Molybdenum
CASRN 7439-98-7

Contents

I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

I.B. REFERENCE CONCENTRATION FOR CHRONIC
INHALATION EXPOSURE (RfC)

II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

VI. BIBLIOGRAPHY

VII. REVISION HISTORY

VIII. SYNONYMS

0425
Molybdenum; CASRN 7439-98-7

Health assessment information on a chemical substance is included in IRIS only after a comprehensive review of chronic toxicity data by U.S. EPA health scientists from several Program Offices and the Office of Research and Development. The summaries presented in Sections I and II represent a consensus reached in the review process. Background information and explanations of the methods used to derive the values given in IRIS are provided in the Background Documents.

STATUS OF DATA FOR Molybdenum
File On-Line 11/01/1992

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<th>Status</th>
<th>Last Revised</th>
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<td>on-line</td>
<td>08/01/1993</td>
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I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name -- Molybdenum
CASRN -- 7439-98-7
Last Revised -- 08/01/1993

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.A.1. ORAL RfD SUMMARY

<table>
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<th>Experimental Doses*</th>
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<th>MF</th>
<th>RfD</th>
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<td>Increased uric acid</td>
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<td>5E-3 mg/kg-day</td>
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<tr>
<td>levels</td>
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Human 6-year to Lifetime Dietary Exposure Study
Koval'skiy et al., 1961
*Conversion Factors: Dose determined from study: molybdenum (Mo) concentration in diet is 10-15 mg/day. Assumed body weight of adult male is 70 kg; 10 mg molybdenum/70-kg body weight = 0.14 mg/kg-day.

I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)


In a cross-sectional epidemiology study in a Morich geoprovine of Armenia, Koval'skiy et al. (1961) correlated the dietary intake of molybdenum with serum uric acid levels, several biochemical endpoints, and with a gout-like sickness affecting the adult population in two settlements, Ankava village and a smaller adjoining settlement. Ankava village is a large settlement over 100 years old, while the adjoining settlement (the control) is smaller and was established in the 6-year period prior to the study. This
particular region was selected for two reasons: high molybdenum content in
the soil and plants (38 and 190 times that of the control area) and low
content of copper (Cu). Based on these figures and dietary estimates, the
average adult person in the Ankava settlement received 10-15 mg of molybdenum
and 5-10 mg of copper. This intake corresponds to molybdenum doses of 0.14-
0.21 mg/kg-day for a 70-kg adult. These values compare with control area
values of 1-2 mg of molybdenum and 10-15 mg of copper. Three hundred
villagers (184 of whom were age 18 or older) from Ankava and 100 villagers (78
adults) from the adjoining settlement underwent medical examinations. Only
limited data on length of residency were reported. The results from the
medical exam indicated that 57 Ankava adults (31% of the adult population) and
14 adults of the new settlement (17.9% of the adult population) had gout-like
symptoms as compared with 1-4% as an overall average rate. This condition was
characterized by pain, swelling, inflammation and deformities of the joints,
and, in all cases, an increase in the uric acid content of the blood. In a
number of cases (exact number not reported), this condition was accompanied by
illnesses of the GI tract, liver, and kidneys. Fifty-two adults from Ankava
and five from the adjoining settlement (controls) underwent a more detailed
examination in which blood copper, molybdenum, uric acid, and xanthine oxidase
concentrations in blood and molybdenum, copper, and uric acid concentrations
in urine were measured. The average uric acid content in blood of the 52
Ankara adults was 6.2 mg as compared with 3.8 mg, the average of the five
controls. Above normal blood uric acid content (>5.5 mg) was found in 29 of
the 52 adults examined; at least 17 of these 29 had gout-like symptoms. When
the 52 inhabitants were segregated as to whether they were sick with gout
symptoms or not, the average concentration of uric acid in blood increased to
8.1 mg (n=17) for those sick and to 5.3 mg (n=35) for those healthy. Both
serum molybdenum and serum xanthine oxidase (a molybdenum-containing enzyme
that converts purines to uric acid) activity were positively correlated with
serum uric acid levels. Increasing urinary excretion of copper was inversely
related to increasing serum levels of molybdenum. Among the group of 52
adults from Ankara, blood uric acid levels increased with increasing residency
time in the region; they increased from 3.75 mg for up to 1 year, to 6.4 mg
after 1-5 years, and to 6.8 mg for 5 years or more. Based on these results, a
molybdenum intake of 0.14 mg/kg-day may result in serum uric acid levels
elevated above the average range of the adult population (2-6 mg; White et
al., 1973). This level is designated as a LOAEL.

The effect of dietary molybdenum on uric acid and copper excretion was
also observed in experiments with four adult men given diets based on sorghum
varieties differing widely in molybdenum content for 10 days (Deosthale and
Gopalan, 1974). The urinary excretion of uric acid was unaltered at low
molybdenum intake levels up to 1540 ug/day (approximately 0.022 mg/kg-day).
The urinary excretion of copper increased in direct proportion to dietary
molybdenum intake; molybdenum intakes of 0.002 or 0.022 mg/kg-day resulted in
the urinary excretion of copper at 24 or 77 ug/day, respectively. Normal
urinary copper excretion is less than 40 ug/day.

The effects of human ingestion of molybdenum in drinking water were
investigated in two Colorado cities over a 2-year period (U.S. EPA, 1979).
Urinary levels of molybdenum and copper and serum levels of ceruloplasmin and
uric acid were compared in individuals consuming city drinking water over a 2-
year period. The low-molybdenum group consisted of 42 individuals from
Denver, Colorado where the molybdenum concentration in the drinking water
ranged from 2 to 50 ug/L. The high-molybdenum group consisted of 13 college
students from Golden, Colorado where the drinking water molybdenum
concentrations were equal to or greater than 200 ug/L.

Among subjects consuming water containing up to 50 ug molybdenum/L, plasma
molybdenum levels were within the normal range. No adverse health effects
were observed. While higher daily urinary molybdenum was associated with
higher molybdenum intake, no adverse biochemical or systemic effects were
noted. The Denver subjects had a mean urinary molybdenum value of
87 +/- 18 ug/day as compared with a value of 187 +/- 34 ug/day for the Golden
subjects. Higher mean serum ceruloplasmin (40.31 mg/100 mL vs.
30.41 mg/100 mL) and lower mean serum uric acid (4.35 mg/100 mL vs.
5.34 mg/100 mL) were also associated with the higher molybdenum intake. The
average dietary intake of molybdenum was 180 ug/day (estimated from foods

When these three studies are viewed collectively, the increased serum ceruloplasmin and urinary excretion of copper observed in human studies indicates that high levels of ingested molybdenum may be associated with potential mineral imbalance. Excretion of sufficient quantities of this element may put individuals at risk for the hypochromic microcytic anemia associated with a dietary copper deficiency. Although increased copper excretion and elevated serum ceruloplasmin are not definitive adverse effects, and as presented here are associated with no frank adverse effects in a human population, the potential for mineral imbalance must be weighed in developing an RfD. Laboratory animal studies discussed below demonstrate that the effects of molybdenum on growth and melanin synthesis are more pronounced under situations where dietary copper intake is low. For this reason, the RfD was derived with the Estimated Safe and Adequate Daily Intake (ESAADI) in mind. It is important to note that the average level of copper intake in the American population from 1982 to 1986 was less than the lower limit of the ESAADI recommendation for all age and sex groups studied in the Food and Drug Administration (FDA) Total Diet Study (Pennington et al., 1989).

__I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)\n
UF -- An uncertainty factor of 3 is used for protection of sensitive human populations and a factor of 10 for the use of a LOAEL, rather than a NOAEL, from a long-term study in a human population. A full factor of 10 is not used for the protection of sensitive human populations because the study was conducted in a relatively large human population. The data base does not contain studies on reproductive and developmental toxicity. However, an additional uncertainty factor for these deficiencies is not considered necessary because the RfD is only slightly above the ESAADI which was derived from the molybdenum content of the average U.S. diet.

MF -- None

__I.A.4. ADDITIONAL STUDIES / COMMENTS (ORAL RfD)\n
Molybdenum is an essential dietary nutrient which is a constituent of several mammalian enzymes including xanthine oxidase, sulfite oxidase and aldehyde oxidase (NRC, 1989). The Food and Nutrition Board of the Subcommittee on the Tenth Edition of the RDAs has established ESAADI values for molybdenum of 15-40 ug/day (2.5-4.45 ug/kg-day) for infants, 25-150 ug/day (1.95-5.36 ug/kg-day) for children, and 75-250 ug/day (1.5-3.6 ug/kg-day) for adolescents and adults (NRC, 1989). These values were derived from the reported molybdenum intake of adults and older children with average American diets (ug/kg-day values are derived from the Second National Health and Nutrition Examination Survey (NHANES II). Values for infants and children were extrapolated from the adult values on the basis of body weight. The dietary intake range reported by Tsongas (1980) from foods purchased in the Denver area was 120-240 ug/day with a mean of 180 ug/day. In the 1984 FDA Total Diet Study, the molybdenum intakes of older children and adults ranged from 74-126 ug/day (Pennington and Jones, 1987). Food for this assay was purchased from grocery stores in several northeastern locations. The data from these dietary surveys support the ESAADI recommendations.

Miller et al. (1956) administered diets to groups of Holtzman rats (21 days old; 4/dosage group). The basal diet (which contained 4 mg copper/kg purchased at Denver area grocery stores) (Tsongas et al., 1980). When the dietary molybdenum was added to the molybdenum from the drinking water, the NOAEL for the Denver subjects was 4 ug/kg-day and 8 ug/kg-day for Golden subjects, assuming a 2-L/day water consumption and a 70-kg body weight.
and 0.2 mg molybdenum/kg) was supplemented with hydrogen molybdate at 75 and 300 ppm (approximately 7.5 and 30 mg molybdenum/kg/day, respectively). Some of the groups also received 2200 ppm sulfate (as a 1:1 mixture of sodium sulfate and potassium sulfate) for 6 weeks. Molybdenum alone exerted a significant (p value not reported) growth inhibition at the 75- and 300-ppm levels (50% and 78% reduction in weight gain, respectively). The addition of sulfate reversed this inhibition at molybdenum levels of 75 ppm and reduced it at 300 ppm. The addition of molybdenum alone increased liver copper and molybdenum concentrations. These increases were reduced by sulfate supplementation. An enlargement of the femoro-tibial joint and a thickening of the epiphysis of the femur and tibia were observed in the rats receiving 75 and 300 ppm molybdenum without sulfate and in the rats receiving 2200 ppm molybdenum with sulfate. Histological examination of the femurs indicated a chondrodystrophy of the epiphyseal cartilage. The femurs in the groups receiving lower molybdenum levels were normal. This study suggested a LOAEL of 7.5 mg molybdenum/kg/day based on body weight loss and bone deformities.

Jeter and Davis (1954) tested the effects of dietary molybdenum and copper on Long-Evans rats (4 or 8 pairs/group). The rats received either the basal diet (1.78 mg copper/kg as CuSO4·5H2O and <1 mg molybdenum/kg as NaMoO4·2H2O) or the basal diet supplemented with molybdenum at approximately 2, 8 or 14 mg/kg, ad libitum daily for 13 weeks. Each diet contained 0.5 mg copper/kg. Two groups of animals also received <1 or 8 mg molybdenum/kg with 2 mg copper/kg. The weight gain of male rats given 2, 8 or 14 mg molybdenum/kg/day at the lower copper level (0.5 mg copper/kg/day) was retarded, while that of females was retarded only at the two higher molybdenum levels. Hemoglobin concentrations were not affected by any diet. Achromotrichia (depigmentation of the hair) followed by varying degrees of alopecia (balding) was observed in some but not all rats in the groups receiving 8 or 15 mg/kg-day of molybdenum. Depigmentation was occasionally observed in rats receiving approximately 2 mg molybdenum/kg/day. The change in hair coloration may be explained by the fact that a copper-containing, mixed function oxidase catalyzes the initial reaction in the synthesis of the melanin hair pigments. The 2-3 mg molybdenum/kg/day dose represents a LOAEL in this study.

The effect of excess dietary molybdenum (added as sodium molybdate) was tested in guinea pigs of unspecified strain (Arthur, 1965). In the first experiment, groups of five guinea pigs were maintained for 8 weeks on diets with varying molybdenum content. The basal diet contained 8.9 mg copper/kg, 0.3 mg molybdenum/kg, and 0.25% sulfate. Molybdenum was increased to 8000 mg molybdenum/kg in increments of 1000 mg molybdenum/kg. Assuming a body weight of 0.75 kg and food consumption of 30 g/day for guinea pigs, a dietary level of 8000 mg molybdenum/kg corresponds to 320 mg molybdenum/kg/day. Weight gains decreased as molybdenum was increased from 40-160 mg molybdenum/kg/day, and weight loss occurred above 160 mg molybdenum/kg/day. The color of the hair of the black guinea pigs changed to gray when the dose was higher than 40 mg molybdenum/kg/day. Some fatalities were reported at 200 mg molybdenum/kg/day, and approximately 75% of the animals receiving 240-320 mg molybdenum/kg/day died.

In the second part of the Arthur study (1965), the levels of copper and molybdenum were both varied with either 0, 10 or 20 mg copper/kg and 0 or 2000 mg molybdenum/kg added to the diet. All of the animals at dietary levels of 2000 mg/kg added molybdenum (80 mg molybdenum/kg/day) and either 0 or 0.4 mg copper/kg/day developed gray hair. The inclusion of 0.8 mg copper/kg/day, however, reversed this effect. All animals receiving added molybdenum accumulated molybdenum in the liver. The animals on 80 mg molybdenum/kg/day had the smallest weight gain. The failure to gain weight was only partially alleviated by the addition of copper.

In the third part of the study, three weanling guinea pigs were supplied a low-copper basal diet (5.6 mg copper/kg and 1.8 mg molybdenum/kg) with dietary additions of 0, 200, 500, 1000 or 2000 mg molybdenum (equivalent to 8, 20, 40 or 80 mg/kg/day) for 8 weeks (Arthur, 1965). Molybdenum in the blood, liver and kidneys increased with dietary molybdenum levels. An increase in copper was observed in the blood and kidneys with increasing molybdenum intake. At 40 and 80 mg molybdenum/kg/day, liver copper concentrations decreased. Guinea pigs appeared to be somewhat less sensitive than rats or rabbits to molybdenum.
toxicity. The level of 40 mg molybdenum/kg/day represents a LOAEL in this study based on loss of copper.

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I.A.5. CONFIDENCE IN THE ORAL RfD

Study -- Medium  
Data Base -- Medium  
RfD -- Medium

The level of confidence in the oral RfD for molybdenum is medium. It is based on the results of a study that examined only gross physical effects of a gout-like disease and examined some blood chemistry parameters normally associated with gout. An exhaustive analysis of blood chemistry and individual dietary habits was not done. Therefore, the results are clearly generalized for a large population. Studies in human and animals suggest that molybdenum has an adverse effect on copper homeostasis, making the changes in serum ceruloplasmin a matter of possible concern. A study that monitored a broader spectrum of hematological or clinical chemistry parameters, especially those related to copper distribution and copper metalloenzyme function, would have helped to characterize the copper-molybdenum interaction, which appears critical to the development of gout-like symptoms at very high levels of molybdenum. The proposed RfD satisfies molybdenum nutrient requirements for all healthy members of the population, based on a comparison with the ESAADI. Dietary studies conducted by Tsongas et al. (1980) and Pennington and Jones (1987) indicate that people in the U.S. are receiving between 76 and 240 ug/day (1.1-3.4 ug/kg-day, based on a 70-kg adult) in their diets. Much of these data served as the basis for the ESAADI.

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I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

The Drinking Water Health Advisory for Molybdenum has received Agency review.
Other EPA Documentation -- None
Verification Date -- 11/06/1991

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I.A.7. EPA CONTACTS (ORAL RfD)

Please contact the Risk Information Hotline for all questions concerning this assessment or IRIS, in general, at (513)569-7254 (phone), (513)569-7159 (FAX) or RIH.IRIS@EPAMAIL.EPA.GOV (internet address).

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I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (Rf

http://www.epa.gov/iris/subst/0425.htm
6/10/99
Not available at this time.

II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

This substance/agent has not undergone a complete evaluation and determination under US EPA's IRIS program for evidence of human carcinogenic potential.

VI. BIBLIOGRAPHY

VI.A. ORAL RfD REFERENCES


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VI.B. INHALATION RfD REFERENCES

None

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VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

None

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VII. REVISION HISTORY

Substance Name -- Molybdenum  
CASRN -- 7439-98-7

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VIII. SYNONYMS

http://www.epa.gov/iris/subst/0425.htm

6/10/99