

# Molybdenum

## Summary

- The molybdenum atom is part of the molybdenum [cofactor](#) in the active site of four [enzymes](#) in humans: sulfite oxidase, xanthine oxidase, aldehyde oxidase, and mitochondrial amidoxime reducing component. ([More information](#))
- Excess molybdenum intake causes fatal copper deficiency diseases in grazing animals. Their [rumen](#) is the site of high sulfide generation, and the interaction of molybdenum with sulfur results in the formation of thiomolybdates. Tetrathiomolybdate, a thiomolybdate with four sulfur atoms, can form complexes with copper preventing its absorption and blocking the activity of copper-dependent enzymes. ([More information](#))
- In humans, tetrathiomolybdate therapy has been developed for Wilson's disease, a genetic disease in which the accumulation of copper in tissues leads to liver and brain damage. More recently, tetrathiomolybdate use has been explored for the treatment of [cancer](#) and [inflammatory](#) diseases. ([More information](#))
- [Mutations](#) in the molybdenum cofactor [biosynthetic](#) pathway lead to the combined deficiency of all molybdenum-dependent enzymes. Molybdenum cofactor deficiency Type A is due to mutations in the *MOCS1* [gene](#), while Type B deficiency is caused by mutations in *MOCS2*. Both Type A and Type B deficiencies result in the loss of sulfite oxidase activity, also observed in isolated sulfite oxidase deficiency and characterized by severe [neurologic](#) abnormalities in affected patients. ([More information](#))
- New treatment options for molybdenum cofactor deficiency are being considered. Cyclic pyranopterin monophosphate supplementation to patients with Type A deficiency could correct the metabolic disorder and prevent neurologic deterioration. Patients with Type B deficiency do not lack this molecule and therefore cannot benefit from this treatment. However, a recent study showed that pyridoxine supplementation in these patients could alleviate suffering by abolishing [seizures](#). ([More information](#))
- The molybdenum content of foods depends on the molybdenum content of soils, which can vary considerably. Variation in [esophageal](#) cancer incidence worldwide has been linked to the molybdenum content in soils and food. Similar observations have been made in order to identify the factors associated with a population's extended lifespan. ([More information](#))

Molybdenum is an essential trace element for virtually all life forms. It functions as a [cofactor](#) for a number of [enzymes](#) that [catalyze](#) important chemical transformations in the global carbon, nitrogen, and sulfur cycles (1). Thus, molybdenum-dependent enzymes are not only required for human health, but also for the health of our ecosystem.

## Function

The biological form of the molybdenum atom is an organic molecule known as the molybdenum cofactor (Moco) present in the active site of Moco-containing enzymes (molybdoenzymes) (2). In humans, molybdenum is known to function as a [cofactor](#) for four enzymes:

- **Sulfite oxidase** [catalyzes](#) the transformation of sulfite to sulfate, a reaction that is necessary for the [metabolism](#) of sulfur-containing [amino acids](#) ([methionine](#) and cysteine).
- **Xanthine oxidase** catalyzes the breakdown of [nucleotides](#) (precursors to [DNA](#) and [RNA](#)) to form [uric acid](#), which contributes to the [plasma antioxidant](#) capacity of the blood.
- **Aldehyde oxidase** and xanthine oxidase catalyze [hydroxylation](#) reactions that involve a number of different molecules with similar chemical structures. Xanthine oxidase and aldehyde oxidase also play a role in the metabolism of drugs and toxins (3).
- **Mitochondrial amidoxime reducing component (mARC)** was described only recently (4), and its precise function is under investigation. Initial studies showed that mARC forms a three-component enzyme system with cytochrome b5 and NADH cytochrome b5 reductase that catalyzes the detoxification of mutagenic N-hydroxylated bases (5).

Of these enzymes, sulfite oxidase is known to be crucial for human health. Hereditary xanthinuria, characterized by a deficiency in xanthine oxidase (Type 1) or by a deficiency in both xanthine oxidase and aldehyde oxidase (Type 2), can be asymptomatic (6). However, in less than half of the cases, affected individuals exhibit a range of health issues of variable severity (7, 8).

## Nutrient interactions

### Copper

An early study reported that molybdenum intakes of 500 mcg/day and 1,500 mcg/day from sorghum increased urinary copper [excretion](#) (2). However, the results of a more recent, well-controlled study indicated that very high dietary molybdenum intakes (up to 1,500 mcg/day) did not adversely affect copper nutritional status in eight, healthy young men (9).

### *Tetrathiomolybdate*

Excess dietary molybdenum has been found to result in copper deficiency in grazing animals ([ruminants](#)). In the digestive tract of ruminants, the formation of compounds containing sulfur and molybdenum, known as thiomolybdates, prevents the absorption of copper and can cause fatal copper-dependent disorders (10). Tetrathiomolybdate (TM) is a molecule that can form high-affinity complexes with copper, controlling free copper (copper that is not bound to [ceruloplasmin](#)), and inhibiting copper [chaperones](#) and copper-containing [enzymes](#) (11, 12). TM's ability to lower free

copper levels is exploited in the treatment of Wilson's disease, a genetic disorder characterized by copper accumulation in tissues responsible for [hepatic](#) and [neurologic](#) disorders. Neurologic worsening has been linked with toxic levels of free copper in the [serum](#) of neurologically presenting patients. TM therapy seems able to stabilize neurologic status and prevent neurologic deterioration in these patients, as opposed to the standard initial treatment of choice ([13](#)).

Copper is also a required [cofactor](#) for enzymes involved in [inflammation](#) and [angiogenesis](#), known to accelerate [cancer](#) progression and [metastasis](#). Copper depletion studies employing TM have been initiated in patients with advanced [malignancies](#) with the aim of preventing disease progression or relapse. These pilot trials showed promising results in individuals with metastatic kidney cancer ([14](#)), metastatic colorectal cancer ([15](#)), and breast cancer with high risk of relapse ([16](#)). TM was relatively well-tolerated and stabilized disease or prevented relapse in correlation with copper depletion. TM's efficacy is also investigated in animal models of inflammatory and immune-related diseases ([17, 18](#)) and, at this point, clinical studies are needed to evaluate whether copper depletion could stabilize diseases and improve survival in humans, as suggested by a trial of TM therapy with patients with [biliary cirrhosis](#) ([19](#)).

## Deficiency

Dietary molybdenum deficiency has never been observed in healthy people ([2](#)).

### Acquired molybdenum deficiency

The only documented case of acquired molybdenum deficiency occurred in a patient with [Crohn's disease](#) on long-term [total parenteral nutrition](#) (TPN) without molybdenum added to the TPN solution ([20](#)). The patient developed rapid heart and respiratory rates, headaches, and night blindness, and ultimately became comatose. The patient was diagnosed with defects in [uric acid](#) production and sulfur [amino acid metabolism](#). The patient's clinical condition improved and the amino acid intolerance disappeared when the TPN solution was discontinued and instead supplemented with molybdenum in the form of ammonium molybdate (160 mcg/day) ([20](#)).

### Inherited molybdenum cofactor deficiency

Because molybdenum functions only in the form of the Moco in humans, any disturbance of Moco metabolism can disrupt the function of all molybdoenzymes. Current understanding of the essentiality of molybdenum in humans is based largely on the study of individuals with very rare inborn metabolic disorders caused by a deficiency in Moco. Moco is synthesized [de novo](#) by a multistep metabolic pathway involving four genes: *MOCS1*, *MOCS2*, *MOCS3*, and *GPHN* (see [figure](#)). To date, more than 60 [mutations](#) affecting mostly *MOCS1* and *MOCS2* have been identified ([21](#)).

The absence of a functional Moco has a direct impact on the activity of the molybdoenzymes. Metabolic disorders specifically associated with deficiency in sulfite oxidase activity include an accumulation of sulfite, taurine, S-sulfocysteine, and thiosulfate (see [figure](#)). This metabolic profile is identical to that observed in isolated sulfite oxidase deficiency (ISOD), an inherited condition caused by mutations in *SUOX* gene that codes for sulfite oxidase ([22](#)). Compared with ISOD, Moco deficiency (MocoD) also affects the xanthine pathway and leads to an accumulation of hypoxanthine and xanthine, and low to undetectable uric acid levels in blood (see [figure](#)). MocoD and ISOD have been diagnosed in more than 100 individuals worldwide. However the global incidence of MocoD is likely to be underestimated as a result of a failure to diagnose or to report ([21, 23, 24](#)). Both disorders result from [recessive traits](#), meaning that only individuals who inherit two copies of the abnormal gene (one from each parent) develop the disease. Individuals who inherit only one copy of the abnormal gene are known as carriers of the trait but do not exhibit any symptoms. ISOD and MocoD can be diagnosed relatively early in pregnancy (10-14 weeks' gestation) by [enzyme](#) activity assays using amniotic cell and chorionic villus sampling and by genetic testing ([23, 25](#)).

MocoD and ISOD typically occur in the first days of life, although a few cases of MocoD with late presentation have been described ([26-28](#)). The loss of sulfite oxidase activity in ISOD and MocoD leads to severe [neurological](#) dysfunction characterized by cerebral [atrophy](#), mental retardation, intractable [seizures](#), and dislocation of [ocular](#) lenses. At present, it is not clear whether the neurologic effects are a result of the accumulation of a toxic metabolite, such as sulfite, or inadequate sulfate production. Patients with ISOD and MocoD were also found with elevated excretion of  $\alpha$ -amino adipic semialdehyde ( $\alpha$ -AASA) ([29](#)).  $\alpha$ -AASA accumulation is the metabolic signature of a deficiency in  $\alpha$ -AASA dehydrogenase observed in patients with [pyridoxine](#)-dependent [epilepsy](#). The enzymatic deficiency in these individuals causes an increase in  $\alpha$ -AASA and its cyclic form piperidine-6-carboxylate (P6C). P6C can trap pyridoxal-5-phosphate (PLP), the active form of vitamin B<sub>6</sub> (pyridoxine), leading to a deficiency in PLP, which is corrected with supplemental pyridoxine. A decrease in PLP has also been observed in the [cerebrospinal fluid](#) from ISOD and MocoD patients ([30](#)). It is not clear whether sulfite is responsible for the accumulation of  $\alpha$ -AASA and the deficiency in PLP in ISOD and MocoD patients. Nevertheless, pyridoxine and folic acid supplementation in patients with MocoD successfully normalized the PLP level and abolished seizures in two patients with mutations in *MOCS2* (MocoD Type B) ([31](#)). Although anti-seizure medications and dietary restriction of sulfur-containing amino acids may be beneficial in some cases ([32](#)), there are no treatment options for patients with mutations in the *MOCS2*, *GPHN* (MocoD Type C), or *SUOX* genes. Pyridoxine supplementation is a new option being considered to alleviate specific clinical features in patients.

A successful treatment using cyclic pyranopterin monophosphate (cPMP) has been described for patients with mutations in the *MOCS1* gene, and a clinical trial using a [retrospective](#) approach is under way to assess its safety. The *MOCS1* gene controls the initial step in the Moco biosynthetic pathway, catalyzing the conversion of guanosine triphosphate into cPMP. Therefore, patients with mutations in the *MOCS1* gene lack cPMP. Daily administration of cPMP to patients resolved all metabolic abnormalities associated with defective sulfite oxidase and xanthine pathways and prevented further

signs of neurologic deterioration (33, 34). Early diagnosis and initiation of treatment are essential to ensure success (34). Since cPMP replacement therapy can only benefit MocoD Type A, additional treatment methods are required.

### The Recommended Dietary Allowance (RDA)

The recommended dietary allowance (RDA) for molybdenum was most recently revised in January 2001 (2). It was based on the results of nutritional balance studies conducted in eight, healthy young men under controlled laboratory conditions (35, 36). The RDA values for molybdenum are listed in the table below in micrograms (mcg)/day by age and gender. Adequate intake (AI) levels were set for infants based on mean molybdenum intake from human milk, exclusively.

<b>Recommended Dietary Allowance (RDA) for Molybdenum</b>			
<b>Life Stage</b>	<b>Age</b>	<b>Males (mcg/day)</b>	<b>Females (mcg/day)</b>
Infants	0-6 months	2 (AI)	2 (AI)
Infants	7-12 months	3 (AI)	3 (AI)
Children	1-3 years	17	17
Children	4-8 years	22	22
Children	9-13 years	34	34
Adolescents	14-18 years	43	43
Adults	19 years and older	45	45
Pregnancy	all ages	-	50
Breastfeeding	all ages	-	50

### Disease Prevention

#### Esophageal cancer

Linxian is a small region in northern China where the incidence of cancer of the esophagus and stomach is very high (10 times higher than the average in China and 100 times higher than the average in the U.S.). The soil in this region is low in molybdenum and other mineral elements; therefore, dietary molybdenum intake is also low. Studies conducted in other areas of low and high incidence of esophageal cancer showed that content of molybdenum and zinc in hair and nails is

significantly lower in inhabitants of high-risk regions compared to cold spots. Moreover, esophageal cancer patients display reduced content of the trace elements compared to healthy relatives ([37, 38](#)).

Increased intake of [nitrosamines](#), which are known [carcinogens](#), may be one of a number of dietary and environmental factors that contributes to the development of esophageal cancer in residents of high-risk regions. Adding ammonium molybdate to the soil may help decrease the risk of esophageal cancer by limiting nitrosamine exposure. It is not clear whether dietary molybdenum supplementation is beneficial in decreasing the risk of esophageal cancer. [Intervention trials](#) conducted in Linxian area using dietary supplementation of minerals and [vitamins](#), including molybdenum (30 mcg/day), failed to decrease incidence and mortality rates of esophageal cancer or other cancers over a five-year period (reviewed in [39](#)).

## **Longevity**

Rugao is a county in Jiangsu province (China) renowned for the longevity of its residents. Extended longevity can hardly be attributed to significant differences in traditions, lifestyles, or dietary habits among the residents, and most longevous people are not related to one another, limiting the possible influence of genetics. However, the county has a large number of different soils whose compositions could affect the distribution of trace elements in water and crops and ultimately be linked with human health and longevity. Significant correlations were found between the ratio of people over 90 years old per 100,000 inhabitants and trace elements, including molybdenum, in soils, drinking water, and rice, which constitute key elements of their natural environment ([40](#)). The percentage of long-lived people (>80 years old) in Zhongxiang (Hubei province) was also positively linked to the content of molybdenum in their staple food, rice ([41](#)). In these regions, it is likely that combinations of trace elements contribute to optimum health and longevity as opposed to the sole effect of molybdenum.

## **Sources**

### **Food sources**

The Total Diet Study, an annual survey of the mineral content in the typical American diet, indicates that the dietary intake of molybdenum averages 76 mcg/day for women and 109 mcg/day for men. Thus, usual molybdenum intakes are well above the [RDA](#) for molybdenum. Legumes, such as beans, lentils, and peas, are the richest sources of molybdenum. Grain products and nuts are considered good sources, while animal products, fruits, and many vegetables are generally low in molybdenum ([2](#)). Because the molybdenum content of plants depends on the soil molybdenum content and other environmental conditions, the molybdenum content of foods can vary considerably ([38, 42](#)).

### **Supplements**

Molybdenum in nutritional supplements is generally in the form of sodium molybdate or ammonium molybdate (43).

## Safety

### Toxicity

The toxicity of molybdenum compounds appears to be relatively low in humans. Increased [serum](#) levels of [uric acid](#) and [ceruloplasmin](#) (an iron-oxidizing enzyme) have been reported in occupationally exposed workers in a molybdenite roasting plant (44). [Gout](#)-like symptoms have also been reported in an Armenian population consuming 10 to 15 milligrams (mg) of molybdenum from food daily (45). In other studies, blood and urinary uric acid levels were not elevated by molybdenum intakes up to 1.5 mg/day (2). There has been only one report of acute toxicity related to molybdenum from a dietary supplement: an adult male reportedly consumed a total of 13.5 mg of molybdenum over a period of 18 days (300-800 mcg/day) and developed acute psychosis with hallucinations, [seizures](#), and other [neurologic](#) symptoms (46). However, a controlled study in four, healthy young men found that molybdenum intakes, ranging from 22 mcg/day to 1,490 mcg/day (almost 1.5 mg/day), elicited no serious adverse effects when molybdenum was given for 24 days (35).

The Food and Nutrition Board (FNB) of the Institute of Medicine found little evidence that molybdenum excess was associated with adverse health outcomes in generally healthy people. To determine the tolerable upper intake level (UL), the FNB selected adverse reproductive effects in rats as the most sensitive index of toxicity and applied a large uncertainty factor because animal data were used (2). The UL for molybdenum is listed by age group in the table below.

<b>Tolerable Upper Intake Level (UL) for Molybdenum</b>	
<b>Age Group</b>	<b>UL (mcg/day)</b>
Infants 0-12 months	Not possible to establish*
Children 1-3 years	300
Children 4-8 years	600
Children 9-13 years	1,100 (1.1 mg/day)
Adolescents 14-18 years	1,700 (1.7 mg/day)
Adults 19 years and older	2,000 (2.0 mg/day)

\*Source of intake should be from food and formula only.

### Drug interactions

High doses of molybdenum have been found to inhibit the [metabolism](#) of acetaminophen in rats [\(47\)](#); however, it is not known whether this occurs at clinically relevant doses in humans.

### **Linus Pauling Institute Recommendation**

The [RDA](#) for molybdenum (45 mcg/day for adults) is sufficient to prevent deficiency. Although the intake of molybdenum most likely to promote optimum health is not known, there is presently no evidence that intakes higher than the RDA are beneficial. Most people in the U.S. consume more than sufficient molybdenum in their diets, making supplementation unnecessary. Following the Linus Pauling Institute's general recommendation to take a multivitamin/mineral supplement that contains 100% of the daily values (DV) for most nutrients is likely to provide 75 mcg/day of molybdenum because the DV for molybdenum has not been revised to reflect the most recent RDA. Although the amount of molybdenum presently found in most multivitamin/mineral supplements is higher than the RDA, it is well below the tolerable upper intake level (UL) of 2,000 mcg/day and should be safe for adults.

### **Older adults (> 50 years)**

Because aging has not been associated with significant changes in the requirement for molybdenum [\(2\)](#), our recommendation for older adults is the same as that for adults 50 and younger.

### **References**

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