEL  △ Animal - LOAEL, Less Serious  △ Animal - LOAEL, More Serious  △ Animal - Cancer Effect Level  △ Minimal Risk Level for effect other than cancer
R-Rat  H-Rabbit  S-Hamster  P-Pig  A-Sheep  G-Guinea Pig  N-Mink

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Figure 3-1. Levels of Significant Exposure to Molybdenum - Inhalation (Continued)
Chronic (≥365 days)

*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer endpoint.
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$_1$) was 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 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 alterations 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 database on the respiratory toxicity of molybdenum in laboratory animals is comprised of acute-, intermediate-, and chronic-duration 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 has 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 were 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$^3$. 

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3. HEALTH EFFECTS

**Cardiovascular Effects.** No histological alterations were observed in the hearts of rats or mice exposed to molybdenum trioxide concentrations as high as 67 mg molybdenum/m³ for 13 weeks or 2 years (NTP 1997).

**Gastrointestinal Effects.** Intermediate- or chronic-duration exposure to ≤67 mg molybdenum/m³ as molybdenum trioxide did not result in histological alterations in the gastrointestinal tract (NTP 1997).

**Hematological Effects.** No significant alterations in hematological parameters were observed in rats or mice following exposure to molybdenum trioxide concentrations as high as 67 mg molybdenum/m³ for 13 weeks (NTP 1997).

**Musculoskeletal Effects.** No histological alterations were observed in the bone of rats or mice exposed to 6.7–67 mg molybdenum/m³ as molybdenum trioxide for 13 weeks or 2 years (NTP 1997). Chronic molybdenum exposure also did not affect femoral bone density or curvature in groups of 10 rats exposed to concentrations as high as 67 mg molybdenum/m³ (NTP 1997).

**Hepatic Effects.** No significant alterations in serum clinical chemistry parameters or liver weights were observed in rats or mice exposed to molybdenum trioxide concentrations as high as 67 mg molybdenum/m³ 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).

**Renal Effects.** Intermediate- or chronic-duration inhalation exposure to molybdenum trioxide (highest concentration tested was 67 mg molybdenum/m³) did not result in histological alterations in the kidney of rats or mice (NTP 1997).

**Endocrine Effects.** Based on histopathology findings, the adrenal, pituitary, pancreas, parathyroid, and thyroid glands were not affected by exposure of rats and mice to ≤67 mg molybdenum/m³ as molybdenum trioxide for 13 weeks or 2 years (NTP 1997).

**Body Weight Effects.** Decreases in body weight gain and weight loss were observed in rats and mice exposed to molybdenum trioxide for 14 days (NTP 1997). Terminal body weights were 10% lower in male rats exposed to 67 mg molybdenum/m³ than in the controls, and weight loss was observed in male rats and mice exposed to 200 mg molybdenum/m³. In female rats and mice exposed to 200 mg molybdenum/m³, 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 molybdenum trioxide concentrations as high as 67 mg molybdenum/m³ for 13 weeks or 2 years (NTP 1997).

Other Systemic Effects. 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/m³ 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.

3.2.1.3 Immunological and Lymphoreticular Effects

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/m³ (NTP 1997).

3.2.1.4 Neurological Effects

No histological alterations were observed in the brain of rats and mice exposed to ≤67 mg molybdenum/m³ as molybdenum trioxide for 13 weeks or 2 years (NTP 1997); the study did not evaluate neurological function.

3.2.1.5 Reproductive Effects

Following a 13-week exposure to molybdenum trioxide, no alterations in sperm count or motility were observed in rats or mice at concentrations as high as 67 mg molybdenum/m³ (NTP 1997). No histological alterations were observed in male or female reproductive tissues following exposure to ≤67 mg molybdenum/m³ for 13 weeks or 2 years (NTP 1997).

3.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans and animals following inhalation exposure to molybdenum.
3.2.1.7 Cancer

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 (odds ratio of 2.1, 95% confidence interval of 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/m³; however, the incidence was within the range of historical controls and NTP considered this to be equivocal evidence of carcinogenic activity. 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/m³, alveolar/bronchiolar adenoma or carcinoma in males at 6.7 and 20 mg molybdenum/m³, alveolar/bronchiolar adenoma in females at 20 and 67 mg molybdenum/m³, and alveolar/bronchiolar adenoma or carcinoma in females at 67 mg molybdenum/m³ (NTP 1997). NTP (1997) concluded that the male and female mouse data provided some evidence of molybdenum carcinogenicity.

3.2.2 Oral Exposure

The highest NOAEL values and all LOAEL values from each reliable study for each end point in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

A number of studies have examined the oral toxicity of molybdenum; most were conducted in laboratory animals and most had a limited scope (examined one or two potential targets); the studies evaluated the toxicity of several molybdenum compounds, predominantly sodium molybdate, ammonium heptamolybdate, and ammonium tetrathiomolybdate. Studies have also been conducted in ruminants, particularly cows and sheep; however, these species are not considered suitable models for humans due to differences in interactions between molybdenum, copper, and sulfate in the rumen (see Section 3.5.2 for more information). Studies in rats provide evidence that copper status, particularly the copper content of
# 3. HEALTH EFFECTS

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

<table>
<thead>
<tr>
<th>Figure key*</th>
<th>Species (strain)</th>
<th>No./group</th>
<th>Exposure parameters/ concentrations</th>
<th>Parameters monitored</th>
<th>System</th>
<th>NOAEL (mg/kg/day)</th>
<th>LOAEL (mg/kg/day)</th>
<th>Serious LOAEL (mg/kg/day)</th>
<th>Results</th>
<th>Reference (compound)</th>
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<tr>
<td><strong>ACUTE EXPOSURE</strong></td>
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<td><strong>Systemic</strong></td>
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<tr>
<td>1</td>
<td>Human</td>
<td>4 M</td>
<td>10 days (F); 0.00237, 0.00771, 0.022 mg/kg/day</td>
<td>UR</td>
<td>Other</td>
<td>0.022</td>
<td></td>
<td></td>
<td>No alterations in urinary uric acid levels</td>
<td>Deosthale and Gopalan 1974 (ammonium molybdate)</td>
</tr>
<tr>
<td>2</td>
<td>Rat (Sprague Dawley)</td>
<td>22 M</td>
<td>PND 4-17; 0 or 50 mg/kg/day</td>
<td>BW, HP</td>
<td>Musc/Skel Bd Wt</td>
<td>50</td>
<td>50</td>
<td></td>
<td>Increased buccal and sulcal enamel lesions following pre-eruptive exposure to molybdenum and administration of a caries promoting diet.</td>
<td>Hunt and Navia 1975 (sodium molybdate)</td>
</tr>
<tr>
<td>3</td>
<td>Rabbit (New Zealand White)</td>
<td>5 F</td>
<td>14 day (F); 0, 1.2 mg/kg/day</td>
<td>BW, HP</td>
<td>Hepatic Renal Bd Wt</td>
<td>1.2</td>
<td>1.2</td>
<td></td>
<td>A 60% increase in serum triglyceride levels was found; no significant alterations in liver or kidney histopathology were found.</td>
<td>Bersenyi et al. 2008 (ammonium heptamolybdate)</td>
</tr>
<tr>
<td>4</td>
<td>Rabbit (New Zealand White)</td>
<td>5 M</td>
<td>14 day (F); 0, 0.58 mg/kg/day</td>
<td>BW, HP</td>
<td>Hepatic Renal Bd Wt</td>
<td>0.58</td>
<td>0.58</td>
<td></td>
<td>No histological alterations in the liver or kidneys or alterations in serum clinical chemistry parameters were observed. The molybdenum in the diet came from carrots grown in molybdenum rich soil.</td>
<td>Bersenyi et al. 2008 (ammonium heptamolybdate)</td>
</tr>
<tr>
<td><strong>Reproductive</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Mouse (ICR)</td>
<td>25 F</td>
<td>14 days (W); 0, 1.3, 2.6, 5.3, and 11 mg/kg/day</td>
<td>HP</td>
<td></td>
<td>5.3&lt;sup&gt;1&lt;/sup&gt;</td>
<td>11</td>
<td></td>
<td>Significant increase in the rate of abnormal MII oocytes and decrease in ovarian weights were observed at 11 mg/kg/day. Ovarian hyperemia was observed at 5.3 and 11 mg/kg/day (incidence and statistical significance were not reported).</td>
<td>Zhang et al. 2013 (sodium molybdate)</td>
</tr>
<tr>
<td>6</td>
<td>Mouse (ICR)</td>
<td>10 M</td>
<td>14 days; 0, 3, 6, 12, 25, and 49 mg/kg/day</td>
<td>OF</td>
<td></td>
<td>12</td>
<td>25</td>
<td></td>
<td>Significant decreases in relative epididymis weight, sperm concentration, and sperm motility and increase in rate of sperm abnormalities.</td>
<td>Zhai et al. 2013 (sodium molybdate)</td>
</tr>
<tr>
<td>7</td>
<td>Rabbit (New Zealand White)</td>
<td>5 F</td>
<td>14 days (F); 0, 1.2 mg/kg/day</td>
<td>BW, HP</td>
<td></td>
<td>1.2</td>
<td></td>
<td></td>
<td>No histological alterations were observed in the ovaries.</td>
<td>Bersenyi et al. 2008 (ammonium heptamolybdate)</td>
</tr>
</tbody>
</table>

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<sup>1</sup> MII oocytes: metaphase II oocytes.
### 3. HEALTH EFFECTS

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

<table>
<thead>
<tr>
<th>Figure key</th>
<th>Species (strain)</th>
<th>Exposure parameters/ concentrations</th>
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<th>NOAEL (mg/kg/day)</th>
<th>Serious LOAEL (mg/kg/day)</th>
<th>Serious LOAEL (mg/kg/day)</th>
<th>Results</th>
<th>Reference (compound)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>Rabbit (New Zealand White)</td>
<td>14 days (F); 0, 0.58 mg/kg/day</td>
<td>BW, HP</td>
<td>0.58</td>
<td>Reduction in germ cells and mature spermatocytes (incidence and statistical significance were not reported)</td>
<td>Bersenyi et al. 2008 (ammonium heptamolybdate)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Rat (Sprague Dawley)</td>
<td>8 weeks (GW); 0, 40, 80 mg/kg/day</td>
<td>BW, OW, UR</td>
<td>Renal Bd Wt</td>
<td>40</td>
<td>80</td>
<td>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. Decrease in body weight gain; terminal body weight was 26% lower than in controls.</td>
<td>Bompart et al. 1990 (ammonium heptamolybdate)</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Rat (Sprague Dawley)</td>
<td>6 weeks (F); 0 or 70 mg/kg/day</td>
<td>BW, HE</td>
<td>Hemato Bd Wt</td>
<td>70</td>
<td>No alterations in mean hemoglobin levels were found.</td>
<td>Gray and Daniel 1954 (sodium molybdate)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Rat (CD)</td>
<td>22-35 days (females)</td>
<td>BW, HE</td>
<td>Hemato Bd Wt</td>
<td>1.5</td>
<td>4.4</td>
<td>Decreases in body weight gain in males starting at day 50. Decreases in erythrocyte count, hemoglobin concentration, and hematocrit in males.</td>
<td>Lyubimov et al. 2004 (ammonium tetraethiolybdate)</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Rat (Wistar)</td>
<td>5 weeks; 0 or 74 mg/kg/day</td>
<td>BW, EA</td>
<td>Bd Wt</td>
<td>74</td>
<td>36% decrease in body weight gain</td>
<td>Mills et al. 1958 (sodium molybdate)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Rat (Sprague Dawley)</td>
<td>90 days (F); 0, 5, 17, or 60 mg/kg/day</td>
<td>CS, BW, BC, HE, FI, GN, HP, OW</td>
<td>Resp Cardio Gastro Hemo Renal Endocr Ocular Bd Wt</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>15.2% lower terminal body weight in males; slight diffuse hyperplasia in the renal proximal tubules in 2/10 female rats exposed to 60 mg/kg/day.</td>
<td>Murray et al. 2013 (sodium molybdate)</td>
</tr>
</tbody>
</table>
### Table 3-2. Levels of Significant Exposure to Molybdenum – Oral

<table>
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<tr>
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<th>NOAEL (mg/kg/day)</th>
<th>LOAEL (mg/kg/day)</th>
<th>Serious LOAEL (mg/kg/day)</th>
<th>Results</th>
<th>Reference (compound)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>Rat (Druckery) 10M</td>
<td>5 days/week 60 days (GW); 0, 4.7, 14, 24 mg/kg</td>
<td>BW</td>
<td>Bd Wt</td>
<td>24</td>
<td></td>
<td></td>
<td>No significant alterations in body weight gain were observed</td>
<td>Pandey and Singh 2002 (sodium molybdate)</td>
</tr>
<tr>
<td>15</td>
<td>Rat (Wistar) 6M</td>
<td>9 weeks (W); 0 or 100 mg/kg/day</td>
<td>BW, BI, OW</td>
<td>Cardio</td>
<td>100</td>
<td>100</td>
<td></td>
<td>Slight decrease (approximately 4%) in systolic blood pressure. No significant alterations in blood triglyceride, glucose, or insulin levels.</td>
<td>Peredo et al. 2013 (sodium molybdate)</td>
</tr>
<tr>
<td>16</td>
<td>Rat (Wistar) 10M or 5M, 5F</td>
<td>4-5 weeks (F); 0 or 110 mg/kg/day</td>
<td>BW, EA</td>
<td>Bd Wt</td>
<td>110</td>
<td></td>
<td></td>
<td>46-48% decrease in body weight gain; no feed intake data were provided.</td>
<td>Van Reen and Williams 1956 (sodium molybdate)</td>
</tr>
<tr>
<td>17</td>
<td>Rat (NMRI-D) 17-18 NR</td>
<td>5 weeks; 0, 2, 4, and 8 mg/kg/day</td>
<td>HP</td>
<td>Musc/Skel</td>
<td>8</td>
<td></td>
<td></td>
<td>No significant alterations in the number of carious teeth and the severity of carious lesions</td>
<td>Van Reen et al. 1962 (sodium molybdate)</td>
</tr>
<tr>
<td>18</td>
<td>Rat (Wistar) 8</td>
<td>6 weeks; 0, or 85 mg/kg/day</td>
<td>BW, EA</td>
<td>Bd Wt</td>
<td>85</td>
<td></td>
<td></td>
<td>No alteration in body weight gain was observed and there was no effect on the ability to acetylated p-aminobenzoic acid. An increase in liver alkaline phosphatase levels was observed. Feed intake of control group was matched to molybdenum group.</td>
<td>Williams and Van Reen 1956 (sodium molybdate)</td>
</tr>
<tr>
<td>19</td>
<td>Rat (Wistar) 8 (sex not reported)</td>
<td>6 weeks; 0, 90, 144, and 185 mg/kg/day</td>
<td>BW, EA</td>
<td>Bd Wt</td>
<td>90</td>
<td></td>
<td></td>
<td>Decreases in body weight gain of 22, 44, and 60% were observed in the 90, 144, and 185 mg/kg/day groups; decreases in feed intake were also observed in these groups.</td>
<td>Williams and Van Reen 1956 (sodium molybdate)</td>
</tr>
<tr>
<td>20</td>
<td>Rat (Sprague Dawley) 10F</td>
<td>8 weeks (W); 0, 0.015, 0.076, 0.15, 0.30, 0.76, and 1.5 mg/kg/day</td>
<td>BW, EA, OW</td>
<td>Bd Wt</td>
<td>1.5</td>
<td></td>
<td></td>
<td>No significant differences in terminal body weights were observed.</td>
<td>Yang and Yang 1989 (sodium molybdate)</td>
</tr>
</tbody>
</table>
3. HEALTH EFFECTS

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

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<th>NOAEL (mg/kg/day)</th>
<th>LOAEL (mg/kg/day)</th>
<th>Serious LOAEL (mg/kg/day)</th>
<th>Results</th>
<th>Reference (compound)</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>Rabbit (Dutch)</td>
<td>30-84 days (F); 0, 7, 1, 25, 54, HE</td>
<td>CS, LE, BW, HE</td>
<td>Hemato Dermal Bd Wt</td>
<td>25 25 25 25 25</td>
<td>54 54 54 54 54</td>
<td>120</td>
<td>120</td>
<td>Weight loss was observed in the 120 and 240 mg/kg/day groups. Anemia was observed in 2/5, 5/5, and 4/5 rabbits in the 54, 120, and 240 mg/kg/day groups and in no rabbits at lower doses. Alopecia was observed in 4/5 and 4/5 rabbits in the 54 and 120 mg/kg/day groups; not observed at lower doses or in the 240 mg/kg/day group.</td>
</tr>
<tr>
<td>22</td>
<td>Rat (Sprague Dawley) 21F</td>
<td>8 weeks (W); 0, 0.76, 1.5, 7.6, and 15 mg/kg/day</td>
<td>BW, WI, OF</td>
<td>0.76 1.5</td>
<td>Prolonged estrus phase (6-12 hours) of the estrous cycle observed at ≥1.5 mg/kg/day. No effect on fertility was observed.</td>
<td>Fungwe et al. 1990 (sodium molybdate)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>Rat (Long Evans) 4M, 4F</td>
<td>At least 8 weeks (F); 0 or 7 mg/kg/day</td>
<td>BW, HE</td>
<td>7</td>
<td>All rats produced litters; rats were maintained on a high copper diet.</td>
<td>Jeter and Davis 1954 (sodium molybdate)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>Rat (CD) 25M, 25F</td>
<td>59-61 days (males) 22-35 days (females) (GW); 0, 0.4, 1.5, 4.4 mg/kg/day</td>
<td>OF, HP</td>
<td>1.5 4.4</td>
<td>Decreases in sperm motility and sperm count, and increased sperm morphological alterations; histological alterations in spermatogenesis in 25/25 males. No alterations in female reproductive parameters.</td>
<td>Lyubimov et al. 2004 (ammonium tetrathiomolybdate)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>Rat (Sprague Dawley) 10M, 10F</td>
<td>90 days (F); 0, 5, 17, or 60 mg/kg/day</td>
<td>CS, BW, BC, HE, FI, GN, HP, OW</td>
<td>17 60</td>
<td>Significant decrease in the percentage of progressively motile sperm; no alterations in overall percentage of motile sperm, spermatid or sperm counts, or sperm morphology. No alterations in vaginal cytology, estrus cycle, or histopathology of male or female reproductive organs.</td>
<td>Murray et al. 2013 (sodium molybdate)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### 3. HEALTH EFFECTS

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

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<th>Serious LOAEL (mg/kg/day)</th>
<th>Serious LOAEL (mg/kg/day) Results</th>
<th>Reference (compound)</th>
</tr>
</thead>
<tbody>
<tr>
<td>26</td>
<td>Rat (Druckery) 10M</td>
<td>5 days/week 60 days (GW); 0, 4.7, 14, 24 mg/kg</td>
<td></td>
<td></td>
<td>4.7</td>
<td>14</td>
<td>Decreases in sperm count and sperm motility and increases in sperm abnormalities were observed at 14 mg/kg and higher. Degeneration of seminiferous tubules were observed in the testes at 24 mg/kg (incidence and statistical significance were not reported.)</td>
<td>Pandey and Singh 2002 (sodium molybdate)</td>
</tr>
<tr>
<td>27</td>
<td>Rat (Druckery) 20M</td>
<td>5 days/week 60 days (GW); 0 or 14 mg/kg</td>
<td>DX, FX</td>
<td></td>
<td>14</td>
<td></td>
<td>Decrease in fertility (60% versus 80% in controls) and increased pre-implantation losses</td>
<td>Pandey and Singh 2002 (sodium molybdate)</td>
</tr>
<tr>
<td>28</td>
<td>Rat (long Evans) 4M, 4F</td>
<td>At least 14 weeks (F); 0 or 7 mg/kg/day</td>
<td>BW, HE</td>
<td></td>
<td>7</td>
<td></td>
<td>All rats produced litters and there were no alterations in birth weight or average weight at weaning.</td>
<td>Jeter and Davis 1954 (sodium molybdate)</td>
</tr>
<tr>
<td>29</td>
<td>Rat (CD) 25M, 25F</td>
<td>59-61 days (males) 22-35 days (females) (GW); 0, 0.4, 1.5, 4.4 mg/kg/day</td>
<td>DX</td>
<td></td>
<td>4.4</td>
<td></td>
<td>No effects on resorptions, pre- or post-implantation losses or viable fetuses</td>
<td>Lyubimov et al. 2004 (ammonium tetrathiomolybdate)</td>
</tr>
<tr>
<td>30</td>
<td>Rat (Sprague Dawley) 25F</td>
<td>GD6-20 (F); 0, 2.8, 9.8, 20.0, and 37.5 mg/kg/day</td>
<td>DX</td>
<td></td>
<td>37.5</td>
<td></td>
<td>No effects on resorptions, post-implantation losses, fetal body weights, or occurrence of fetal malformations.</td>
<td>Murray et al. 2014 (sodium molybdate)</td>
</tr>
<tr>
<td>31</td>
<td>Rat (Druckery) 20M</td>
<td>5 days/week 60 days (GW); 0 or 14 mg/kg</td>
<td>DX, FX</td>
<td></td>
<td>14</td>
<td></td>
<td>Increased post-implantation losses, increased resorptions, decreased number of live fetuses, and decreases in fetal weight and crown-rump length. Males mated with unexposed females</td>
<td>Pandey and Singh 2002 (sodium molybdate)</td>
</tr>
</tbody>
</table>

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***DRAFT FOR PUBLIC COMMENT***
### Table 3-2. Levels of Significant Exposure to Molybdenum – Oral

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<tr>
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<th>Serious LOAEL (mg/kg/day)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**a**The number corresponds to entries in Figure 3-2.

**b**Used to derive an acute-duration oral minimal risk level (MRL) of 0.053 m molybdenum/kg/day based on the NOAEL of 5.3 mg molybdenum/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

**c**Used to derive an intermediate-duration oral MRL of 0.0076 mg molybdenum/kg/day based on the NOAEL of 0.76 mg molybdenum/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

BC = biochemistry; BW = body weight; Cardio = cardiovascular; CS = clinical signs; d = day(s); DX = developmental; EA = enzyme activity; Endocr = endocrine; F = female(s); F = food; FI = feed intake; FX = function testing; Gastro = gastrointestinal; GN = gross necropsy; GW = gavage in water; HE = hematology; Hemato = hematology; HP = histopathology; hr = hour(s); MRL = Minimal Risk Level; NS = not specified; Musc/Skel = musculoskeletal; OP = ophthalmology; OW = organ weight; Resp = respiratory; sec = second(s); UR = urinalysis; WI = water intake; wk = week(s)
Figure 3-2. Levels of Significant Exposure to Molybdenum - Oral
Acute (≤ 14 days)

Systemic
Figure 3-2. Levels of Significant Exposure to Molybdenum - Oral (Continued)
Intermediate (15-364 days)

Systemic

***DRAFT FOR PUBLIC COMMENT***
the diet, can influence the toxicokinetics of molybdenum and possibly its toxicity. The current recommended dietary copper concentrations of 5, 6, and 3 ppm have been set 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). Administration of 150 and/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, respectively, in the copper-adequate rats as compared to 6 and 4 times higher in the copper-deficient rats. Additionally, the relative increase in copper levels in the liver and kidneys was greater in the rats fed the copper-deficient diet, as compared to those fed the copper-adequate diet. Administration of tetrathiomolybdate compounds, as compared to molybdate compounds, results in more dramatic shifts in copper levels in rats fed copper adequate diets (Mills et al. 1981a). Since it is not known whether the differences in the distribution of copper and molybdenum influence the molybdenum toxicity, 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 was adequate dietary copper levels, and are not included in the LSE table or figure. Additionally, laboratory animal studies in which the diet provided an inadequate amount of copper are not likely to be a good model for the U.S. population since the median copper intake of adults in the United States exceeds the nutritional requirement (RDA) for copper (NAS 2001).

3.2.2.1 Death

Several oral studies have reported deaths in rabbits 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. 2013, 2014; Pandey and Singh 2002).
3. HEALTH EFFECTS

3.2.2.2 Systemic Effects

**Respiratory Effects.** Only one animal study 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. 2013).

**Cardiovascular Effects.** Using the NHANES dataset (2009–2012), Shiue and Hristova (2014) found a significant positive association between urinary molybdenum levels and high blood pressure among adults after adjusting for potential confounders (adjusted odds ratio of 1.45; 95% confidence interval 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 population-based 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.

No alterations in heart weight or histopathology were observed in rats ingesting ≤60 mg molybdenum/kg/day as sodium molybdate for 90 days (Murray et al. 2013). 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.

**Gastrointestinal Effects.** 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. 2013). 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).
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.

**Hematological Effects.** In general, the hematological system does not appear to be a target of molybdenum 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. 2013). 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 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.

**Musculoskeletal Effects.** A number of animal studies 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
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the femur without fracture, and impaired fibrogenesis at ligamentous attachments to bone. A thickening and widening of the epiphyseal growth plate was 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
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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).

**Hepatic Effects.** There are limited data on the hepatotoxicity of molybdenum in humans. Using the NHANES 2007–2008 data, Mendy et al. (2012) found a significant association between urinary molybdenum levels and the risk of having a self-reported liver condition (odds ratio of 3.09; 95% confidence interval of 1.24–7.73). The geometric mean urinary molybdenum level of the population was 43.8 μg/g creatinine (95% confidence interval of 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 effects have been observed at higher doses. 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. 2013); 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. (2013) 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” (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); body weight was not assessed in every study.

**Renal Effects.** The available data from laboratory animal studies suggest that the kidney may be a target of molybdenum toxicity. Most of these studies involved exposure to ammonium molybdate or ammonium heptamolybdate and it is possible that the renal effects may be due to the ammonium ion rather than the molybdate. 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. (2013) 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. 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.
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**Endocrine Effects.** 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 data set (Yorita Christensen 2013). Significant 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. A 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 percentile, 70th–85th percentile, and >85th percentile). The study did not find a significant association with thyroid stimulating hormone and blood molybdenum levels.

In 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. Murray et al. (2013) did not find increases in histological alterations in the adrenal glands, pituitary gland, or thyroid of rats exposed to 60 mg molybdenum/kg/day as sodium molybdate in the diet for 90 days. 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 resulted decreases in food intake and body weight contributed to the thyroid toxicity.

**Dermal Effects.** There are limited data on the dermal toxicity of molybdenum following oral exposure. In the first 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
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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.

Ocular Effects. 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. 2013); no other studies examined ocular end points.

Body Weight Effects. A large number of animal studies have reported alterations in body weight following acute- or intermediate-duration 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. 1983; 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 1969; Lyubimov et al. 2004; Mills et al. 1958; Murray et al. 2013; Van Reen and Williams 1956). Studies in rats in which the basal diet contained at least twice the amount of copper recommended by the NAS (1995) reported significant decreases in body weight gain 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. 2013; 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 very low LOAEL of 4.4 mg molybdenum/kg/day for decreases in body weight gain (Lyubimov et al. 2004); there are insufficient data to assess whether this is evidence of differences between molybdenum compounds. Decreases in food intake have also been reported in dietary exposure studies (Murray et al. 2013; 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. (2013) 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.

**Metabolic Effects.** The potential of molybdenum to induce metabolic alterations has not been fully investigated. 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. 2013; 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 hind limb 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.

**Other Systemic Effects.** Koval’skiy et al. (1961) reported a significant increase in blood uric acid levels and symptoms of gout in 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.
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(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. 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. (2013) 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. (2013) 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 were consistent with normal variability. Quantitative data for the serum clinical chemistry parameters were not provided in the published paper.
3.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological and lymphoreticular effects in humans and animals following oral exposure to molybdenum.

3.2.2.4 Neurological Effects

There are limited data on the neurotoxicity of molybdenum; no human or animal studies were designed to assess sensitive neurological end points. No overt signs of neurotoxicity were observed in laboratory animal studies (e.g., Murray et al. 2013); Murray et al. (2013) did not report any histological alterations in the brain.

3.2.2.5 Reproductive Effects

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). Meeker et al. (2008) reported a negative significant association between higher molybdenum blood levels (>85th percentile, based on molybdenum levels in blood) and sperm concentration (adjusted odds ratio of 3.48, 95% confidence interval of 1.12–10.8) after adjustment for potential confounders and other metal exposures. No significant associations were found for sperm morphology (adjusted odds ratio of 2.61, 95% confidence interval of 0.97–7.0) or sperm motility (adjusted odds ratio of 2.24, 95% confidence interval of 0.77–6.49). In another study, Meeker et al. (2010) reported a negative 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. A significant negative association between a biomarker of molybdenum exposure (urinary levels) and serum testosterone levels was also observed in a study of males participating in NHANES (2011–2012) (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 statistically significant associations, they do not establish causality and the alterations in reproductive parameters may be due to multiple factors rather than only to molybdenum exposure.
Several studies have evaluated the reproductive toxicity in male laboratory animals. Decreases in sperm motility and concentration and increases in sperm morphological changes were observed in rats administered via gavage 4.4 mg molybdenum/kg/day as ammonium tetrathiomolybdate for 59–61 days (Lyubimov et al. 2004) or 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 epididymis, seminal vesicle, and/or prostate gland weights (Lyubimov et al. 2004; Pandey and Singh 2002; Zhai et al. 2013). 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 age 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. 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 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. In contrast to these findings, Murray et al. (2013) 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. Although the study found no alterations in the percentage of motile sperm, a 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%). Given the results of the Lyubimov et al. (2004), Pandey and Singh (2002), and Zhai et al. (2013) studies, the 60 mg molybdenum/kg/day dose level was considered a LOAEL for male reproductive effects. It should be noted that the basal diet in this study exceeded the NAS (1995) recommendation; the copper content was 14.23 ppm.

Effects have also been observed in female laboratory animals. An increase in the rate of M II 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 (Zhang et al. 2013).
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). Murray et al. (2013) did not find any alterations in vaginal cytology or estrus cycle in female rats exposed to ≤60 mg molybdenum/kg/day as sodium molybdate and Bersenyi et al. (2008) did not find histological alterations in the ovaries of rabbits exposed to 1.2 mg molybdenum/kg/day as ammonium heptamolybdate in the diet for 14 days.

Several intermediate-duration 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) 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 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.

3.2.2.6 Developmental Effects

There are limited data on the developmental effects of molybdenum in humans from two population studies. 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 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 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.
Several studies have examined the effect of molybdenum on development in laboratory animals. 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; Lyubimov et al. 2004; Murray et al. 2014). Murray et al. (2014) reported no effects on litter size, embryofetal survival, sex ratio, fetal body weight, or fetal malformations and variations in rats exposed to 38 mg molybdenum/kg/day as sodium molybdate in the diet on gestation days 6–20. Similarly, 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 gestation days 0–6) in females. 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). However, a fourth 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. 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 gestation days 6–17. Exposure on gestation days 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).

Developmental effects have also been reported in studies in which the copper content of the diets were 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 gestation day 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).
3.2.2.7 Cancer

No studies were located regarding cancer in humans and animals following oral exposure to molybdenum.

3.2.3 Dermal Exposure

3.2.3.1 Death

No studies were located regarding death in humans and animals following dermal exposure to molybdenum.

3.2.3.2 Systemic Effects

No studies were located regarding systemic effects in humans and animals following dermal exposure to molybdenum.

3.2.3.3 Immunological and Lymphoreticular Effects

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.

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).
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3.2.3.4 Neurological Effects

No studies were located regarding neurological effects in humans and animals following dermal exposure to molybdenum.

3.2.3.5 Reproductive Effects

No studies were located regarding reproductive effects in humans and animals following dermal exposure to molybdenum.

3.2.3.6 Developmental Effects

No studies were located regarding developmental effects in humans and animals following dermal exposure to molybdenum.

3.2.3.7 Cancer

No studies were located regarding cancer in humans and animals following dermal exposure to molybdenum.

3.3 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 \textit{in vitro} assays utilizing prokaryotic organisms and in mammalian cells. Limited information is available regarding the \textit{in vivo} genotoxicity of molybdenum.

As shown in Table 3-3, sodium molybdate induced a modest, but statistically significant, increase in micronucleated bone marrow cells (polychromatic erythrocytes, PCE) from male C57BL/6J mice following two intraperitoneal injections of 200 or 400 mg/kg sodium molybdate on two 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
<table>
<thead>
<tr>
<th>Species</th>
<th>Compound</th>
<th>End point</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse (male C57BL/6J)</td>
<td>Sodium molybdate</td>
<td>Micronuclei in bone marrow cells</td>
<td>(+)</td>
<td>Titenko-Holland et al. 1998</td>
</tr>
<tr>
<td>Mouse (male C57BL/6J)</td>
<td>Sodium molybdate</td>
<td>Dominant lethal assay</td>
<td>(+)</td>
<td>Titenko-Holland et al. 1998</td>
</tr>
<tr>
<td>Drosophila melanogaster</td>
<td>Molybdenum chloride</td>
<td>Gene mutation</td>
<td>+</td>
<td>Ogawa et al. 1994</td>
</tr>
</tbody>
</table>

+ = positive result; (+) = weakly positive result
3. HEALTH EFFECTS

did not significantly affect pregnancy rate, but induced a significant dose-related increase in post-implantation loss, which was attributed to an effect on post-meiotic male germ cells.

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 3-4 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). The investigator speculated that because molybdenum has a valence of +6 in both compounds, molybdate is an oxidizing agent and the positive effect might reflect an oxidation capacity.

The few studies that tested molybdenum compounds in mammalian cells provided mixed results (Table 3-4). Different results were reported by NTP (1997) and Gibson et al. (1997) in experiments with molybdenum trioxide: negative in the former study for chromosomal aberrations, and positive in the latter for micronuclei formation. Aside from the differences in end point tested, it should be noted that NTP (1997) tested concentrations of molybdenum trioxide of up to 10 µg/mL, whereas Gibson et al. (1997) tested concentrations of molybdenum trioxide ranging from 250 to 750 µg/mL. Titenko-Holland et al. (1998) reported positive results for micronuclei formation in human peripheral lymphocytes incubated with sodium or ammonium molybdate. However, because blood was collected from only two donors, the results should be interpreted with caution.

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 provided mixed results, but there is suggestive evidence that molybdenum valence +6, as in molybdate compounds (MoO₄²⁻), could induce genotoxicity due to its oxidative capacity. Too few studies were available regarding effects of molybdenum compounds in mammalian cells in vitro to draw a meaningful

***DRAFT FOR PUBLIC COMMENT***
### Table 3-4. Genotoxicity of Molybdenum Compounds *In Vitro*

<table>
<thead>
<tr>
<th>Species (test system)</th>
<th>Compound</th>
<th>End point</th>
<th>Results With activation</th>
<th>Results Without activation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prokaryotic organisms:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Salmonella typhimurium</em>, TA98, TA100, TA1535, TA1537, 1538</td>
<td>Ammonium molybdate</td>
<td>Gene mutation</td>
<td>No data</td>
<td>–</td>
<td>Arlauskas et al. 1985</td>
</tr>
<tr>
<td><em>S. typhimurium</em>, TA97, TA98, TA100, TA 1535, TA1537</td>
<td>Molybdenum trioxide</td>
<td>Gene mutation</td>
<td>–</td>
<td>–</td>
<td>NTP 1997; Zeiger et al. 1992</td>
</tr>
<tr>
<td><em>Saccharomyces cerevisiae</em> D3</td>
<td>Sodium molybdate</td>
<td>Gene conversion and mutation</td>
<td>No data</td>
<td>–</td>
<td>Singh 1983</td>
</tr>
<tr>
<td><em>Escherichia coli</em>, WP2uvrA</td>
<td>Ammonium molybdate</td>
<td>Reverse gene mutation</td>
<td>No data</td>
<td>–</td>
<td>Arlauskas et al. 1985</td>
</tr>
<tr>
<td><em>E. coli</em>, 2 WP2 strains</td>
<td>Ammonium molybdate</td>
<td>Reverse gene mutation</td>
<td>No data</td>
<td>+</td>
<td>Nishioka 1975</td>
</tr>
<tr>
<td><em>E. coli</em>, CM571</td>
<td>Ammonium molybdate</td>
<td>Reverse gene mutation</td>
<td>No data</td>
<td>–</td>
<td>Nishioka 1975</td>
</tr>
<tr>
<td><em>E. coli</em> PQ37</td>
<td>Molybdenum chloride</td>
<td>DNA damage</td>
<td>No data</td>
<td>–</td>
<td>Olivier and Marzin 1987</td>
</tr>
<tr>
<td><em>E. coli</em> WP2s(λ)</td>
<td>Sodium molybdate</td>
<td>DNA damage</td>
<td>No data</td>
<td>(+)</td>
<td>Rossman et al. 1984</td>
</tr>
<tr>
<td><em>E. coli</em> WP2d(λ)</td>
<td>Sodium molybdate</td>
<td>DNA damage</td>
<td>No data</td>
<td>(+)</td>
<td>Rossman et al. 1991</td>
</tr>
<tr>
<td><em>Bacillus subtilis</em>, H17 and M45</td>
<td>Molybdic acid</td>
<td>DNA repair assay</td>
<td>No data</td>
<td>–</td>
<td>Kanematsu et al. 1980</td>
</tr>
<tr>
<td><em>B. subtilis</em> H17 and M45</td>
<td>Molybdenum disulfide</td>
<td>DNA repair assay</td>
<td>No data</td>
<td>–</td>
<td>Kanematsu et al. 1980</td>
</tr>
<tr>
<td><em>B. subtilis</em> H17 and M45</td>
<td>Molybdenum chloride</td>
<td>DNA repair assay</td>
<td>No data</td>
<td>–</td>
<td>Nishioka 1975</td>
</tr>
<tr>
<td><em>B. subtilis</em> H17 and M45</td>
<td>Potassium molybdate</td>
<td>DNA repair assay</td>
<td>No data</td>
<td>+</td>
<td>Nishioka 1975</td>
</tr>
<tr>
<td><em>B. subtilis</em> H17 and M45</td>
<td>Ammonium molybdate</td>
<td>DNA repair assay</td>
<td>No data</td>
<td>+</td>
<td>Nishioka 1975</td>
</tr>
<tr>
<td><em>Photobacterium fischeri</em></td>
<td>Sodium molybdate</td>
<td>Direct mutation</td>
<td>No data</td>
<td>–</td>
<td>Ulitzur and Barak 1988</td>
</tr>
<tr>
<td>Mammalian cells:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human peripheral lymphocytes</td>
<td>Sodium molybdate</td>
<td>Micronucleus assay</td>
<td>No data</td>
<td>(+)</td>
<td>Titenko-Holland et al. 1998</td>
</tr>
<tr>
<td>Human peripheral lymphocytes</td>
<td>Ammonium molybdate</td>
<td>Micronucleus assay</td>
<td>No data</td>
<td>+</td>
<td>Titenko-Holland et al. 1998</td>
</tr>
</tbody>
</table>
### Table 3-4. Genotoxicity of Molybdenum Compounds *In Vitro*

<table>
<thead>
<tr>
<th>Species (test system)</th>
<th>Compound</th>
<th>End point</th>
<th>With activation</th>
<th>Without activation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syrian hamster embryo (SHE) cells</td>
<td>Molybdenum trioxide</td>
<td>Micronucleus assay</td>
<td>No data</td>
<td>+</td>
<td>Gibson et al. 1997</td>
</tr>
<tr>
<td>Chinese hamster ovary (CHO) cells</td>
<td>Molybdenum trioxide</td>
<td>Chromosomal aberrations</td>
<td>–</td>
<td>–</td>
<td>NTP 1997</td>
</tr>
<tr>
<td>CHO cells</td>
<td>Molybdenum trioxide</td>
<td>Sister chromatid exchanges</td>
<td>–</td>
<td>–</td>
<td>NTP 1997</td>
</tr>
</tbody>
</table>

+ = positive result; (+) = weakly positive result; – = negative result; ± = equivocal result
conclusion, although two studies found positive results and a third study found weak positive results in the micronuclei assay.

3.4 TOXICOKINETICS

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

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 (Baily et al. 2007; ICRP 1994). More soluble forms of molybdenum, such as molybdenum trioxide (MoV\textsubscript{2}O\textsubscript{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\textsuperscript{3}, 6 hours/day, 5 days/week for 2 years), exposure-dependent increases in blood molybdenum were observed (NTP 1997). The respectively blood molybdenum levels in the 0, 6.7, 20, and 67 mg
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Molybdenum/m³ 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.

3.4.1.2 Oral Exposure

Absorption of ingested molybdenum has been studied in human adults and infants (Cantone et al. 1993, 1997; Engle et al. 1967; Giussani et al. 1998, 2006, 2007; Novotny and Turnlund 2006, 2007; Robinson et al. 1993; 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 (⁹⁵Mo, ⁹⁶Mo), 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, typically, the isotope dosing material was prepared from an acid dissolution of metallic molybdenum (Mo⁰). The resulting material dissolved in water most likely was a mixture of soluble molybdate anion (Mo⁶⁺O₄²⁻) 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 Mo/kg dissolved in water and decreased with increasing dose level; absorption was 60% after a dose of 60 µg Mo/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 96Mo (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 Mo/kg/day), compared to 94% when fed a diet containing 467 µg Mo/day (approximately 7 µg Mo/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 (Giussani 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\(\text{VI}_{2}\text{S}_4\text{O}_6\)) 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).
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3.4.1.3 Dermal Exposure

Studies evaluating the absorption of molybdenum following dermal exposure were not identified.

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

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/m³, 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.

3.4.2.2 Oral Exposure

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 Mo/g wet in liver (700–2,700 µg) and 0.2–0.4 µg Mo/g wet in kidney (55–120 µg). Coughtrey and Thorne (1983) reported relatively high concentrations (56 µg Mo/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. 2014; Pandey et al. 2002). Generally, the highest molybdenum tissue concentration is observed in the kidney. Molybdenum also is distributed to liver, spleen, brain, lung, heart, bone, muscle, testis, epididymis, seminal vesicles, prostate, blood cells, and plasma. Studies conducted in rats have shown that molybdenum absorbed following ingestion of tetrathiomolybdate from the diet distributes to the kidneys and liver (Mills et al. 1981a).
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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).

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 Mo/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. 1999; 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 (mean concentration of 72 µg/L) and maternal molybdenum intake (mean intake of 132 µg/day).

3.4.2.3 Dermal Exposure

Studies evaluating the distribution of molybdenum following dermal exposure were not identified.

3.4.3 Metabolism

Molybdenum exists in several valence states and may undergo oxidation and reduction. Although molybdenum can exist in biological systems in several different valence states (3+, 4+, 5+, and 6+), the primary form of molybdenum that interacts with enzyme systems is Mo\(^{VI}\), as the molybdate anion
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(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).

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

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

3.4.4.2 Oral Exposure

Absorbed molybdenum is excreted in urine and feces in humans. Urine is the dominant excretion route, accounting for 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 ^100Mo/day) and administered intravenous doses of stable isotope of molybdenum (33 μg ^97Mo). Six days after exposure to ^100Mo in the diet, 17.8% of the ^100Mo 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 ^100Mo was excreted in the urine. A similar pattern of urinary excretion was found when ^97Mo 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 ^100Mo dose was excreted in the feces; at the highest dose, 7.5% of the ^100Mo dose was excreted in the feces. In contrast, no consistent pattern of fecal ^97Mo 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 rats have shown that, following an intravenous dose of Mo\textsuperscript{VII} or Mo\textsuperscript{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\textsuperscript{VII} at doses <3 µg Mo/kg, elimination was mono-phasic with a half-time of approximately 47 hours. Following doses >3 µg Mo/kg, the rate of elimination increased, with an increasing proportion of elimination contributed by a fast phase having a half-time of 6 hours.

### 3.4.4.3 Dermal Exposure

Studies evaluating the elimination and excretion of molybdenum following dermal exposure were not identified.

### 3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (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 end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and Krishnan 1994; Andersen et al. 1987). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of
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PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parameterization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. However, if the uptake and disposition of the chemical substance(s) are adequately described, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-3 shows a conceptualized representation of a PBPK model.

If PBPK models for molybdenum exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

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
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Figure 3-3. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance

Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

Source: Krishnan and Andersen 1994
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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 (Giussani 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 3-4 and parameter values are presented in Table 3-5. Data used to derive and evaluate the model are described in Giussani (2008) and included human clinical studies in which subjects were administered intravenous or oral doses of stable isotopes of molybdenum (Giussani 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%).

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) (ICRP 1994; Baily et al. 2007).
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Figure 3-4. The Proposed Systemic Model for Molybdenum Radionuclides

*From alimentary tract, respiratory tract, wounds*

ECF = extracellular fluid

Source: Reprinted from Giussani (2008) with permission from Elsevier.
### Table 3-5. Transfer Rates (Day⁻¹) for the Molybdenum Model

<table>
<thead>
<tr>
<th>Transfer rate</th>
<th>Value (day⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECF1 to ECF2</td>
<td>12.5</td>
</tr>
<tr>
<td>ECF1 to liver</td>
<td>14.2</td>
</tr>
<tr>
<td>ECF1 to urinary bladder contents</td>
<td>6.5</td>
</tr>
<tr>
<td>ECF2 to urinary path</td>
<td>1.7</td>
</tr>
<tr>
<td>ECF2 to other kidney tissues</td>
<td>0.115</td>
</tr>
<tr>
<td>ECF2 to other tissues</td>
<td>1.73</td>
</tr>
<tr>
<td>Liver to alimentary tract</td>
<td></td>
</tr>
<tr>
<td>Liver to ECF2</td>
<td>0.0048</td>
</tr>
<tr>
<td>Other kidney tissues to ECF2</td>
<td>0.0122</td>
</tr>
<tr>
<td>Other tissues to ECF2</td>
<td>0.0323</td>
</tr>
<tr>
<td>Urinary path to urinary bladder contents</td>
<td>1.40</td>
</tr>
<tr>
<td>Urinary bladder contents to urine</td>
<td>12</td>
</tr>
<tr>
<td>Modified parameters of the alimentary tract</td>
<td></td>
</tr>
<tr>
<td>Stomach to small intestine (liquid form)</td>
<td>100</td>
</tr>
<tr>
<td>Stomach to small intestine (diet)</td>
<td>40</td>
</tr>
<tr>
<td>Small intestine to right colon (liquid form)</td>
<td>10</td>
</tr>
<tr>
<td>Small intestine to right colon (diet)</td>
<td>16</td>
</tr>
<tr>
<td>$f_A$ (liquid form)(^a)</td>
<td>0.9</td>
</tr>
<tr>
<td>$f_A$ (diet)(^a)</td>
<td>0.6</td>
</tr>
</tbody>
</table>

\(^a\)Dimensionless number.

ECF = extracellular fluid

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

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 Mo/day) and found that certain model parameters were dependent on dietary intake. These included, in association with increasing dietary intake, an increase 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 Mo/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 Mo/day) result in physiological adaptations that increase excretion of absorbed molybdenum (Novotny and Turnlund 2007).

### 3.5 MECHANISMS OF ACTION

#### 3.5.1 Pharmacokinetic Mechanisms

**Absorption.** Mechanisms that participate in absorptive transport of molybdenum in the gastrointestinal tract have not been characterized. Molybdate (MoO₄²⁻) and sulfate (SO₄²⁻) 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⁺/SO₄²⁻ 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 et al. 2000).

**Distribution.** Bacteria and eukaryotes express cell membrane molybdate transporters, one of which (MoT2) 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). MoT2 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⁻/HCO₃⁻ anion exchanger (Gimenez et al. 1993).

**Metabolism.** Molybdenum-dependent enzymes contain a molybdopterin cofactor (Moco), which is formed in a series of enzymatically catalyzed steps (Mendel and Bittner 2006). The final step, insertion of molybdate into Moco, may involve displacement of copper from the molybdate binding site, which may provide a mechanism for copper-molybdenum interactions in regulating Moco synthesis and copper-induced deficiency in molybdenum-dependent enzymes (Mendel and Bittner 2006). Binding of molybdenum to plasma proteins involves formation of a Cu-Mo-S complex (Nederbragt 1980, 1982).

**Excretion.** Mechanisms that participate in the renal excretion of molybdenum have not been characterized. In sheep, reabsorption of filtered molybdate (MoO₄²⁻) 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 (MoO₄²⁻) and sulfate (SO₄²⁻) exhibit mutual inhibition (Ryan et al. 1987). This is consistent with participation of the Na⁺/SO₄²⁻ 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).

### 3.5.2 Mechanisms of Toxicity

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 alterations 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, including 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 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).

Other investigators have suggested that the molybdenum-induced effects are due to oxidative damage (Zhai et al. 2013; Zhang et al. 2013). Zhai et al. (2013) showed that the levels of two enzymatic antioxidants (superoxide dismutase and glutathione peroxidase) 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 and the rate of MII oocyte abnormalities.

### 3.5.3 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, see Section 3.5.2).
3.6 HAZARD IDENTIFICATION AND MINIMAL RISK LEVELS

3.6.1 Hazard Identification

Systematic review of the available human and animal studies that assessed potential health effects associated with inhalation and oral exposure to molybdenum identified a number of potential targets of toxicity. Hazard identification conclusions for molybdenum, resulting from this systematic review, are presented in Appendix B and are summarized as follows:

- Molybdenum is presumed to cause respiratory effects following inhalation exposure, based on an inadequate level of evidence from human studies and a high level of evidence from animal studies.

- Molybdenum is suspected to cause hepatic effects, based on an inadequate level of evidence from human studies and a moderate level of evidence from animal studies.

- Molybdenum is presumed to cause renal effects, based on a high level of evidence from animal studies; human data are lacking.

- Molybdenum is suspected to cause reproductive effects, based on a low level of evidence from human studies and a moderate level of evidence from animal studies.

- The data are not classifiable as to determine whether molybdenum results in developmental toxicity because some human and animal studies have reported developmental effects and other studies have not found effects.

- The data are not classifiable as to determine whether molybdenum results in alterations in uric acid levels based on a high level of evidence of no effect in animal studies and an inadequate level of evidence from human studies.

3.6.2 Minimal Risk Levels (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for molybdenum. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. 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 within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.
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Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

3.6.2.1 Inhalation MRLs

**Acute-Duration.** The database on the acute inhalation toxicity of molybdenum is limited to a study conducted by NTP (1997) that evaluated the effect of molybdenum trioxide on the nasal cavity and on body weight. No adverse effects were observed in the nasal cavity. However, weight loss was observed at the highest concentration tested (200 mg molybdenum/m³); decreases in body weight gain were observed in male rats exposed to 67 mg molybdenum/m³ and in female rats and mice exposed to 200 mg/m³. Given the limited number of end points 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.

**Intermediate-Duration.** As with the acute-duration database, data on the intermediate-duration toxicity of molybdenum is limited to 90-day studies in rats and mice conducted by NTP (1997) that examined a wide range of potential targets, including reproductive end points. No toxicologically significant alterations were observed at concentrations of molybdenum trioxide as high as 67 mg/m³. Consistent with ATSDR’s practice of not using free-standing NOAELs as a point of departure (POD), an intermediate-duration inhalation MRL was not derived.

**Chronic-Duration.** 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/m³. 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 B for additional information).
NTP (1997) conducted a 2-year study in rats and mice that 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 specific types of lesions and the incidence data are presented in Table 3-6.

Benchmark dose (BMD) modeling was used to fit the data for effects with statistically significant increases in incidences at the lowest concentration (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 results of the modeling are presented in Appendix A. Benchmark models provided adequate fit for most of the datasets, predicting benchmark concentrations (BMCs) ranging from 0.46 to 5.73 mg molybdenum/m³ and 95% lower confidence limits on the BMC (BMCL) ranging from 0.19 to 4.26 mg molybdenum/m³. Human equivalent concentrations (HECs) were calculated by adjusting the BMCLs for intermittent exposure (6 hours/day, 5 days/week) and multiplying by the regional deposited dose ratio (RDDR) for the appropriate region of the respiratory tract. The lowest HEC was 0.012 mg molybdenum/m³ for squamous metaplasia of the epiglottis in female mice. This HEC was divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans using dosimetric adjustments and 10 for human variability), resulting in an MRL of 0.0004 mg molybdenum/m³.

3.6.2.2  Oral MRLs

Acute-Duration. A small number of studies have evaluated the acute toxicity of molybdenum. One human study (Deosthale and Gopalan 1974) that looked at a limited number of potential end points 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. 2013).

Reproductive effects have been observed in male and female mice and rabbits. In females, an increased rate of abnormal MII oocytes was observed at 11 mg molybdenum/kg/day in mice (Zhang et al. 2013); a second study did not find histological alterations in the ovaries of rabbits (Bersenyi et al. 2008). In males,
### Table 3-6. Incidence of Non-Neoplastic Respiratory Tract Lesions in Rats and Mice Exposed to Molybdenum Trioxide for 2 Years

<table>
<thead>
<tr>
<th>Concentration (mg molybdenum/m³)</th>
<th>0</th>
<th>6.7</th>
<th>20</th>
<th>67</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male rats</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyaline degeneration of nasal respiratory epithelium</td>
<td>2/50</td>
<td>7/49</td>
<td>48/49&lt;sup&gt;a&lt;/sup&gt;</td>
<td>49/50&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Squamous metaplasia of epiglottis</td>
<td>0/49</td>
<td>11/48&lt;sup&gt;a&lt;/sup&gt;</td>
<td>16/49&lt;sup&gt;a&lt;/sup&gt;</td>
<td>39/49&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Chronic lung inflammation in alveolus</td>
<td>2/50</td>
<td>3/50</td>
<td>25/50&lt;sup&gt;a&lt;/sup&gt;</td>
<td>47/50&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Female rats</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyaline degeneration of nasal respiratory epithelium</td>
<td>1/48</td>
<td>13/49&lt;sup&gt;a&lt;/sup&gt;</td>
<td>50/50&lt;sup&gt;a&lt;/sup&gt;</td>
<td>50/50&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hyaline degeneration of nasal olfactory epithelium</td>
<td>39/48</td>
<td>47/49&lt;sup&gt;b&lt;/sup&gt;</td>
<td>50/50&lt;sup&gt;a&lt;/sup&gt;</td>
<td>50/50&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Squamous metaplasia of epiglottis</td>
<td>0/49</td>
<td>18/49&lt;sup&gt;a&lt;/sup&gt;</td>
<td>29/49&lt;sup&gt;a&lt;/sup&gt;</td>
<td>49/50&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Chronic lung inflammation</td>
<td>14/50</td>
<td>13/50</td>
<td>43/50&lt;sup&gt;a&lt;/sup&gt;</td>
<td>49/50&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Male mice</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal suppurative inflammation</td>
<td>2/50</td>
<td>6/50</td>
<td>10/49&lt;sup&gt;b&lt;/sup&gt;</td>
<td>8/50&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Nasal olfactory epithelium atrophy</td>
<td>3/50</td>
<td>5/50</td>
<td>3/49</td>
<td>10/50&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hyaline degeneration of nasal respiratory epithelium</td>
<td>11/50</td>
<td>13/50</td>
<td>11/49</td>
<td>41/50&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Squamous metaplasia of epiglottis</td>
<td>0/50</td>
<td>26/49&lt;sup&gt;a&lt;/sup&gt;</td>
<td>37/48&lt;sup&gt;a&lt;/sup&gt;</td>
<td>49/50&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Laryngeal hyperplasia</td>
<td>1/50</td>
<td>3/49</td>
<td>6/48</td>
<td>41/50</td>
</tr>
<tr>
<td>Histiocyte infiltration in the lungs</td>
<td>2/50</td>
<td>16/50&lt;sup&gt;a&lt;/sup&gt;</td>
<td>9/49&lt;sup&gt;b&lt;/sup&gt;</td>
<td>9/50&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Alveolar epithelial metaplasia</td>
<td>0/50</td>
<td>32/50&lt;sup&gt;a&lt;/sup&gt;</td>
<td>36/49&lt;sup&gt;a&lt;/sup&gt;</td>
<td>49/50&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Female mice</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyaline degeneration of nasal respiratory epithelium</td>
<td>26/49</td>
<td>23/50</td>
<td>28/49</td>
<td>48/49&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hyaline degeneration of nasal olfactory epithelium</td>
<td>22/49</td>
<td>14/50</td>
<td>14/49</td>
<td>36/49&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Squamous metaplasia of epiglottis</td>
<td>1/49</td>
<td>36/50&lt;sup&gt;a&lt;/sup&gt;</td>
<td>43/49&lt;sup&gt;a&lt;/sup&gt;</td>
<td>49/50&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Laryngeal hyperplasia</td>
<td>1/49</td>
<td>1/50</td>
<td>7/49</td>
<td>35/50</td>
</tr>
<tr>
<td>Alveolar epithelial metaplasia</td>
<td>2/50</td>
<td>26/50&lt;sup&gt;a&lt;/sup&gt;</td>
<td>39/49&lt;sup&gt;a&lt;/sup&gt;</td>
<td>46/49&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Significantly different from controls; p≤0.01.<br>
<sup>b</sup>Significantly different from controls; p≤0.05.

Source: NTP 1997
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). Although the Bersenyi et al. (2008) study in male rabbits identified the lowest LOAEL for reproductive effects, it was not selected as the basis of the acute MRL because the incidence of the reduction in mature spermatocytes was not reported. Rather, the Zhang et al. (2013) was selected as the key study for the acute-duration oral MRL.

The data were not considered suitable for BMD modeling (see Appendix A); thus, a NOAEL/LOAEL approach was used to identify the POD for the MRL. The MRL of 0.05 mg molybdenum/kg/day was calculated by dividing the NOAEL of 5.3 mg molybdenum/kg/day by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability). It should be noted that 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.

**Intermediate-Duration.** Studies in laboratory animals have evaluated the intermediate-duration toxicity of molybdenum. A number of adverse effects have been reported including kidney damage (Bompart et al. 1990; Murray et al. 2013), decreases in body weight gain (Bompart et al. 1990; Lyubimov et al. 2004; Mills et al. 1958; Murray et al. 2013; Van Reen and Williams 1956), hematological effects (Arrington and Davis 1953; Lyubimov et al. 2004), neurological effects (Arrington and Davis 1953), reproductive effects (Fungwe et al. 1990; Jeter and Davis 1954; Lyubimov et al. 2004; Murray et al. 2013; Pandey and Singh 2002), and developmental effects (Pandey and Singh 2002). The lowest LOAEL values identified are 1.5 mg molybdenum/kg/day for prolonged estrus phase without an effect on fertility in rats exposed to sodium molybdate in drinking water for 8 weeks (Fungwe et al. 1990) and 4.4 mg molybdenum/kg/day for anemia, decreases in body weight gain, and decreases in sperm motility and count in rats administered via gavage ammonium tetrathiomolybdate for 22–35 days (females) or 59–61 days (males) (Lyubimov et al. 2004). The observed renal effects included slight diffuse hyperplasia in rats exposed to 60 mg molybdenum/kg/day as sodium molybdate in the diet (Murray et al. 2013) and increases in diuresis and creatinuria and decreases in creatinine clearance in rats administered 80 mg molybdenum/kg/day as ammonium heptamolybdate (Bompart et al. 1990); the NOAELs identified in these studies are 17 and 40 mg molybdenum/kg/day, respectively. Two studies have reported hematological effects—decreases in erythrocyte count, hemoglobin concentrations, and hematocrit levels in rats exposed to 4.4 mg molybdenum/kg/day as ammonium tetrathiomolybdate (Lyubimov et al. 2004) and in rabbits exposed to 54 mg molybdenum/kg/day as sodium molybdate (Arrington and Davis 1953);
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However, other studies have not found hematological effects in rats exposed to 60 or 70 mg molybdenum/kg/day as sodium molybdate (Gray and Daniel 1954; Murray et al. 2013). Neurological effects consisting of weakness of the front legs progressing to an “inability to maintain weight and legs spread outward” was observed in young rabbits exposed to 54 mg molybdenum/kg/day as sodium molybdate (Arrington and Davis 1953); no neurological effects were observed at 25 mg molybdenum/kg/day or in mature rabbits exposed to doses as high as 120 mg molybdenum/kg/day (Arrington and Davis 1953). Although several studies have reported reproductive effects, particularly alterations in sperm parameters, there is considerable overlap between the identified NOAELs and LOAELs that are summarized in Table 3-2. Some of the overlap may be explained by the copper content of the diet. In the Jeter and Davis (1954) and Murray et al. (2013) studies, the copper content of the diet exceeded the recommended intake for rats (5 ppm) (NAS 1995) by a factor of 4 or 2.8, respectively. Four studies examined the developmental toxicity of molybdenum following intermediate-duration exposure. No alterations in resorptions, post-implantation losses, or fetal body weights were observed in three studies with doses as high as 37.5 mg molybdenum/kg/day (Jeter and Davis 1954; Lyubimov et al. 2004; Murray et al. 2014). A fourth study reported increases in post-implantation losses, increased resorption, and decreases in fetal growth in a study in which males only were administered 14 mg molybdenum/kg (5 days/week) for 60 days (Pandey and Singh 2002).

Reproductive toxicity in males and females consistently has the lowest LOAEL values. Reproductive effects have also been observed following acute-duration exposure, and the systematic review of the available human and animal data (Appendix B) showed that reproductive toxicity is “suspected to be a health effect following oral exposure.” The Fungwe et al. (1990) study identified the lowest LOAEL of 1.5 mg molybdenum/kg/day; the NOAEL was 0.76 mg molybdenum/kg/day.

BMD modeling of the estrous cycle length data from the Fungwe et al. (1990) study was conducted to identify the POD for the MRL using a benchmark response (BMR) of 1 SD change from the control. The continuous variable models did not adequately fit the data and a NOAEL/LOAEL approach was used to identify the POD for the MRL. An MRL of 0.008 mg/kg/day was derived by dividing the NOAEL of 0.76 mg molybdenum/kg/day by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability). 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. The MRL is approximately 10-fold higher than the recommended dietary allowance of 0.0006 mg/kg/day (estimated using a reference body weight of 70 kg) (NAS 2001).
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Chronic-Duration. 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. No chronic-duration animal toxicity studies were identified.

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.

3.7 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as endocrine disruptors. However, appropriate terminology to describe such effects remains controversial. The terminology endocrine disruptors, initially used by Thomas and Colborn (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for “...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...”. To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in
1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavonoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

No studies were located regarding endocrine disruption in humans and/or animals after exposure to molybdenum. No *in vitro* studies were located regarding endocrine disruption of molybdenum.

### 3.8 CHILDREN’S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when most biological systems will have fully developed. 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. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children’s unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6, Exposures of Children.
Children sometimes differ from adults in their susceptibility to adverse health effects from exposure to hazardous chemicals, but whether there is a difference depends on the chemical(s) (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to exposure-related health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life that are most sensitive to disruption from exposure to hazardous substances. Damage from exposure in one stage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water, and their brains and livers are proportionately larger (Altmann and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). Past literature has often described the fetus/infant as having an immature (developing) blood-brain barrier that is leaky and poorly intact (Costa et al. 2004). However, current evidence suggests that the blood-brain barrier is anatomically and physically intact at this stage of development, and the restrictive intracellular junctions that exist at the blood-CNS interface are fully formed, intact, and functionally effective (Saunders et al. 2008, 2012).

However, during development of the brain, there are differences between fetuses/infants and adults that are toxicologically important. These differences mainly involve variations in physiological transport systems that form during development (Ek et al. 2012). These transport mechanisms (influx and efflux) play an important role in the movement of amino acids and other vital substances across the blood-brain barrier in the developing brain; these transport mechanisms are far more active in the developing brain than in the adult. Because many drugs or potential toxins may be transported into the brain using these same transport mechanisms—the developing brain may be rendered more vulnerable than the adult. Thus, concern regarding possible involvement of the blood-brain barrier with enhanced susceptibility of the developing brain to toxins is valid. It is important to note however, that this potential selective vulnerability of the developing brain is associated with essential normal physiological mechanisms; and not because of an absence or deficiency of anatomical/physical barrier mechanisms.

The presence of these unique transport systems in the developing brain of the fetus/infant is intriguing; whether these mechanisms provide protection for the developing brain or render it more vulnerable to...
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toxic injury is an important toxicological question. Chemical exposure should be assessed on a case-by-case basis. Research continues into the function and structure of the blood-brain barrier in early life (Kearns et al. 2003; Saunders et al. 2012; Scheuplein et al. 2002).

Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns given their low glomerular filtration rate and not having developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

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 were not observed 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). But 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 4.4 or 38 mg molybdenum/kg/day (Lyubimov et al. 2004; Murray et al. 2014). 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).

3.9 BIOMARKERS OF EXPOSURE AND EFFECT

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

The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of a generalizable sample of the exposure of the U.S. population to environmental chemicals using biomonitoring. This report is available at http://www.cdc.gov/exposurereport/. The biomonitoring data for molybdenum from this report is discussed in Section 6.5. 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. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to molybdenum are discussed in Section 3.9.1.

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 effects caused by molybdenum are discussed in Section 3.9.2.

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 3.11, Populations That Are Unusually Susceptible.

### 3.9.1 Biomarkers Used to Identify or Quantify Exposure to Molybdenum

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±.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 were an indicator of dietary intake, but urinary levels were more directly related to molybdenum intake.

Molybdenum levels were measured in urine samples collected during National Health and Nutrition Surveys. 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 6.5 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.

### 3.9.2 Biomarkers Used to Characterize Effects Caused by Molybdenum

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

### 3.10 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 (Valli et al. 1969; Widjajakuma et al. 1973), marked decreases in body weight gain and weight loss (Brinkman and Miller 1961; Johnson and Miller 1961; Sasmal et al. 1968; Valli et al. 1969; Van Reen 1959), and anemia (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. 2013; 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, 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). 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).

3.11 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to molybdenum than will most
persons exposed to the same level of molybdenum 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 result in reduced detoxification or excretion of
molybdenum, or compromised function of organs affected by molybdenum. Populations who are at
greater risk due to their unusually high exposure to molybdenum are discussed in Section 6.7, Populations
with Potentially High Exposures.

The available data demonstrate the interaction between copper and molybdenum; more severe effects are
observed in animals maintained on a copper-deficient diet (Brinkman and Miller 1961; Franke and
Moxon 1961; 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). The findings in the animal studies are supported by a report by Koval’skiy
et al. (1961) that gout-like symptoms and increased uric acid levels were observed in a population with
high molybdenum levels in the soil and low copper intakes, but were not observed in an area with high
molybdenum levels and adequate copper intakes. Thus, individuals with low copper intakes may be
unusually susceptible to the toxicity of molybdenum.

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 (Bandyopadhay 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.
Since molybdenum is primarily excreted in the urine, individuals with kidney disease may also be more susceptible to molybdenum toxicity; however, this has not been investigated in humans or animals.

### 3.12 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to molybdenum. Because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to molybdenum. When specific exposures have occurred, poison control centers, board certified medical toxicologists, board-certified occupational medicine physicians and/or other medical specialists with expertise and experience treating patients overexposed to molybdenum can be consulted for medical advice.

No texts were located that provided specific information about treatment following exposures to molybdenum.

Additional relevant information can be found in the front section of this profile under QUICK REFERENCE FOR HEALTH CARE PROVIDERS.

#### 3.12.1 Reducing Peak Absorption Following Exposure

There are no established methods for managing initial exposure to molybdenum or for reducing peak absorption.

#### 3.12.2 Reducing Body Burden

Molybdenum is readily eliminated from the body, and there is evidence that ingestion of high molybdenum doses results in physiological adaptations that increase urinary excretion (Novotny and Turnlund 2007).

#### 3.12.3 Interfering with the Mechanism of Action for Toxic Effects

The mechanism of molybdenum toxicity has not been well established. Studies in laboratory animals suggest that co-administration of a high copper diet can reduce the toxicity of molybdenum, but this has not been tested in humans, and exposure to high levels of copper may be toxic.
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3.13 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 the National Toxicology Program (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.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They 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.

3.13.1 Existing Information on Health Effects of Molybdenum

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to molybdenum are summarized in Figure 3-5. The purpose of this figure is to illustrate the existing information concerning the health effects of molybdenum. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure 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 (Agency for Toxic Substances and Disease Registry 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. A more detailed summary of the number of studies examining specific end points is presented in Tables B-3 and B-4 in Appendix B.

Data on the toxicity of inhaled molybdenum are limited to two occupational exposure studies in which the exposure is poorly characterized. A number of cross-sectional studies have examined the associations between a biomarker of molybdenum exposure (blood or urine levels) and a specific health effect. These studies are not sufficient to establish causality. Additionally, one study examined a community living in an area with high levels of molybdenum in the soil and locally grown foodstuffs. Human data on the
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Figure 3-5. Existing Information on Health Effects of Molybdenum

- **Existing Studies**

**Human**

**Animal**
dermal toxicity of molybdenum are limited to two patch testing studies of individuals undergoing knee or hip replacement.

Acute-duration studies examining a limited number of end points and comprehensive intermediate- and chronic-duration studies in rats and mice have investigated the inhalation toxicity of molybdenum. The chronic studies provided evidence that the respiratory tract is a primary target of toxicity and suggestive evidence of carcinogenicity; the intermediate-duration study did not identify adverse health effects. A number of studies in laboratory animals have examined the oral toxicity of molybdenum following acute- or intermediate-duration exposures. Studies in which the basal diet contained adequate levels of copper identified several targets of toxicity including the kidney, liver, and reproductive system; there was some indication that molybdenum exposure may also result in alterations in uric acid levels and developmental toxicity, but the data were not considered adequate for conclusive hazard identification. Data on the dermal toxicity of molybdenum are limited to a guinea pig sensitization assay.

3.13.2 Identification of Data Needs

**Acute-Duration Exposure.** 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 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 end points would be useful for characterizing the hazard of molybdenum following acute inhalation exposure.

In an acute experiment, no alterations in uric acid levels were observed in volunteers (Deosthale and Gopalan 1974); the study did not examine other potential end points. A small number of studies have examined the acute oral toxicity in laboratory animals, and none of them examined a wide-range of end points. 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 studies examining reproductive end points suggest that this is a sensitive target of acute molybdenum toxicity (Bersenyi et al. 2008; Zhai et al. 2013; Zhang et al. 2013). These studies identified LOAELs for effects on oocytes and sperm and were used to derive an acute-duration oral MRL for molybdenum.
Data on the dermal toxicity of molybdenum are limited to a contact sensitization study in guinea pigs, which found positive effects (Boman et al. 1979). The acute dermal toxicity database is considered inadequate for identifying sensitive targets of toxicity; additional studies examining a wide range of potential end points are needed.

**Intermediate-Duration Exposure.** The available data on the toxicity of molybdenum following intermediate-duration inhalation exposure are limited to 90-day studies 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 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 liver, kidney, reproductive system, and possibly the developing organism (Bompart et al. 1990; Fungwe et al. 1990; Jeter and Davis 1954; Lyubimov et al. 2004; Murray et al. 2013; Pandey and Singh 2002). Based on a comparison of LOAEL values, the reproductive system appeared to be the most sensitive target of toxicity. An intermediate-duration oral MRL was derived based on alterations in oocyte morphology (Fungwe et al. 1990).

No studies have examined the dermal toxicity of molybdenum following intermediate-duration exposure; studies are needed to identify potential targets of toxicity for humans.

**Chronic-Duration Exposure and Cancer.** 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 toxicity (NTP 1997), and an inhalation MRL was derived based on the findings in the animal studies.

A number of studies have evaluated the chronic toxicity of ingested molybdenum in humans. A study of residents living in an area of Armenia with high molybdenum and low copper levels in the soil found increases in uric acid levels and gout-like symptoms (Koval’skiy et al. 1961); other studies in which residents were exposed to high levels of molybdenum in the water did not find alterations in uric acid (EPA 1979). Other 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 end points are needed to identify the hazards associated with chronic ingestion of high levels of molybdenum and establish dose-response relationships.

One study evaluated the carcinogenicity of molybdenum in humans (Droste et al. 1999) and found a higher risk of lung cancer among workers in jobs related to molybdenum exposure; however, there was potential exposure to a number of other carcinogens. In the NTP (1997) rat and mouse studies, equivocal evidence for lung cancer was observed in male rats and some evidence of carcinogenicity was observed in male and female mice. No studies have examined the carcinogenicity of molybdenum following oral or dermal exposure. Chronic studies by these routes of exposure are needed to evaluate carcinogenicity.

**Genotoxicity.** There are limited data on the in vivo genotoxicity of molybdenum; a mouse study found weakly positive effects for micronuclei formation and dominant lethality (Titenko-Holland et al. 1998). Additional in vivo studies, as well as monitoring workers for genotoxicity, would be useful for assessing the genotoxic potential in humans. In vitro studies were negative for micronuclei formation (Gibson et al. 1997; Titenko-Holland et al. 1998) and positive for chromosomal aberrations and sister chromatid exchange (NTP 1997), but both were only tested in one study. Mixed results were found in tests of DNA repair, which may be reflective of the molybdenum compound tested (Kanematsu et al. 1980; Nishioka 1975); additional studies are needed to clarify these conflicting results.

**Reproductive Toxicity.** 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; however, oral exposure studies in laboratory animals support the reproductive system as a target of molybdenum toxicity (Bersenyi et al. 2008; Fungwe et al. 1990; Lyubimov et al. 2004; Pandey and Singh 2002; Zhai et al. 2013; Zhang et al. 2013). Although reproductive effects are the basis of the acute- and intermediate-duration oral MRLs for molybdenum, there is considerable inconsistency across studies, and some studies testing higher doses have not found effects (Jeter and Davis 1954; Murray et al. 2013). Additional studies designed to assess potential
differences in routes of oral exposure and with different molybdenum compounds could help explain the conflicting results.

**Developmental Toxicity.** Two studies examined whether there was a relationship between molybdenum exposure and developmental effects in humans (Shirai et al. 2010; Vazquez-Salas et al. 2014) and found mixed results. Two studies in rats failed to find a relationship between oral exposure to molybdenum and birth outcomes (Lyubimov et al. 2004; Murray et al. 2014). A third study found decreases in fetal growth in a male-only exposure study (Pandey and Singh 2002).

**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 guinea pigs in a sensitization assay with molybdenum pentachloride (Boman et al. 1979). Studies examining immune function would be useful in evaluating whether this is a target of molybdenum toxicity.

**Neurotoxicity.** There are limited data on the neurotoxicity of molybdenum. No histological alterations in the brain or overt signs of toxicity were observed in laboratory animals after intermediate-duration inhalation (NTP 1997) or oral (Murray et al. 2013) exposure or chronic-duration inhalation exposure (NTP 1997). Additional studies, particularly in young animals, should be conducted to assess whether molybdenum affects the neuromuscular system, in the absence of copper deficiency.

**Epidemiological and Human Dosimetry Studies.** A small number of epidemiology studies were identified for molybdenum; however, most of these studies presumably involve background environmental exposure to molybdenum. Two occupational exposure studies found conflicting results regarding the respiratory toxicity of molybdenum (Walravens et al. 197; Ott et al. 2004). Additional studies of worker populations examining a wide range of potential end points, 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. One study of a community living in an area with high molybdenum in the soil reported gout-like symptoms and increased uric acid levels (Koval’skiy et al. 1961); however, low intakes of copper may have contributed to these effects. Additional studies to confirm the results of this study would be valuable.

**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 2015). 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.

**Effect.** No biomarkers of effect were identified. The available data have identified the following sensitive targets: respiratory tract (inhalation only), kidney, and 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\[VI\]O₄²⁻) 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 tetrathiomolybdate (Mo\[VII\]S₄²⁻) or Mo\[IV\] compounds. Studies conducted in rats have shown that molybdenum is absorbed following exposure to tetrathiomolybdate (Mills et al. 1981a). No quantitative information is available on the toxicokinetics of molybdenum in humans following chronic oral exposure, and there is no information on inhalation or dermal exposures. A study conducted in mice showed that molybdenum is absorbed following inhalation exposure to molybdenum trioxide (NTP 1997).

Studies conducted in humans have provided data for 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.

Methods for Reducing Toxic Effects. No information was identified on methods for reducing toxic effects of molybdenum. Although animal studies provide evidence that a high copper diet may decrease molybdenum toxicity, it is unclear whether this would be effective in humans.

Children’s Susceptibility. Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

There are limited data on the toxicity of molybdenum in children; studies are needed to evaluate whether the susceptibility of children differs from adults.

Child health data needs relating to exposure are discussed in Section 6.8.1, Identification of Data Needs: Exposures of Children.

3.13.3 Ongoing Studies

No ongoing studies on the toxicity of molybdenum or its toxicokinetic properties were identified in the National Institute of Health (NIH) RePORTER (2015) database. The International Molybdenum Association is currently sponsoring a 2-generation reproductive toxicity study in rats orally exposed to sodium molybdate.