Molybdenum functions as a cofactor for a limited number of enzymes in humans. The primary criterion used to set an Estimated Average Requirement (EAR) is molybdenum balance in controlled studies with specific amounts of molybdenum consumed. Adjustments are made for the bioavailability of molybdenum. The Recommended Dietary Allowance (RDA) for adult men and women is 45 µg/day. The average dietary intake of molybdenum by adult men and women is 109 and 76 µg/day, respectively. The Tolerable Upper Intake Level (UL) is 2 mg/day, a level based on impaired reproduction and growth in animals.

Function

Molybdenum has been shown to act as a cofactor for a limited number of enzymes in humans: sulfite oxidase, which is believed to be most important for health, xanthine oxidase, and aldehyde oxidase. In all mammalian molybdoenzymes, functional molybdenum is present as an organic component called molybdopterin (Rajagopalan, 1988). These enzymes are involved in catabolism of sulfur amino acids and heterocyclic compounds, including purines and pyridines. A clear molybdenum deficiency syndrome producing physiological signs of molybdenum restriction has not been
achieved in animals, despite major reduction in the activity of these molybdoenzymes. Rather, molybdenum essentiality is based on a genetic defect that prevents sulfite oxidase synthesis. Because sulfite is not oxidized to sulfate, severe neurological damage leading to early death occurs with this inborn error of metabolism (Johnson, 1997). Further support for an essential metabolic role for molybdenum relates to amino acid intolerance in a patient who received long-term total parenteral nutrition without molybdenum (Abumrad et al., 1981). The intolerance, which was probably due to abnormal sulfur amino acid metabolism, was reversed with intravenous repletion of ammonium molybdate.

Physiology of Absorption, Metabolism, and Excretion

The high efficiency of molybdenum absorption over an extensive range of intakes suggests that molybdenum absorption is a passive (nonmediated) process. The competitive inhibition of molybdenum uptake by sulfate that has been observed in rat intestines suggests a carrier may be involved. The mechanism of molybdenum absorption (transcellular or paracellular transport) and the location(s) within the gastrointestinal tract responsible for absorption have not been studied (Nielsen, 1999). Molybdenum concentrations in whole blood vary widely but average about 5 nmol/L (Versieck et al., 1978). Protein-bound molybdenum constitutes between 83 and 97 percent of the total molybdenum in erythrocytes. Potential plasma molybdenum transport proteins include α-macroglobulin. Molybdenum retention may be conserved in part through formation of the molybdopterin complex. Urinary excretion is a direct reflection of the dietary molybdenum intake level (Turnlund et al., 1995a, 1995b). Stable isotope studies showing molybdenum retention at low molybdenum intakes and rapid excretion at high intakes suggest that the kidney is the primary site of molybdenum homeostatic regulation. However, widely different oral test doses of molybdenum, between 22 and 1,490 µg/day, resulted in only a small difference in absorption of 88 and 93 percent, respectively. The source of fecal molybdenum is not clear, but could include biliary molybdenum (Nielsen, 1999).

Clinical Effects of Inadequate Intake

Molybdenum deficiency has not been observed in healthy people. A severe metabolic defect, molybdenum cofactor deficiency, had been identified in 47 patients by 1993. The disease results in defi-
ciency in the three molybdenum enzymes known to occur in humans: sulfite oxidase, xanthine dehydrogenase, and aldehyde oxidase. Few infants with these defects survive the first days of life (Johnson et al., 1993), and those who survive have severe neurological abnormalities and a variety of other abnormalities. Only one case of molybdenum deficiency that might be considered a dietary deficiency has been reported in humans (Abumrad et al., 1981). A man with Crohn’s disease who was on total parenteral nutrition (TPN) for the last 18 months of his life developed symptoms of tachycardia, headache, night blindness, and other symptoms during the final 6 months of TPN. Biochemical changes included elevated plasma methionine concentration, low serum uric acid concentration, high urinary thiosulfate, and low urinary uric acid and sulfate. After administration of ammonium molybdate, the biochemical abnormalities were reversed.

**SELECTION OF INDICATORS FOR ESTIMATING THE REQUIREMENT FOR MOLYBDENUM**

*Plasma and Serum Molybdenum Concentration*

Plasma and serum molybdenum concentrations are very low in humans and are difficult to measure. As a consequence, there are few reports on plasma or serum molybdenum concentrations. The concentration in plasma increases with dietary intake, peaks about an hour after meals, and then returns to basal levels (Cantone et al., 1995; Versieck et al., 1978). Infused tracers of molybdenum disappear rapidly from the blood, with only 2.5 to 5 percent remaining after 1 hour (Cantone et al., 1995; Rosoff and Spencer, 1964). Therefore, plasma concentrations do not reflect molybdenum status and cannot be used as an indicator for estimating requirements.

*Urinary Molybdenum*

The primary route of molybdenum excretion is the urine (Rosoff and Spencer, 1964; Turnlund et al., 1995a, 1995b). Urinary molybdenum reflects dietary intake, increasing as dietary intake increases. When molybdenum intake is low, about 60 percent of ingested molybdenum is excreted in the urine, but when molybdenum intake is high, over 90 percent is excreted in the urine (Turnlund et al., 1995a, 1995b). In the United States, the average concentration of urinary molybdenum is 69 µg/L (Paschal et al., 1998). Although
related to dietary intake, urinary molybdenum alone does not reflect status.

**Biochemical Indicators**

Several biochemical changes have been observed in special situations. In molybdenum cofactor deficiency and in the one case of molybdenum deficiency reported, urinary sulfate was low and urinary sulfite was present. Serum uric acid concentrations were low, urinary xanthine and hypoxanthine increased, and plasma methionine was increased (Abumrad et al., 1981; Johnson et al., 1993). However, these observations have not been associated with molybdenum intakes in normal, healthy people and cannot be used as indicators for estimating the molybdenum requirement.

**Molybdenum Balance**

Balance studies are used to establish whether homeostasis is maintained and whether body stores are being depleted or increased. Ideally, sufficient time (at least 12 days or longer) is allowed for the body to adapt to each dietary intake before collecting balance data, diets are constant, and conditions are controlled to assure food consumption and sample collections are complete. Two balance studies have been conducted in adult men (Turnlund et al., 1995a, 1995b). These studies provided adaptation periods and were conducted in metabolic research facilities. Diets were controlled and molybdenum intake was constant at each amount. Balance in these studies could be achieved over a broad range of intakes. In one study, five levels of molybdenum ranging from 22 to 1,490 µg/day were provided for 24 days each (Turnlund et al., 1995a). In another study, a low molybdenum diet (22 µg/day) was provided for 102 days, followed by a higher molybdenum diet (467 µg/day) (Turnlund et al., 1995b). Miscellaneous losses, such as sweat and integument, were too low to measure and were not accounted for. The minimum requirement was estimated to be approximately 25 µg/day. Balance studies were conducted among preadolescent girls between 1956 and 1962 for 6 to 56 days (Engel et al., 1967). They demonstrated that balance was positive (3 to 33 µg/day) in all of 36 girls between the ages of 6 and 10 years when intake ranged from 43 to 80 µg/day.
FACTORS AFFECTING THE MOLYBDENUM REQUIREMENT

Interactions

Molybdenum:Tungsten Ratio

Tungsten and molybdenum are both Group 6B elements and thus have similar atomic size and valence states. Tungsten has been used as an antagonist of molybdenum absorption in animal studies to produce molybdenum deficiency as measured by molybdoenzyme activity (Rajagopalan, 1988). Major effects of such treatment have not been observed in humans. The interaction is not considered significant in human nutrition.

Molybdenum:Copper and Sulfate Ratios

Excess molybdenum intake has been documented to produce copper deficiency in ruminants and is a potential practical feeding problem in some areas of the world (Bremner, 1979). The mechanism could be an interaction that involves formation of a thiomolybdate complex with copper. The interaction is not considered to be of significance to humans.

There is one report of increased urinary copper excretion with molybdenum intake from sorghum with molybdenum intakes of 500 and 1,500 µg (Deosthale and Gopalan, 1974). The effect was not confirmed in a controlled study at those levels of dietary molybdenum (Turnlund and Keyes, 2000).

Bioavailability

Little is known about the bioavailability of molybdenum from different food sources, but one study among men and another among women demonstrated that it is less efficiently absorbed from soy, which contains relatively high amounts (Turnlund et al., 1999). Bioavailability of other minerals is also lower from soy than from many other dietary sources (Hurrell et al., 1992; O’Dell, 1989). In one study with 12 young women, the absorption of stable isotopically labeled molybdenum was 87.5 percent from extrinsic molybdenum, 86.1 percent from kale, and 56.7 percent from soy (Turnlund et al., 1999). A study in young men with higher (300 µg) molybdenum intakes demonstrated that molybdenum absorption was 92.8 percent from foods extrinsically labeled with molybdenum and 58.3 percent from soy (Turnlund et al., 1999). The absorption of molyb-
Molybdenum was 35 and 37 percent less from soy than from an extrinsic source of molybdenum and from the molybdenum in kale. Utilization of absorbed molybdenum was similar regardless of source. It is unlikely that molybdenum in other commonly consumed foods would be less available than the molybdenum in soy.

**FINDINGS BY LIFE STAGE AND GENDER GROUP**

**Infants Ages 0 through 12 Months**

*Method Used to Set the Adequate Intake*

No functional criteria of molybdenum status have been demonstrated that reflect response to dietary intake in infants. Thus, recommended intakes of molybdenum are based on an Adequate Intake (AI) that reflects the observed mean molybdenum intake of infants principally fed human milk.

**Ages 0 through 6 Months.** With use of the method described in Chapter 2, the AI for young infants is based on mean intake data from infants fed human milk as the principal food during their first 6 months, and it uses the molybdenum concentration of milk produced by well-nourished mothers. There are no reports of full-term infants exclusively and freely fed human milk from U.S. and Canadian mothers who manifested any signs of a molybdenum deficiency. Friel and coworkers (1999) found that the molybdenum concentration of human milk of mothers of premature infants ranged from 2.1 to 23 µg/L with a median concentration of 5 µg/L. Studies by Bougle and coworkers (1988) found that the molybdenum concentration of human milk decreases rapidly from 15 µg/L on day 1, to 4.8 µg/L at 7 to 10 days postpartum, and 2.6 µg/L by 1 month (Table 11-1). Rossipal and Krachler (1998) found human milk to contain 1.42 µg/L at 42 to 60 days postpartum and 1.78 µg/L at 97 to 293 days postpartum. Biego and coworkers (1998) reported an average molybdenum concentration of 4 µg/L in human milk with stage of lactation not reported and much higher concentrations of molybdenum in cow’s milk and infant formula. With an average molybdenum concentration of 2 µg/L, an average milk volume of 0.78 L/day (Chapter 2), and rounding, the AI is 2 µg/day.

**Ages 7 through 12 months.** One method of estimating the AI for infants receiving human milk from 7 through 12 months of age is based on the average breast milk content and 0.6 L/day, the aver-
**TABLE 11-1 Molybdenum Concentration in Human Milk**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Group</th>
<th>Stage of Lactation</th>
<th>Milk Concentration (µg/L)</th>
<th>Estimated Molybdenum Intake of Infants (µg/d)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casey and Neville, 1987</td>
<td>13 women</td>
<td>5 d</td>
<td>Not reported</td>
<td>5.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14 d</td>
<td></td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>21 d</td>
<td></td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>28 d</td>
<td></td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>35 d</td>
<td></td>
<td>2.1</td>
</tr>
<tr>
<td>Bougle et al., 1988</td>
<td>6 women</td>
<td>1 d</td>
<td>15</td>
<td>11.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3–5 d</td>
<td>10.2</td>
<td>7.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7–10 d</td>
<td>4.8</td>
<td>3.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14 d</td>
<td>1.5</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 mo</td>
<td>2.6</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 mo</td>
<td>0.2</td>
<td>0.15</td>
</tr>
<tr>
<td>Anderson, 1992</td>
<td>7 women</td>
<td>Up to 5 mo</td>
<td>17.0</td>
<td>13.2</td>
</tr>
<tr>
<td>Aquilio et al., 1996</td>
<td>14 women</td>
<td>21 d</td>
<td>4.1</td>
<td>3.2</td>
</tr>
<tr>
<td>Biego et al., 1998</td>
<td>17 milk samples</td>
<td>Mature milk</td>
<td>4</td>
<td>3.1</td>
</tr>
<tr>
<td>Krachler et al., 1998</td>
<td>46 women</td>
<td>Up to 293 d</td>
<td>3.6</td>
<td>2.8</td>
</tr>
<tr>
<td>Rossipal and Krachler, 1998</td>
<td>42–60 d</td>
<td></td>
<td>1.42</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>97–293 d</td>
<td></td>
<td>1.78</td>
<td>1.1</td>
</tr>
</tbody>
</table>

**NOTE:** Maternal intakes were not reported in these studies.

*<sup>a</sup>Molybdenum intake based on reported data or concentration (µg/L) × 0.78 L/day for 0–6 months postpartum and concentration (µg/L) × 0.6 L/day for 7–12 months postpartum.*

The age volume of milk consumed in this age group, plus an added increment for complementary food (see Chapter 2). However, data on molybdenum content of weaning foods are not available. By using the reference weight ratio method described in Chapter 2 to extrapolate from the AI for infants ages 0 through 6 months, the AI is 3 µg/day after rounding.
Molybdenum AI Summary, Ages 0 through 12 Months

AI for Infants

0–6 months  2 µg/day of molybdenum  0.3 µg/kg/day
7–12 months 3 µg/day of molybdenum  0.3 µg/kg/day

Special Considerations

Cow milk contains considerably more molybdenum (50 µg/L) than human milk, as does soymilk (Tsongas et al., 1980). Data on the bioavailability of molybdenum in cow milk and infant formulas are not available.

Children and Adolescents Ages 1 through 18 Years

Evidence Considered in Estimating the Average Requirement

No data are available on which to base an Estimated Average Requirement (EAR) for children or adolescents. EARs for these groups were extrapolated from adult EARs by the method described in Chapter 2. Although there are no studies available to indicate that the molybdenum requirement is associated with energy expenditure, metabolic weight (kg$^{0.75}$) was used for extrapolating because of the functional role of molybdenum in a select number of enzymes, and because using metabolic weight yields an EAR that is higher than when total body weight is used.

Molybdenum EAR and RDA Summary, Ages 1 through 18 years

EAR for Children

1–3 years  13 µg/day of molybdenum
4–8 years  17 µg/day of molybdenum

EAR for Boys

9–13 years  26 µg/day of molybdenum
14–18 years  33 µg/day of molybdenum

EAR for Girls

9–13 years  26 µg/day of molybdenum
14–18 years  33 µg/day of molybdenum

The Recommended Dietary Allowance (RDA) for molybdenum is set by using a coefficient of variation (CV) of 15 percent (see “Adults
Ages 19 Years and Older”). The RDA is defined as equal to the EAR plus twice the CV to cover the needs of 97 to 98 percent of individuals in the group (therefore, for molybdenum the RDA is 130 percent of the EAR). The calculated RDA is rounded to the nearest 1 µg.

**RDA for Children**
- 1–3 years: 17 µg/day of molybdenum
- 4–8 years: 22 µg/day of molybdenum

**RDA for Boys**
- 9–13 years: 34 µg/day of molybdenum
- 14–18 years: 43 µg/day of molybdenum

**RDA for Girls**
- 9–13 years: 34 µg/day of molybdenum
- 14–18 years: 43 µg/day of molybdenum

**Adults Ages 19 Years and Older**

*Evidence Considered in Estimating the Average Requirement*

The basis for an EAR for molybdenum was molybdenum balance in controlled studies with specific amounts of molybdenum consumed. Average balance achieved in four young men with an intake of 22 µg/day is shown in 6-day intervals in Figure 11-1 (Turnlund et al., 1995b). From day 1 to day 48, average balance was negative. Beginning at day 49, balance became slightly positive; through day 102, the average balance was positive in six of nine 6-day periods and negative in the other three 6-day periods. Over that entire period, average balance was near 0 (0.2 µg/day). Sixteen of the 36 individual 6-day balance periods were negative and 20 were positive. The average standard deviation of the nine 6-day balance periods was 2.6 µg/day with a range of 1.2 to 4.3 µg/day. The variability in balance for the 54-day balance period was 1.5 µg/day, or 7 percent of the dietary intake. The variability in the nine 6-day balance periods averaged 2.6 µg/day, or 12 percent.

The balance data suggest that 22 µg/day is near the minimum requirement. No clinical signs of deficiency were observed and biochemical changes associated with molybdenum deficiency were not found. Another group of four young men showed a similar balance pattern with negative balance during the first 6 days and becoming less negative over a 24-day period (Turnlund et al., 1995a). Twenty-
Molybdenum balance of four individuals who consumed 22 and 467 µg/day. Mean ± standard deviation.


Figure 11-1 Molybdenum balance of four individuals who consumed 22 and 467 µg/day. Mean ± standard deviation.

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The values are the same for women and older adults.

**Molybdenum EAR and RDA Summary, Ages 19 Years and Older**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>EAR for Men</th>
<th>RDA for Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>19–50 years</td>
<td>34 µg/day of molybdenum</td>
<td>45 µg/day of molybdenum</td>
</tr>
<tr>
<td>51–70 years</td>
<td>34 µg/day of molybdenum</td>
<td>45 µg/day of molybdenum</td>
</tr>
<tr>
<td>&gt; 70 years</td>
<td>34 µg/day of molybdenum</td>
<td>45 µg/day of molybdenum</td>
</tr>
</tbody>
</table>

The number of molybdenum levels in the adult depletion/repletion study was very limited, and the number of subjects was low. Thus, a CV of 15 percent is used; the RDA is defined as the EAR plus twice the CV to cover the needs of 97 to 98 percent of the individuals in the group (therefore, for molybdenum the RDA is set at 130 percent of the EAR). The calculated RDA was rounded up.

**Pregnancy**

**Evidence Considered in Estimating the Average Requirement**

No direct data are available for determining the additional daily requirement for molybdenum during pregnancy. The additional molybdenum requirement during pregnancy is determined by extrapolating up from adolescent and adult women as described in Chapter 2. Carmichael and coworkers (1997) reported that the median weight gain of 7,002 women who had good pregnancy outcomes was 16 kg. No consistent relationship between maternal age...
and weight gain was observed in six studies of U.S. women (IOM, 1990). Therefore, 16 kg is added to the reference weight for adolescent girls and adult women for extrapolation.

**Molybdenum EAR and RDA Summary, Pregnancy**

**EAR for Pregnancy**

14–18 years 40 µg/day of molybdenum  
19–30 years 40 µg/day of molybdenum  
31–50 years 40 µg/day of molybdenum

The RDA for molybdenum is set by using a CV of 15 percent (see “Adults Ages 19 Years and Older”). The RDA is defined as the EAR plus twice the CV to cover the needs of 97 to 98 percent of the individuals in the group (therefore, for molybdenum the RDA is set at 130 percent of the EAR). The calculated RDA is rounded to the nearest 10 µg.

**RDA for Pregnancy**

14–18 years 50 µg/day of molybdenum  
19–30 years 50 µg/day of molybdenum  
31–50 years 50 µg/day of molybdenum

**Lactation**

**Evidence Considered in Estimating the Average Requirement**

The EAR for lactation is estimated as the sum of the molybdenum intake necessary to replace the molybdenum secreted daily in human milk and the EAR for adolescent girls and women. Based on a daily excretion of 2 µg/day, the EAR for molybdenum is set at 35 and 36 µg/day for lactating adolescents and adults, respectively.

**Molybdenum EAR and RDA Summary, Lactation**

**EAR for Lactation**

14–18 years 35 µg/day of molybdenum  
19–30 years 36 µg/day of molybdenum  
31–50 years 36 µg/day of molybdenum

The RDA for molybdenum is set by using a CV of 15 percent (see “Adults Ages 19 Years and Older”). The RDA is defined as the EAR plus twice the CV to cover the needs of 97 to 98 percent of the...
individuals in the group (therefore, for molybdenum the RDA is set at 130 percent of the EAR). The calculated RDA is rounded to the nearest 10 µg.

RDA for Lactation

- 14–18 years: 50 µg/day of molybdenum
- 19–30 years: 50 µg/day of molybdenum
- 31–50 years: 50 µg/day of molybdenum

INTAKE OF MOLYBDENUM

Food Sources

The molybdenum content of plant foods varies depending upon the soil content in which they are grown. Legumes are major contributors of molybdenum in the diet, as well as grain products and nuts (Pennington and Jones, 1987; Tsongas et al., 1980). Animal products, fruits, and many vegetables are generally low in molybdenum.

Dietary Intake

Information on dietary intake of molybdenum is limited because of lack of a simple, reliable analytical method for determining molybdenum. One U.S. study reported intakes ranging from 120 to 240 µg/day, with an average intake of 180 µg/day (Tsongas et al., 1980). Data from the Total Diet Study indicate an average molybdenum intake of 76 µg/day for women and 109 µg/day for men (Pennington and Jones, 1987). Reports of molybdenum intake from other countries vary widely, probably because of differences in analytical methods and differences in the molybdenum content of soils in which foods are grown. Usual intake is well above the dietary molybdenum requirement.

Intake from Supplements

Based on data from Third National Health and Nutrition Examination Survey (Appendix Table C-21), the median intake of molybdenum from supplements was approximately 23 and 24 µg/day for men and women who took supplements, respectively.
MOLYBDENUM

TOLERABLE UPPER INTAKE LEVELS

The Tolerable Upper Intake Level (UL) is the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects for almost all individuals. Although members of the general population should be advised not to routinely exceed the UL, intake above the UL may be appropriate for investigation within well-controlled clinical trials. Clinical trials of doses above the UL should not be discouraged, as long as subjects participating in these trials have signed informed consent documents regarding possible toxicity, and as long as these trials employ appropriate safety monitoring of trial subjects. In addition, the UL is not meant to apply to individuals who are receiving molybdenum under medical supervision.

Hazard Identification

Adverse Effects

Molybdenum compounds appear to have low toxicity in humans. More soluble forms of molybdenum have greater toxicity than insoluble or less soluble forms. The UL applies to all forms of molybdenum.

There are limited toxicity data for molybdenum in humans; most of the toxicity data are for animals, especially ruminants. Ruminants are more sensitive to molybdenum than monogastric animals, but the basis for the toxicity of molybdenum in ruminants is not relevant for humans. In monogastric laboratory animals, molybdenum has been associated with reduced growth or weight loss, renal failure, skeletal abnormalities, infertility, anemia, diarrhea, and thyroid injury (Vyskocil and Viau, 1999). Since none of these effects have been observed in humans, it is impossible to determine which ones might be considered most relevant to humans.

Molybdenum toxicity in animals varies according to age, species, sex, and duration of exposure (Vyskocil and Viau, 1999). In ruminants, the relative amounts of copper and sulfur in the diet are also important determinants of toxicity (Rajagopalan, 1988), but the effect of molybdenum on copper metabolism in humans is not significant (Turnlund and Keyes, 2000). The data on adverse effects of molybdenum intake are summarized below.

Renal Failure. Mild renal failure has been observed in rats after subchronic ingestion (by gastric intubation) at 80 mg/kg/day but not at 40 mg/kg/day of a molybdenum salt (Bompart et al., 1990).
There is weak evidence of diuresis and proteinuria after high dose molybdenum intake in animals (Bompart et al., 1990). Asmangulyan (1965) evaluated the effects of molybdenum in rabbits receiving four different oral doses (0.025, 0.5, 5, and 50 mg/kg/day) for 6 months. At a dose of 5 mg/kg/day, histological changes were observed in kidney and liver along with body weight loss. No effects were observed at lower molybdenum dosage levels.

**Increased Uric Acid in Plasma and Urine.** Key human studies on this endpoint include Chappell and coworkers (1979), Deosthale and Gopalan (1974), and Kovalsky and coworkers (1961). Kovalsky and coworkers (1961) observed hyperuricemia and arthralgias in Armenians who consumed 10 to 15 mg/day of molybdenum from food. Serum molybdenum concentration was positively correlated with serum uric acid concentration. Elevations in blood molybdenum concentrations were accompanied by decreases in blood copper concentrations. However, serious methodological difficulties are noted with this particular study including possible analytical problems in the assessment of blood and urinary copper levels and the very small size of the control group in contrast to the molybdenum-exposed group.

Other studies in humans do not support the existence of this particular adverse manifestation in association with elevated dietary intakes of molybdenum. For example, Chappell and coworkers (1979) reported reduced uric acid concentrations in serum after molybdenum intakes of greater than 7 µg/kg/day from drinking water. Deosthale and Gopalan (1974) reported no change in uric acid excretion at intakes up to 1.5 mg/day in four volunteers.

**Impaired Copper Utilization.** Impaired utilization of copper has been observed in ruminants (Mills and Davis, 1987) and is based on an interaction between molybdenum, copper, and sulfur that occurs in ruminants but not in humans. A human study involving doses up to 1.5 mg/day showed no adverse effects on copper utilization (Turnlund and Keyes, 2000).

**Reproductive Effects.** The administration of supplemental dietary molybdenum was associated with a prolonged estrus cycle, decreased gestational weight gain of the pups, and several adverse effects on embryogenesis in female Sprague-Dawley rats (Fungwe et al., 1990). These effects were not observed at 0.9 mg/kg/day, but were observed at doses of 1.6 mg/kg/day (based on a gestational weight of 100 g). Schroeder and Mitchener (1971) evaluated the effect of
Molybdate in drinking water (10 mg/L) on the reproduction of mice over three generations. Because water consumption was not reported in the publication, daily molybdenum intake can only be estimated. Vyskocil and Viau (1999) estimated that a 20-mg mouse’s consumption of 3 mL of water (10 mg/L) daily would result in a dose of 1.5 mg/kg/day of molybdenum. At this dose, Schroeder and Mitchener (1971) reported some early deaths of offspring, dead litters, maternal deaths, and failure to breed.

Other Endpoints. There is no evidence that molybdenum causes cancer in humans or animals (Vyskocil and Viau, 1999). There are consistent findings of decreased hemoglobin concentration and hematocrit in rabbits (Arrington and Davis, 1953; McCarter et al., 1962; Ostrom et al., 1961; Valli et al., 1969). These effects were seen at doses of 25 mg/kg/day or more.

Growth depression has been noted in several studies with monogastric laboratory animals (Arthur, 1965; Jeter and Davis, 1954; Miller et al., 1956). In the study by Jeter and Davis (1954), rats were administered four different doses of molybdenum (20, 80, 140, and 700 mg/kg of diet) for 13 weeks. Growth depression was noted in female rats fed 80 mg/kg, which according to Vyskocil and Viau (1999), corresponds to 8 mg/kg/day of molybdenum. Miller and coworkers (1956) observed body weight loss and bone deformities in rats fed 75 and 300 mg/kg of diet molybdenum for 6 weeks. The lowest dose corresponds to 7.5 mg/kg/day according to Vyskocil and Viau (1999). Arthur (1965) fed guinea pigs diets containing various levels of molybdenum for 8 weeks. At the lowest dose (estimated to be 75 mg/kg/day), growth depression, loss of copper, and achromotrichia were observed.

Bioavailability and Toxicokinetics. Possible reasons for the presumed low toxicity of molybdenum include its rapid excretion in the urine, especially at higher intake levels (Miller et al., 1956; Turnlund et al., 1995b).

Summary

Because of the deficiencies in the study conducted in Armenia (Kovalsky et al., 1961), inadequate data exist to identify a causal association between excess molybdenum intake in normal, apparently healthy individuals and any adverse health outcomes. In addition, studies have identified levels of dietary molybdenum intake that appear to be associated with no harm (Deosthale and Gopalan,
Thus, reproductive effects in rats were selected as the most definitive toxicological indices.

Dose-Response Assessment

Adults

Data Selection. In the absence of adequate human studies, animal studies were evaluated. Rats, mice, and rabbits appear to be more sensitive than guinea pigs to the adverse effects of dietary molybdenum. The effects of molybdenum on reproduction and fetal development in rats and mice were found to be the most sensitive and therefore were used to set the UL.

Identification of a No-Observed-Adverse-Effect Level (NOAEL) and Lowest-Observed-Adverse-Effect Level (LOAEL). The study of Fungwe and co-workers (1990) provides a dose-response relationship for adverse reproductive effects in female rats. The NOAEL from this study was 0.9 mg/kg/day and the LOAEL was 1.6 mg/kg/day of molybdenum. This study is supported by observations of reproductive effects in mice in a three-generation study at a single dose of 1.5 mg/kg/day (Schroeder and Mitchener, 1971). Since only one level was used in this study, it is difficult to use this study independently to determine a LOAEL. In addition, Jeter and Davis (1954) noted decreased fertility in male rats after 13 weeks of exposure to 8 mg/kg/day of molybdenum. The NOAEL from that study was 2 mg/kg/day. Taken together, these observations suggest that numerous adverse reproductive effects were encountered in rats and mice at dietary molybdenum levels exceeding the NOAEL of 0.9 mg/kg/day established from the study of Fungwe and coworkers (1990).

Uncertainty Assessment. There do not appear to be sufficient data to justify lowering the degree of uncertainty from the usual uncertainty factor (UF) for extrapolating from experimental animals to humans. Thus, the usual value of 10 was selected. A UF of 3 for intraspecies variation was based on the expected similarity in pharmokinetics of molybdenum among humans. Although Vyskocil and Viau (1999) have argued for a larger UF for intraspecies differences, they have based their concerns on possible interactions with copper and concerns about copper-deficient humans. Recent information suggests that molybdenum does not have any effect on copper metabolism in humans (Turnlund and Keyes, 2000). Thus, these two UFs are multiplied to yield a UF of 30.
Derivation of a UL. The NOAEL of 0.9 mg/kg/day was divided by the overall UF of 30 to obtain a UL of 30 µg/kg/day for humans. The value of 30 µg/kg/day was multiplied by the average of the reference body weights for adult women, 61 kg, from Chapter 1 (Table 1-1). The resulting UL for adults is rounded to 2 mg/day (2,000 µg/day).

\[
UL = \frac{NOAEL}{UF} = \frac{0.9 \text{ mg/kg/day}}{30} \times 68.5 \text{ kg} \approx 2 \text{ mg/day (2,000 µg/day)}
\]

Although adult men and women have different reference body weights, the uncertainties in the estimation of the UL were considerable and distinction of separate ULs for men and women was therefore not attempted. This level is supported by limited human data from Deosthale and Gopalan (1974) who demonstrated no effect on uric acid or copper excretion in humans exposed to 22 µg/kg/day or 1.5 mg/day for an adult. Only four subjects were included in that study and no LOAEL was established. In addition, Turnlund and Keyes (2000) demonstrated no effect of 1.5 mg/day on copper metabolism in humans.

Molybdenum UL Summary, Ages 19 Years and Older

UL for Adults
\[\geq 19 \text{ years} \quad 2 \text{ mg/day (2,000 µg/day) of molybdenum}\]

Other Life Stage Groups

Infants. For infants, the UL was judged not determinable because of insufficient data on adverse effects in this age group and concern about the infant’s ability to handle excess amounts. To prevent high levels of intake, the only source of intake for infants should be from food and formula.

Children and Adolescents. There are no reports of molybdenum toxicity in children and adolescents. Given the dearth of information, the UL values for children and adolescents are extrapolated from those established for adults. Thus, the adult UL of 2 mg/day of molybdenum was adjusted for children and adolescents on the basis of relative body weight as described in Chapter 2 with use of refer-
ence weights from Chapter 1 (Table 1-1). Values have been rounded down.

*Pregnancy and Lactation.* Because the UL is based on adverse reproductive effects in animals and because there are no reports of molybdenum toxicity in lactating women, the UL for pregnant and lactating women is the same as that for the nonpregnant and nonlactating female.

**Molybdenum UL Summary, Ages 0 through 18 Years, Pregnancy, Lactation**

**UL for Infants**

<table>
<thead>
<tr>
<th>Age Range</th>
<th>UL for Infants</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–12 months</td>
<td>Not possible to establish; source of intake should be from food and formula only</td>
</tr>
</tbody>
</table>

**UL for Children**

<table>
<thead>
<tr>
<th>Age Range</th>
<th>UL for Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–3 years</td>
<td>0.3 mg/day (300 µg/day) of molybdenum</td>
</tr>
<tr>
<td>4–8 years</td>
<td>0.6 mg/day (600 µg/day) of molybdenum</td>
</tr>
<tr>
<td>9–13 years</td>
<td>1.1 mg/day (1,100 µg/day) of molybdenum</td>
</tr>
</tbody>
</table>

**UL for Adolescents**

<table>
<thead>
<tr>
<th>Age Range</th>
<th>UL for Adolescents</th>
</tr>
</thead>
<tbody>
<tr>
<td>14–18 years</td>
<td>1.7 mg/day (1,700 µg/day) of molybdenum</td>
</tr>
</tbody>
</table>

**UL for Pregnancy**

<table>
<thead>
<tr>
<th>Age Range</th>
<th>UL for Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>14–18 years</td>
<td>1.7 mg/day (1,700 µg/day) of molybdenum</td>
</tr>
<tr>
<td>19–50 years</td>
<td>2.0 mg/day (2,000 µg/day) of molybdenum</td>
</tr>
</tbody>
</table>

**UL for Lactation**

<table>
<thead>
<tr>
<th>Age Range</th>
<th>UL for Lactation</th>
</tr>
</thead>
<tbody>
<tr>
<td>14–18 years</td>
<td>1.7 mg/day (1,700 µg/day) of molybdenum</td>
</tr>
<tr>
<td>19–50 years</td>
<td>2.0 mg/day (2,000 µg/day) of molybdenum</td>
</tr>
</tbody>
</table>

Special Considerations

Individuals who are deficient in dietary copper intake or have some dysfunction in copper metabolism that makes them copper-deficient could be at increased risk of molybdenum toxicity. However, the effect of molybdenum intake on copper status in humans remains to be clearly established.
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Intake Assessment

National surveys do not provide percentile data on the dietary intake of molybdenum. Data available from the 1988–1994 Third National Health and Nutrition Examination Survey (Appendix Table C-21) indicate that the average U.S. intake of molybdenum from supplements at the ninety-fifth percentile was 80 and 84 µg/day for men and women, respectively.

Risk Characterization

Because there is no information from national surveys on percentile distribution of molybdenum intakes, the risk of adverse effects cannot be characterized.

RESEARCH RECOMMENDATIONS FOR MOLYBDENUM

• Bioavailability of molybdenum.
• Further data to estimate an average requirement for molybdenum.

REFERENCES


