# Molybdenum

olybdenum, a trace element essential for microorganisms, plants, and animals, was discovered in 1778 by a Swedish chemist named Karl Scheele. Initially mistaken for lead, molybdenum was named after the Greek work molybdos, meaning lead-like. In the 1930s, it was recognized that ingestion of forage with high amounts of molybdenum by cattle caused a debilitating condition. In the 1950s, the essentiality of molybdenum was established with the discovery of the first molybdenum-containing enzymes. In humans, only 4 enzymes requiring molybdenum have been identified to date: sulfite oxidase, xanthine oxidase, aldehyde oxidase, and mitochondrial amidoximereducing component (mARC). Sulfite oxidase, an enzyme found in mitochondria, catalyzes oxidation of sulfite to sulfate, the final step in oxidation of sulfur amino acids (cysteine and methionine). Xanthine oxidase converts hypoxanthine to xanthine, and further converts xanthine to uric acid, preventing hypoxanthine, formed from spontaneous deamination of adenine, from leading to DNA mutations if paired with cytosine in place of thymine. Aldehyde oxidase is abundant in the liver and is an important enzyme in phase 1 drug metabolism. Finally, mARC, discovered less than a decade ago, works in concert with cytochrome b<sub>s</sub> type B and NAD(H) cytochrome b<sub>5</sub> reductase to reduce a variety of N-hydroxylated substrates, although the physiologic significance is still unclear. In the case of each of the molybdenum enzymes, activity is catalyzed via a tricyclic cofactor composed of a pterin, a dithiolene, and a pyran ring, called molybdenum cofactor (MoCo) (1).

## **Deficiencies**

Nutritional deficiency induced by low dietary molybdenum has never been observed in humans to our knowledge. There is one isolated report of molybdenum deficiency related to inadequate provision of molybdenum in 1981. A 24-y-old male patient with Crohn disease was receiving long-term total parenteral nutrition, and after many months, developed nausea, rapid breathing and heart rate, vision problems, and ultimately coma. Biochemical measures showed that he had high plasma methionine, low serum uric acid, and high urinary thiosulfate, which led his care team to postulate molybdenum deficiency. The team added ammonium molybdate to the total parenteral nutrition solution at 300  $\mu$ g/d and his clinical symptoms resolved quickly (1).

Failed functionality of molybdenum can occur with rare genetic defects in enzymes that produce MoCo. MoCo is synthesized through a multistep process, and mutations in any of the MoCo synthesis enzymes result in inadequate activity of all molybdenum enzymes. These mutations can occur in any one of several enzymes involved in the MoCo synthesis scheme, with >60 different mutations identified. These defects are very rare, occurring in an estimated 1 in

100,000–200,000 live births. Symptoms include feeding difficulties, seizures, and severe developmental delays. The clinical result is severe neurodegeneration and ultimately death during childhood (2).

## **Dietary Recommendations**

Balance studies over a broad intake range (22  $\mu$ g/d to 1.5 mg/d) have been used as the basis for an Estimated Average Requirement for molybdenum (3). Even at intakes as low as 22  $\mu$ g/d, urinary molybdenum excretion showed balance over several months. On the basis of these data, the Food and Nutrition Board of the US National Academy of Sciences' Institute of Medicine established the average minimum molybdenum requirement to be 22  $\mu$ g/d plus an additional 3  $\mu$ g/d to allow for miscellaneous losses, such as perspiration, resulting in a minimum requirement of 25  $\mu$ g/d. With incorporation of a factor of 75% for bioavailability of molybdenum from different food sources, the Estimated Average Requirement for adults was set to 34  $\mu$ g/d and the RDA was set to 45  $\mu$ g/d (4). Daily intakes generally exceed these values. In the United States, mean intakes have been reported as 76  $\mu$ g/d for women and 109  $\mu$ g/d for men; and in Korea, mean intakes are 123  $\mu$ g/d for women and 136  $\mu$ g/d for men. In Japan, rice and soy consumption contributes to an intake of 225  $\mu$ g/d, whereas in France, the mean intake was estimated to be 275  $\mu$ g/d (1).

# **Food Sources**

Beans are among the richest sources of molybdenum. Lima beans are especially high in molybdenum, as well as small white beans, red beans, green beans, pinto beans, and peas. Grains, including wheat, oat, and rice, can also be good sources of molybdenum. Certain vegetables, such as asparagus, some dark-leafy vegetables, and certain Brassica vegetables, also have notable quantities of molybdenum. Soil content of molybdenum varies and can result in a wide range of molybdenum content for a given food, depending on where the crops were grown. Despite having lower molybdenum concentrations than other food sources, milk and cheese products provide most of the dietary molybdenum in youth, accounting for 27–40% of intake, by virtue of the amount consumed. For adults, grain products are the primary source of dietary molybdenum, accounting for 19–20% of intake (5, 6).

## **Clinical Uses**

Molybdenum has been used clinically to treat Wilson disease (7). In Wilson disease, copper that is not bound to ceruloplasmin circulates and accumulates in tissues, resulting in liver damage, neurological complications, and brain damage. Molybdenum as tetrathiomolybdate can form a strong complex with copper and protein. Tetrathiomolybdate given with food forms complexes with dietary copper and protein and

prevents copper absorption. Tetrathiomolybdate given without food is absorbed into the bloodstream and forms complexes with circulating copper and albumen, preventing the copper from accumulating in cells and causing toxicity.

#### Toxicity

Molybdenum can be very toxic to certain animals, especially cattle and sheep, because high intakes of molybdenum induce secondary copper deficiency in these animals. However, the potential for molybdenum toxicity in humans is low. In Armenia, where soil concentrations of molybdenum are unusually high, intakes of 10-15 mg/d have been associated with aching joints, gout-like symptoms, hyperuricosuria, and elevated blood molybdenum. Acute toxicity was reported in one case study in which molybdenum supplements were taken at 300–800  $\mu$ g/d over an 18-d period, resulting in hallucinations and seizures (1).

Toxicity studies have been conducted in rodents. Very high intakes in these studies produced growth retardation, kidney and liver histological changes, renal failure, reproductive failure, bone deformities, and anemia. On the basis of these toxicity studies, the Food and Nutrition Board of the National Academy of Sciences' Institute of Medicine set the Tolerable Upper Intake Level to 2 mg/d (4).

## **Recent Research**

The molybdenum enzyme mARC was only very recently described, and its functionality is still not well understood. Research continues to probe the mechanisms and physiologic function of the mARC enzyme, with new activities of the enzyme being recently identified (8). In addition, the copperchelating ability of tetrathiomolybdate, the form of molybdenum used to treat Wilson disease, has led to interest in its use for antitumor therapy. Copper promotes angiogenesis, and angiogenesis is an important step in the progression of cancer, because tumors need to become vascularized as they grow. Preclinical studies to date have been generally promising. Cell studies have shown that tetrathiomolybdate can reduce angiogenesis and cancer cell proliferation. Furthermore, thiomolybdate administered to dogs with various advanced tumors showed stabilization or tumor reduction in 9 of 13 of the dogs. Promising preclinical studies have led to several phase 1 and phase 2 clinical trials, most recently with high-risk breast cancer patients (9). The administration of tetrathiomolybdate for 2 y was well tolerated and resulted in lowering of a biochemical marker of angiogenesis. Tetrathiomolybdate has also been found to inhibit profibrotic and proinflammatory cytokines, leading to the investigation of tetrathiomolybdate for the treatment of diseases such as arthritis and multiple sclerosis.

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#### References

- 1. Novotny JA. Molybdenum nutriture in humans. J Evid Compl Alt Med 2011;163:164-8.
- 2. Atwal PS, Scaglia F. Molybdenum cofactor deficiency. Mol Genet Metab 2016;117(1):1-4.
- 3. Novotny JA, Turnlund JR. Molybdenum intake influences molybdenum kinetics in men. J Nutr 2007;137:37-42.
- 4. Food and Nutrition Board, Institute of Medicine. Molybdenum. In: Dietary Reference Intakes for vitamin A, vitamin K, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. Washington (DC): National Academies Press; 2001. p. 420-41.
- 5. Hunt CD, Meacham SL. Aluminum, boron, calcium, copper, iron, magnesium, manganese, molybdenum, phosphorus, potassium, sodium, and zinc: concentrations in common Western foods and estimated daily intakes by infants; toddlers; and male and female adolescents, adults, and seniors in the United States. J Am Diet Assoc 2001;101:1058-60.
- 6. Tsongas TA, Meglen RR, Walravens PA, Chappell WR. Molybdenum in the diet: an estimate of average daily intake in the United States. Am J Clin Nutr 1980;33:1103-7.
- 7. Brewer GJ, Askari F, Dick RB, Sitterly J, Fink JK, Carlson M, Kluin KJ, Lorincz MT. Treatment of Wilson's disease with tetrathiomolybdate: V. Control of free copper by tetrathiomolybdate and a comparison with trientine. Transl Res 2009;154:70-7.
- 8. Llamas A, Chamizo-Ampudia A, Tejada-Jimenez M, Galvan A, Fernandez E. The molybdenum cofactor enzyme mARC: moonlighting or promiscuous enzyme? Biofactors 2017;43:486-94.
- 9. Chan N, Willis A, Kornhauser N, Ward MM, Lee SB, Nackos E, Seo BR, Chuang E, Cigler T, Moore A,, et al. Influencing the tumor microenvironment: a phase II study of copper depletion using tetrathiomolybdate in patients with breast cancer at high risk for recurrence and in preclinical models of lung metastases. Clin Cancer Res 2017;23(3):666-76.

### For further information:

Novotny JA. Molybdenum nutriture in humans. J Evid Compl Alt Med 2011;163:164-8.

Food and Nutrition Board, Institute of Medicine. Molybdenum. In: Dietary Reference Intakes for vitamin A, vitamin K, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. Washington (DC): National Academies Press; 2001, p. 420-41.