

Risk Assessment

Molybdenum

General information

Chemistry

The transition element molybdenum exists in five oxidation states (II – IV), the predominant states are Mo (IV) and Mo (VI). Within this risk assessment, the word molybdenum refers to ionic molybdenum except where the specific compound is stated.

Natural occurrence

Molybdenum does not exist naturally in the metallic state, but occurs in association with other elements. The predominant form of molybdenum occurring in soil and natural waters is the molybdate anion, MoO_4^{2-} .

Occurrence in food, food supplements and medicines

Generally, foodstuffs from above ground plant material, such as legumes, leafy vegetables and cauliflower, contain relatively high concentrations of molybdenum compared with food from tubers or animals. The 1994 TDS found the highest levels of molybdenum in nuts (0.96 mg/kg fresh weight), canned vegetables (0.31 mg/kg fresh weight) and cereals (0.23 mg/kg fresh weight). Few data are available on the variability of molybdenum content of individual plant species, but it is affected by the soil molybdenum concentration and pH, with molybdenum uptake increasing with soil pH. Foodstuffs from plants grown in alkaline or neutral soils with high molybdenum concentrations can be expected to have the highest molybdenum levels.

Molybdenum is available in food supplements at levels up to 0.33 mg and licensed medicines. The latter are used (maximum daily dose 0.25 mg) to treat patients with malabsorption states and conditions leading to hypoproteinaemia and in perioperative nutritional support.

Other sources of exposure

Most natural waters contain low levels of molybdenum. The WHO recommends a maximum level of molybdenum in drinking water of 0.07 mg/L and notes that concentrations of molybdenum in drinking water are typically less than 0.01 mg/L. However, in areas near mining sites, molybdenum concentrations up to 0.2 mg/L have been reported (WHO, 1993).

Recommended amounts

COMA has not set a RNI value for molybdenum. WHO (1993) estimated a daily requirement for molybdenum of between 0.1 and 0.3 mg/day for adults.

Analysis of tissue levels and molybdenum status

Molybdenum can be measured in whole blood, serum and various tissues.

Brief overview of non-nutritional beneficial effects

Molybdenum has been reported to be beneficial to various groups of individuals, including those with sulphite sensitivity, asthmatics with elevated urinary ratios of sulphites to sulphates, and those intolerant to intravenous sulphur containing amino acids.

Molybdenum has been claimed to reduce the incidence and severity of dental caries.

Function

The basis of the importance of molybdenum is in its role in metalloenzymes. All of the molybdoenzymes are oxidoreductases, which exploit the variable valency states of molybdenum. The molybdenum in molybdoenzymes is inserted as part of a prosthetic group, known as the 'molybdenum cofactor'. In humans, xanthine oxidase and sulphite oxidase are important molybdoenzymes.

Deficiency

Molybdenum deficiency has not been identified in free-living human or animal species. It has, however, been identified in a single subject receiving total parenteral nutrition and can be achieved in animal studies. In goats, a molybdenum deficient diet was associated with reduced fertility and increased mortality in both the mothers and the offspring.

In a rare inherited metabolic disorder, molybdenum deficiency is associated with genetic deficiency of the molybdenum pterin cofactors. Neurological disorders, abnormal urinary metabolites, dislocated ocular lenses and failure to thrive are observed. The disorder is fatal by the age of 2-3 years.

Interactions

It is recognised that molybdenum interacts with copper and sulphates in living organisms, but the mechanism of this interaction has not been elucidated. The presence of dietary copper and sulphate affects the amount of molybdenum absorbed and retained by the body.

Absorption

Absorption of molybdenum varies over a wide range (25 – 93%). Reports suggest that soluble molybdenum compounds are readily absorbed, whilst insoluble compounds are not.

Distribution

Molybdenum occurs in low concentrations in all the fluids and tissues of the body. The greatest amounts are found in the kidney, liver, small intestine and adrenals. It is found largely as molybdoenzymes. In plasma, molybdenum is bound specifically to α_2 -macroglobulin.

Excretion

Molybdenum is primarily excreted in the urine and experimental data from humans suggest that up to 80% of the absorbed amount is excreted via urine. Normally only small amounts are excreted in the faeces with exceptions in certain gastrointestinal disorders.

Toxicity

Human data

Few data are available on human toxicity following ingestion. Food or water must contain more than 100 mg/kg to produce signs of toxicity, which include diarrhoea, anaemia and high levels of uric acid in the blood. Elevated uric acid levels, which are associated with the onset of gout, are hypothesised to be caused by stimulation of xanthine oxidase by high molybdenum intake. Occupational exposure, by inhalation, to molybdenum containing dusts has been associated with pneumoconiosis.

Animal data

Although non-ruminant animals will develop symptoms of toxicity when fed high molybdenum diets, ruminants are much more sensitive. Thus the toxicity seen in these species cannot be related to the effects that would be expected in man. The toxicity is primarily expressed as a copper deficiency and the ambient sulphate level has a marked effect on the interaction between copper and molybdenum. Molybdenum toxicity in animals is commonly referred to as molybdenosis or teart. In appearance it is similar to the disease of copper deficiency. Signs of molybdenum toxicity in animals include anaemia, anorexia, profound diarrhoea, joint abnormalities, osteoporosis, hair discoloration, reduced sexual activity and death.

Carcinogenicity and genotoxicity

There is no evidence of carcinogenicity of molybdenum. No data are available on the genotoxicity of molybdenum compounds *in vitro*, although there is limited evidence of genotoxicity from *in vivo* tests, the reliability of which is questionable.

Mechanism of toxicity

No data have been identified.

Dose response characterisation

No data have been identified.

Vulnerable groups

No vulnerable groups have been identified.

Genetic variations

No genetic variations have been identified.

Studies of particular importance in the risk assessment

(For full review see <http://www.food.gov.uk/science/ouradvisors/vitandmin/evmpapers> or the enclosed CD).

Human data

Kovalsky et al., 1961

In a retrospective study of environmental exposure to increased molybdenum (form unclear), medical reports revealed a prevalence of gout in 31% and 18% of the exposed and control populations, respectively. Intake was calculated to be 10 – 15 mg molybdenum per day in the exposed population compared to 1 – 2 mg/day in the control area. It is possible that the 1-2 mg intake produced a low level of response. Symptoms included arthralgia in the hand, feet and knee joints, accompanied by elevated blood and urine molybdenum levels.

Animal data

Fairhall et al., 1945

Molybdenum (as the trivalent form molybdenite, and as the hexavalent forms molybdenum trioxide, calcium molybdate and ammonium molybdate) was administered in the diet to rats at levels of 10 – 500 mg molybdenum/animal/day, for periods up to 232 days. No signs of toxicity were observed in the groups ingesting molybdenite. In the groups receiving hexavalent molybdenum, signs of toxicity were observed at all dose levels and included loss of appetite, weight loss, a tendency to become quiet and listless and premature death. One hundred percent mortality was recorded in the groups receiving >100 mg hexavalent molybdenum/animal/day. Limited experimental details were provided.

Arrington & Davies, 1953

Hexavalent molybdenum (sodium molybdate) was administered in the diet to groups of 2-5 weanling or mature rabbits at levels of 140, 500, 1000, 2000 and 4000 mg/kg diet (4, 15, 30, 60 or 120 mg/kg bw/day – estimated) for up to 12 weeks (average survival being 3 – 54 days in the higher dose groups). In the highest dose group 100% mortality was observed and 80% mortality in the group receiving 60 mg/kg bw/day. Anaemia, anorexia, loss of weight, alopecia, dermatosis and effects on the skeletal system were noted in animals receiving 30 mg/kg bw/day and above. Limited experimental details were provided. Haemoglobin levels appear to decrease by >50% within a few weeks of treatment. It is uncertain whether this is a specific effect or related to factors such as haemodilution. Data for the 500 ppm (4 and 15 mg/kg bw) group are not provided so it is uncertain whether the decrease would have also have been apparent at this level.

Schroeder & Mitchener, 1971

Sodium molybdate (hexavalent molybdenum) was administered in drinking water (0.0025 mg/kg bw/day) and diet (0.07 mg/kg bw/day) in lifetime studies over three generations of mice. In the first and second generations, 15/238 and 7/242 premature deaths, respectively, were observed, compared to 0/209 and 6/248 in the control populations. In the third generation increased numbers of premature deaths, maternal deaths, failure to breed, runting and production of single sex or dead litters were observed.

Exposure assessment

Total exposure/intake:

Food	Mean: 0.11 mg/day (1994 TDS) 97.5th percentile: 0.21 mg/day
Drinking Water	0.02 mg/day (estimated from 0.01 mg/L – WHO, 1993)
Supplements	up to 0.33 mg molybdenum (Annex 4)

Estimated maximum intake: $0.21 + 0.02 + 0.33 = 0.56$ mg/day

No potential high intake groups were identified.

Risk assessment

Few data are available concerning oral molybdenum toxicity in humans, but some data exist that suggest an increased incidence in gout-like symptoms (joint pains and increased serum uric acid) in populations with a high molybdenum intake (1 – 15 mg/person/day). The form of the molybdenum is uncertain. Few details of this study are available.

Some data are available from limited animal studies, which suggest that intakes of trivalent molybdenum of up to 500 mg/rat/day may be without adverse effects, although these are not sufficiently reliable to draw any conclusions. It should be noted from the animal studies that signs of toxicity were observed in studies in which hexavalent molybdenum was administered.

ESTABLISHMENT OF A GUIDANCE LEVEL

There are insufficient data from human or animal studies to establish a Safe Upper Level for molybdenum.

There are few reliable data on the oral toxicity of molybdenum. A limited human study (Kovalsky *et al.*, 1961) suggests that intakes of >1 mg/day could be associated with an increase in gout-like symptoms – joint pains and increased serum uric acid levels. The form of molybdenum to which the population was exposed is unclear, but as exposure is via water and locally grown/produced food, it is most likely to be the more toxic hexavalent molybdate ion. However, this epidemiological evidence is not robust, as there is no means of unbiased assessment, no control group and the exposure to molybdenum cannot accurately be determined. Lack of evidence makes it impossible to determine whether higher intakes would be problematic.

The available animal data are also limited. Signs of general/systemic toxicity have been reported at doses of 30-75 mg/kg bw/day hexavalent molybdenum (e.g. molybdate), whereas molybdenite, a trivalent form of molybdenum, appears to be less toxic. A multi-generation study in which mice were fed 0.0025 mg/kg bw/day and 0.075 mg/kg sodium molybdate in drinking water and food respectively

also produced adverse effects such that the colony was not viable beyond the F₂ generation. The level at which this effect occurred was lower than intakes causing adverse effects in other studies. The limited details available on the study make it impossible to establish whether the effect was real, or whether an effect unrelated to treatment occurred as a result of inbreeding.

The molybdenum intake from the UK diet (estimated maximum intake 0.23 mg/day) is not expected to present any risk to health, but there are insufficient data on the safety of molybdenum intakes in excess of those naturally occurring in the diet to be able to provide further guidance.

References

- Arrington, L.R. and Davies, G.K. (1953) Molybdenum toxicity in the rabbit. *Journal of Nutrition* **51**, 295-304.
- Fairhall, L.T., Dunn, R.C., Sharpless, N.E., Pritchard, E.A. (1945) The toxicity of molybdenum. US Public Health Service. Public Health Bulletin No. 293, 1-36.
- Kovalsky, V.V., Yarovaya, G.A., Shmavonyan, D.M. (1961) The change in purine metabolism of humans and animals under the conditions of molybdenum biogeochemical provinces. *Zhurnal Obshchei Biologii* **22**, 179-191 (Full translation of original Russian paper obtained).
- Schroeder, H.A and Mitchener, M. (1971) Toxic effects of trace elements on the reproduction of mice and rats. *Archives of Environmental Health* **23**, 102-106.
- WHO (1993) Guidelines for drinking water quality. Second edition. World Health Organisation, Geneva.