

Molybdenum

Function

Molybdenum is the activator for three enzymes—aldehyde dehydrogenase, sulfite oxidase, and xanthine oxidase—and is a nutritionally essential element. Attempts to produce deficiency in experimental animals have succeeded only when the diet contained large amounts of tungsten, an antagonist of molybdenum metabolism (Nielsen 1996, 1999). Molybdenum deficiency in experimental animals inhibits growth and development, especially in prenatal and neonatal stages of development. Human deficiencies of molybdenum function have been linked not to simple dietary deficiency, but rather to inborn errors of metabolism (Nielsen 1996, 1999).

Safety Evidence

Ruminant animals are susceptible to adverse effects of molybdenum under conditions of copper deficiency and marginal sulfur amino acid intake (Underwood 1977). Men who consumed 10 to 15 mg of molybdenum per day for prolonged periods developed abnormally high serum uric acid levels and increased cellular xanthine oxidase activity. Intakes as low as 0.54 mg (540 µg) per day have been associated with a loss of copper in the urine (Food and Nutrition Board 2001). It is not clear whether this effect has clinical consequences, but an increase in plasma uric acid levels observed with molybdenum intakes of 10 to 15 mg per day may result directly from excess activation of xanthine oxidase. Adverse effects with a causally uncertain relationship to molybdenum were observed in an epidemiological study of men consuming 10 to 15 mg of molybdenum per day (Kovalsky et al. 1961). The EPA has used this study as the basis for its regulatory assessment of molybdenum safety (Environmental Protection Agency 2004).

Published Official Reviews of Molybdenum Safety

The FNB examined the data of Kovalsky and coworkers and found methodological deficiencies extensive enough to preclude use of these data to establish a UL value. Instead of using human data of limited quality, FNB used animal data as the basis for the UL (Food and Nutrition Board 2001). The adverse effects of high molybdenum intake on reproduction and fetal development of rats and mice were found to be the most sensitive, and therefore served as the basis for the FNB UL. Specifically, FNB identified a NOAEL of 0.9 mg per kg per day and a LOAEL of 1.6 mg per kg per day for reproductive toxicity in female rats (Fungwe et al. 1990). Using this NOAEL, FNB selected a composite UF of 30 (10 for interspecies differences and 3 for intraspecies

variability) and corrected to a human adult body weight of 68.5 kg to derive a UL of 2,000 µg per day for molybdenum intake from all sources. The FNB estimated the intake of molybdenum from food to be 109 µg for men in the U.S.

The EC SCF concluded that there were no well-designed human studies that could serve as the basis for a risk assessment of molybdenum (Scientific Committee on Food 2000). Like FNB, EC SCF identified a NOAEL of 0.9 mg per kg per day from rodent reproductive effects (Fungwe et al. 1990) and selected a composite UF of 100 (10 for interspecies differences and 10 for intraspecies variability) to derive a UL of 100 µg per kg per day. To this value, EC SCF applied a 60 kg body weight to calculate a daily UL of 600 µg for adults.

The UK EVM concluded that some human data suggested an increase in gout-like symptoms in populations consuming 1 to 15 mg of molybdenum per day, but that the majority of human data or the relevance of animal data were too uncertain to serve as the basis for an SUL (Expert Group on Vitamins and Minerals 2003). In the face of such large uncertainties, but with some data suggesting adverse effects at lower levels, UK EVM identified a GL for total intake, equal to intake from foods in the UK (230 µg per day). The UK EVM declined to offer guidance about supplemental intake.

The EPA utilized the epidemiological (human) data of Kovalsky and coworkers (Kovalsky et al. 1961) that suggested a LOAEL of 140 µg per kg per day. From this LOAEL value, the RfD was calculated by applying a composite UF of 30 (10 for LOAEL-to-NOAEL extrapolation, and 3 for variability within the human population). The resulting RfD is 5 µg per kg per day, or 350 µg per day for a 70 kg person.

CRN ULS for Molybdenum

Abnormal plasma uric acid levels are associated with human intakes of 140 µg per kg per day of molybdenum, but there has been no corroboration of this finding in other human studies. Although the data are not sufficient for a confident identification of a LOAEL value, CRN prefers to rely upon human rather than animal data when possible. Considering both the large amount of uncertainty and the relatively small intake from foods (109 µg in the U.S.), CRN deems the RfD calculation by EPA to be sufficiently conservative to identify 350 µg as the CRN ULS. This conclusion is more conservative than it would have been had it been based on the animal data used by FNB and EC SCF for their UL values.

Higher amounts of molybdenum are safe for short periods. For example, 1,490 µg of supplement had no adverse effects in adults over a twenty-four-day treatment period (Turnlund et al. 1995).

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Comparison of Safety Values for Molybdenum

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|------------------------------|---|
| CRN ULS | 350 µg |
| US FNB UL | 2,000 µg |
| EC SCF UL | 600 µg |
| EC supplement maximum | Not established (as of May 2004) |
| UK EVM GL | 230 µg for food; no guidance for supplements |

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