Molybdenum

Introduction

Molybdenum is present in food and water in the form of soluble molybdates. It is a component of and/or cofactor for various enzymes in plants and animal organisms (European Commission, Scientific Committee on Food [EC SCF] 2000). In humans, molybdenum acts as a cofactor for several enzymes, including aldehyde oxidase, sulfite oxidase, and xanthine oxidase (EC SCF 2000; Institute of Medicine [IOM] 2001). These and perhaps other functions make it 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 1994, 1996). 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, specifically a genetic defect in the molybdenum cofactor that prevents the synthesis of sulfite oxidase, resulting in the accumulation of sulfite, severe neurological damage, and early death (Nielsen 1994, 1999; Johnson, 1997).

Safety Considerations

Most of the toxicity data pertaining to molybdenum in animals is in ruminants, which are susceptible to the adverse effects of molybdenum under conditions of copper deficiency and marginal sulfur amino acid intake (Underwood 1977). However, the basis for toxicity in ruminants is not considered to be of relevance to humans (IOM 2001). In monogastric laboratory animals, variable responses to excess molybdenum have been reported, including growth depression, renal effects, and skeletal abnormalities (EC SCF 2000; IOM 2001). Supplemental molybdenum intakes of 1.6 mg per kg per day and higher from its addition to drinking water adversely impacted several reproductive and developmental parameters in rats (Fungwe et al. 1990). The NOAEL for this study was 0.9 mg molybdenum per kg per day.

Limited data on the toxicity of molybdenum in humans are available. In one study, 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 (Kovalsky et al. 1961). However, serum uric acid levels were not adversely impacted in another study in which subjects consumed water containing molybdenum at levels providing up to 7 µg per kg per day (Chappell et al. 1979).

Official Reviews

Environmental Protection Agency (EPA 1992). The EPA utilized the epidemiological (human) data of Kovalsky and coworkers (1961) that suggested a LOAEL of 140 µg per kg per day. From this LOAEL value, a reference dose (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 value is 5 µg per kg per day, or 350 µg per day for a 70-kg person.

EC SCF (2000). The EC SCF concluded that there were no well-designed human studies that could serve as the basis for a risk assessment of molybdenum. Like the IOM, the 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, the EC SCF applied a 60-kg body weight to calculate a daily UL of 600 µg for adults.

IOM (2001). The IOM 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, the IOM used animal data as the basis for the UL. 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 IOM UL. Specifically, the IOM 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, the IOM 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 IOM estimated the intake of molybdenum from food to be 109 µg for men in the U.S.

Expert Group on Vitamins and Minerals (EVM 2003). The UK's 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 was too uncertain to serve as the basis for an SUL. In the face of such large uncertainties, but with some data suggesting adverse effects at lower levels, the EVM identified a guidance level for total intake that is equal to intake from foods in the United Kingdom (230 µg per day). The EVM declined to offer guidance about supplemental intakes.

CRN Recommendations

Abnormal plasma uric acid levels were associated with human intakes of 140 µg per kg per day of molybdenum in Kovalsky et al. (1961). However, 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 UL for supplements. This conclusion is more conservative than it would have been had it been based on the animal data used by the IOM 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 24-day treatment period (Turnland et al. 1995).

Quantitative Summary for Molybdenum

CRN UL, supplemental intake	350 µg/day
IOM UL, total intake	2,000 µg/day
EC SCF UL, total intake	600 µg/day
EC supplement maximum	Not determined
EVM, guidance level, total intake	230 µg/day from food; no guidance on supplemental intake

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