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Molybdenum: Role in biological system

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Abstract
Molybdenum functions as a cofactor for a limited number of enzymes in humans. The primary criterion used to set an Estimated Average Requirement (EAR), which 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.

Keywords: Molybdenum, biological system, estimated average requirement, recommended dietary allowance

Introduction
Molybdenum has been shown to act as a cofactor for a limited number of enzymes in humans: sulfite oxidase, xanthine oxidase, and aldehyde oxidase. In all mammalian molybdoenzymes, functional molybdenum is present as an organic component called molybdopterin (Rajagopalan, 1988) [11]. 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) [5]. 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) [1]. 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 (non-mediated) 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) [8]. Molybdenum concentrations in whole blood vary widely but average about 5 nmol/L (Versieck *et al.,* 1978) [17]. 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) [14, 15]. 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) [8].

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 deficiency in the three molybdoenzymes 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) [6], 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) [1]. 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 would be reversed.

Factors Affecting the Molybdenum Requirement

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) [11]. 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) [2]. 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.

Bioavailability

Less 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) [16]. Bioavailability of other minerals is also lower from soy than from many other dietary sources (Hurrell *et al.,* 1992 [14]; O'Dell, 1989) [9]. 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) [16]. 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) [16]. The absorption of 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.

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 [10]; Tsongas *et al.,* 1980) [12]. 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) [12]. 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) [10]. 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, the median intake of molybdenum from supplements was approximately 23 and 24 µg/day for men and women who took supplements, respectively.

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. In addition, the UL is not meant to apply to individuals who are receiving molybdenum under medical supervision.

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) [18]. 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) [18]. In ruminants, the relative amounts of copper and sulfur in the diet are also important determinants of toxicity (Rajagopalan, 1988) [11], but the effect of molybdenum on copper metabolism in humans is not significant (Turnlund and Keyes, 2000) [13]. The data on adverse effects of molybdenum intake shows renal failure, Increased Uric Acid in Plasma and Urine, Impaired Copper Utilization and Reproductive Effects

Conclusion

Because of the deficiencies in the study conducted in Armenia (Kovalsky *et al.,* 1961) [7], 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, 1974 [3]; Turnlund and Keyes, 2000) [13]. Thus, reproductive effects in rats were selected as the most definitive toxicological indices.

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