Vitenskapskomiteen for mat og miljø
Norwegian Scientific Committee for Food and Environment

VKM Report 2018: 05

Assessment of dietary intake of molybdenum in relation to tolerable upper intake level

Opinion of the Panel on Nutrition, Dietetic Products, Novel Food and Allergy of the Norwegian Scientific Committee for Food and Environment

Report from the Norwegian Scientific Committee for Food and Environment (VKM) 2018: 05
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14.03.2018

ISBN: 978-82-8259-302-1
ISSN 2535-4019
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Cover photo: iStock photo

Suggested citation: VKM (2018). Assessment of dietary intake of molybdenum in relation to tolerable upper intake. Opinion of the Panel on Nutrition, Dietetic Products, Novel Food and Allergy of the Norwegian Scientific Committee for Food and Environment. VKM Report 2018: 05, ISBN: 978-82-8259-302-1, Oslo, Norway. Available online: vkm.no

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Author preparing the draft statement

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Assessed and approved

The opinion has been assessed by the Panel on Nutrition, Dietetic Products, Novel Food and Allergy of the Norwegian Scientific Committee for Food and Environment (Vitenskapskomiteen for mat og miljø, VKM). Kristin Holvik (chair), Livar Frøyland, Margaretha Haugen, Sigrun Henjum, Martinus Løvik, Tonje Holte Stea, Tor A. Strand and Christine Louise Parr (external expert).

(Panel members in alphabetical order after chair of the panel)

Acknowledgment

The Panel on Nutrition, Dietetic Products, Novel Food and Allergy has answered the request from the Norwegian Food Safety Authority. Project leader from the VKM secretariat has been Bente Mangschou. Tor A Strand is acknowledged for his valuable work on this opinion.

Competence of VKM experts

Persons working for VKM, either as appointed members of the Committee or as external experts, do this by virtue of their scientific expertise, not as representatives for their employers or third party interests. The Civil Services Act instructions on legal competence apply for all work prepared by VKM.

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Summary

The Norwegian Scientific Committee for Food and Environment (Vitenskapskomiteen for mat og miljø, VKM) has, at the request of the Norwegian Food Safety Authority (Mattilsynet; NFSA), evaluated the intake of molybdenum. VKM has also conducted scenario calculations to illustrate the consequences of amending maximum limits for molybdenum to 100, 250, 500 or 1000 µg/day in food supplements. The previous maximum limit was 250 µg/day.

Molybdenum is as a cofactor for some important enzymes in humans. These enzymes are involved in the catabolism of sulfur amino acids and heterocyclic compounds, including purines and pyridines. A distinct molybdenum deficiency has not been described in animals when subjected to molybdenum restriction, despite considerable reduction in the activity of molybdoenzymes. Molybdenum deficiency is not observed in healthy humans. The estimated Adequate Intake (AI) proposed by the European Food Safety Authority (EFSA) is 65 µg per day for men and women. Legumes, grains, and nuts are major contributors of molybdenum in the diet.

Molybdenum is a potential antagonist to copper absorption, but symptoms of copper deficiencies due to excess molybdenum intake have only been observed in ruminants. Based on the effect on reproduction and growth in animals, tolerable upper intake levels (ULs) have been estimated to be 2 mg/day by the U.S. Institute of Medicine (IOM) in 2001 and 0.6 mg/day by the Scientific Committee on Food (SCF) in 2000. These ULs were based on the same scientific evidence, but IOM used an uncertainty factor (UF) of 30 and SCF used a UF of 100 because the evidence base was considered to be weak.

Because of the limited safety data on molybdenum, VKM support the use of the default uncertainty factors at 100 for extrapolation of data from animal studies to humans. Additionally, molybdenum deficiency is very rare and no studies have indicated a nutritional need for additional molybdenum from dietary supplements. The ULs for children were derived by adjusting the adult UL according to default body weights.

According to the scenario estimations, only the highest suggested maximum limit of 1000 µg molybdenum from food supplements will lead to exceedance of the UL for adults. For 1-3 year old children, all the suggested maximum limits for molybdenum will lead to exceedance of the UL. In children 4-10 years, supplements with 250, 500 or 1000 µg molybdenum will lead to exceedance of the ULs, whereas for adolescents 11-17 years, the UL will be exceeded with supplemental doses at 500 or 1000 µg per day.

VKM emphasises that the current assessment of maximum limits for molybdenum in food supplements is merely based on published reports concerning upper levels from the SCF (2000, EU), IOM (2001, USA), EVM (2003, UK) and NNR (2012, Nordic countries). VKM has not conducted any systematic review of the literature for the current opinion, as this was outside the scope of the terms of reference from NFSA.

Key words: VKM, risk assessment, Norwegian Scientific Committee for Food and Environment, molybdenum, food supplement, upper level, exposure.

Sammendrag på norsk

Vitenskapskomiteen for mat og miljø (VKM) har vurdert inntaket av molybden i befolkningen på oppdrag fra Mattilsynet.

VKM har også gjort scenarioberegninger for å illustrere konsekvensene av å fastsette maksimumsgrensene for molybden i kosttilskudd til 100, 250, 500 eller 1000 µg/dag. Den tidligere maksimumsgrensen for molybden var 250 µg per døgndose.

Molybden er en kofaktor for noen viktige enzymer i mennesker. Disse enzymene er involvert i katabolismen av svovelaminosyrer og heterocykliske forbindelser, inkludert puriner og pyridiner. Til tross for betydelig reduksjon i enzymaktiviteten er det ikke rapportert om manifestert molybdenmangel i dyr som er utsatt for molybdenrestriksjoner. Molybdenmangel er ikke vist hos friske mennesker. Adekvat inntak (AI) er beregnet til 65 µg per dag for menn og kvinner. Belgfrukter, korn og nøtter er viktige kilder til molybden i maten.

Molybden kan påvirke absorbsjon av kobber, men symptomer på kobbermangel på grunn av høyt inntak av molybden er kun observert i drøvtyggere. Øvre tolerabelt inntaksnivå (UL) har blitt estimert til å være mellom 2 og 0,6 mg per dag, og er basert på effekten på reproduksjon og vekst hos dyr. Nivåene er fastsatt av henholdsvis U.S. Institute of Medicine (IOM) i 2001 og Scientific Committee on Food (SCF) i 2000. Den samme vitenskapelige evidensen ligger til grunn for begge disse øvre tolerable inntaksnivåene, men IOM brukte en usikkerhetsfaktor på 30, mens SCF brukte en usikkerhetsfaktor på 100 fordi evidensgrunnlaget ble vurdert som svakt.

På grunn av usikkerheten i de vitenskapelige studiene som er lagt til grunn for det øvre tolerable inntaksnivået samt inntaksdataene og den lave risikoen for molybdenmangel, støtter VKM SCFs bruk av en høyere usikkerhetsfaktor og et øvre tolerabelt inntaksnivå på 0,6 mg/dag for voksne. Øvre tolerable inntaksnivåer for barn er fastsatt ved å justere denne verdien i forhold til standard kroppsvekter hos de ulike aldersgruppene.

I henhold til scenarioberegningene vil kun den høyeste maksimumsgrensen for molybden i kosttilskudd på 1000 µg per dag føre til en overskridelse av øvre tolerable inntaksnivå hos voksne. For barn 1-3 år vil alle de foreslåtte maksimumsgrensene medføre overskridelse av øvre tolerabelt inntaksnivå. For barn 4-10 år vil tilskudd med 250, 500 eller 1000 µg molybden medføre overskridelse av øvre tolerabelt inntaksnivå, mens for ungdom 11-17 år, vil øvre tolerable inntaksnivå overskrides ved doser på 500 eller 1000 µg molybden per dag.

VKM presiserer at denne vurderingen av maksimumsgrenser for molybden i kosttilskudd er basert på publiserte rapporter om øvre inntaksnivåer fra SCF (2000, EU), IOM (2001, USA), EVM (2003, Storbritannia) og NNR (2012, de nordiske landene) og EFSA. Ettersom mandatet i bestillingen fra Mattilsynet var å vurdere øvre inntaksnivå basert på allerede eksisterende rapporter, har VKM ikke gjennomført et eget systematisk litteratursøk for å vurdere det samlede kunnskapsgrunnlaget i denne vurderingen.

Abbreviations and/or glossary

Abbreviations

AI – adequate intake
AR – average requirement
bw – body weight
CI – confidence interval
DRI – dietary reference intake
DRV – dietary reference value
DTU – Technical University of Denmark
EAR – estimated average requirement (IOM).
EFSA – European Food Safety Authority
EVM – Expert group on vitamins and minerals of the Food Standard Agency, UK
IOM – Institute of Medicine, USA
IU – international unit
LOAEL – lowest observed adverse effect level
NFSA – Norwegian Food Safety Authority [*Norw.*: Mattilsynet]
NNR – Nordic Nutrition Recommendations
NOAEL – no observed adverse effect level
PRI – population reference intakes
RDA – recommended dietary allowances
RI – recommended intake
SCF – Scientific Committee on Food
SUL – safe upper intake level
UF – uncertainty factor
UL – tolerable upper intake level
VKM – Norwegian Scientific Committee for Food and Environment [*Norw.*: Vitenskapskomiteen for mat og miljø]

Glossary

P5, P25, P50, P75 or P95-exposure is the calculated exposure at the 5, 25, 50, 75 or 95-percentile.

Percentile is a term for visualising the low, medium and high occurrences of a measurement by splitting the whole distribution into one hundred equal parts. A percentile is a statistical measure indicating the value below which a given percentage of the observations fall. E.g. the 95-percentile is the value (or score) below which 95 percent of the observations are found.

EFSA - Dietary Reference Values (DRVs) (EFSA, 2010)

Average Requirement (AR) is the level of intake of a defined group of individuals estimated to satisfy the physiological requirement of metabolic demand, as defined by a the specific criterion for adequacy for the nutrient, in half of the heathy individuals in a life stage or sex group, on the assumption that the supply of other nutrients and energy is adequate.

If an AR cannot be determined than an Adequate Intake is used.

Adequate Intake (AI) is defined as the average (median) daily level of intake based on observed, or experimentally determined approximations or estimates of a nutrient intake, by a group (or groups) of apparently healthy people, and therefore assumed to be adequate. The practical implication of an AI is similar to that of a population reference intake, i.e. to describe the level of intake that is considered adequate for health reasons. The terminological distinction relates to the different ways in which these values are derived and to the resultant difference in the "firmness" of the value.

Population Reference Intake (PRI) is derived from AR of a defined group of individuals in an attempt to take into account the variation of requirements between individuals.

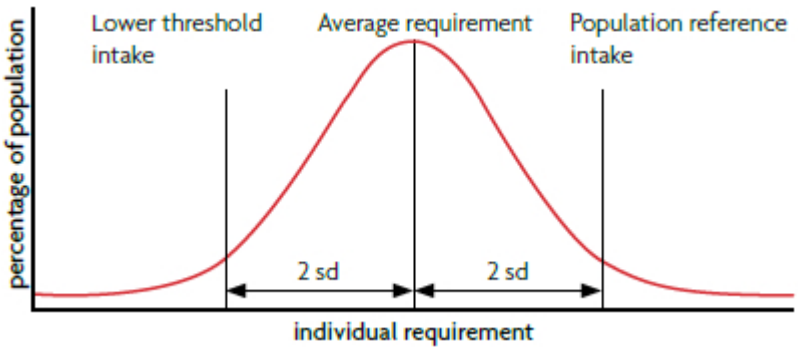

Figure 1: Population reference intake (PRI and average requirements (AR), if the requirement has a normal distribution and the inter-individual variation is known (EFSA, 2010).

Lower Threshold Intake (LTI) is the lowest estimate of requirement from the normal distribution curve, and is generally calculated on the basis of the AR minus twice its SD. This will meet the requirement of only 2.5% of the individuals in the population.

Tolerable Upper intake Level (UL) is the maximum level of total chronic daily intake of a nutrient (from all sources) judged to be unlikely to pose a risk of adverse health effects to humans.

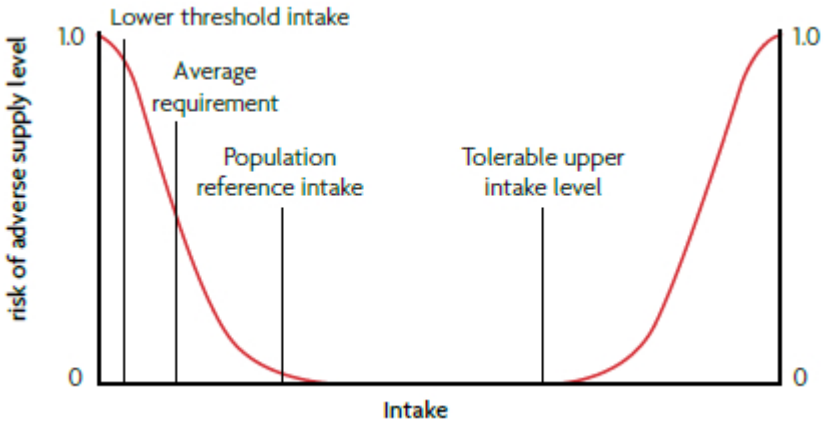

Figure 2: Relationship between individual intake and risk of adverse effects due to insufficient or excessive intake.

IOM - Dietary Reference Intakes (DRIs) (IOM, 2000)

Estimated Average Requirement (EAR) is a nutrient intake value that is estimated to meet the requirement of half the healthy individuals in a life stage and gender group.

Recommended Dietary Allowances (RDA) is the dietary intake level that is sufficient to meet the nutrient requirement of nearly all (97 to 98 percent) healthy individuals in a particular life stage and gender group. RDA = EAR + 2 SD_{EAR} or if insufficient data to calculate SD a factor of 1.2 is used to calculate RDA; RDA = 1.2*EAR

Adequate Intake (AI) is the recommended intake value based on observed or experimentally determined approximations or estimates of nutrient intake by a group (or groups) of healthy people that are assumed to be adequate – used when an RDA cannot be determined

Tolerable Upper Intake Level (UL) is the highest level of nutrient intake that is likely to pose no risk of adverse health effects for almost all individuals in the general population.

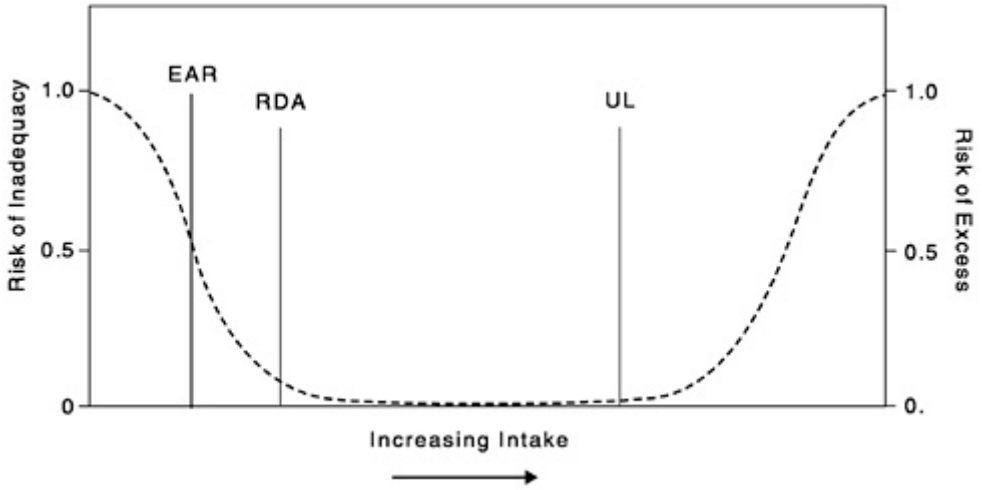

Figure 3: Dietary reference intakes.

NNR -Recommended Intake (NNR Project Group, 2012)

Average Requirement (AR) is defined as the lowest long-term intake level of a nutrient that will maintain a defined level of nutritional status in an individual i.e. the level of a nutrient that is sufficient to cover the requirement for half of a defined group of individuals provided that there is a normal distribution of the requirement.

$AR_{NNR} = EAR_{IOM} = AR_{EFSA}$

Recommended Intake (RI) is defined as the amount of a nutrient that meets the known requirement and maintains good nutritional status among practically all healthy individuals in a particular life stage or gender group. $RI = AR + 2SD_{AR.}$

$RI_{NNR} = RDA_{IOM} = PRI_{EFSA}$

Upper Intake Level (UL) is defined as the maximum level of long-term (months or years) daily nutrient intake that is unlikely to pose a risk of adverse health effects in humans.

$UL_{NNR} = UL_{IOM} = UL_{EFSA}$

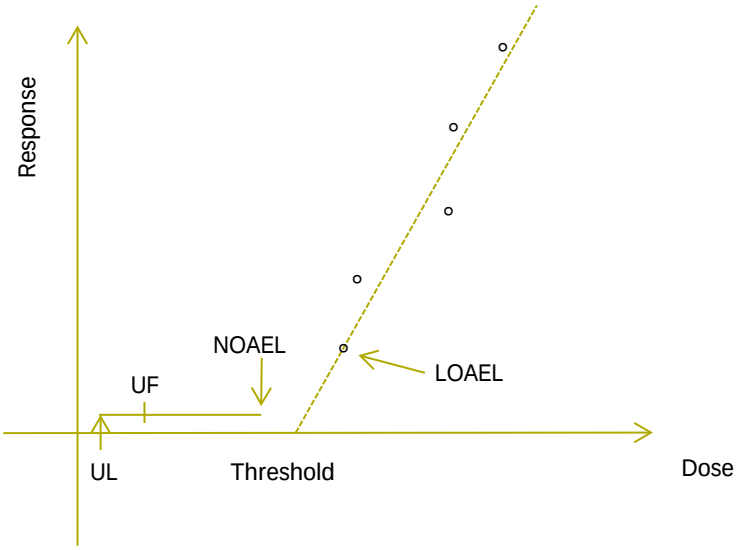

Figure 4: Derivation of Upper Intake Level (UL)

UF: Uncertainty factor

Expert group on vitamins and minerals (EVM), UK (EVM, 2003)

Safe Upper Intake Level (SUL): EVM used SUL instead of UL and defined SUL as the determination of doses of vitamins and minerals that potentially susceptible individuals could take daily on a life-long basis, without medical supervision in reasonable safety. The setting of these levels provided a framework within which the consumer could make an informed decision about intake, having confidence that harm should not ensue. The levels so set will therefore tend to be conservative.

Background as provided by the Norwegian Food Safety Authority

Directive 2002/46/EC on food supplements was implemented into Norwegian law in 2004 in Regulation 20 May 2004 No. 755 on food supplements. Pursuant to Directive 2002/46/EC, common maximum and minimum levels of vitamins and minerals in food supplements shall be set in the EU. The European Commission started to establish common limits in 2006, but the work was temporarily put on standstill in 2009. The time frame for the further work is not known.

National maximum limits for vitamins and minerals were established in the former vitamin and mineral supplements regulation from 1986 and were continued in the 2004 regulation.

The national maximum and minimum limits in the food supplement regulation were established a long time before the food supplement directive was adopted, and the limits were consequently not established in accordance with the criteria for limits set in the food supplement directive. Maximum limits for vitamins and minerals which were not already revised according to the criteria in article 5 in the food supplement directive, were therefore repealed from 30 May 2017.

Maximum limits for levels of vitamins and minerals in food supplements shall be set on basis of the following criteria, pursuant to article 5 in Directive 2002/46/EC:

- Upper safe levels of vitamins and minerals established by scientific risk assessment based on generally accepted scientific data, taking into account, as appropriate, the varying degrees of sensitivity of different consumer groups
- Intake of vitamins and minerals from other dietary sources

When the maximum levels are set, due account should also be taken of reference intakes of vitamins and minerals for the population.

Pending establishment of common maximums limits in the EU, the Norwegian Food Safety Authority is evaluating the national maximum limits for vitamins and minerals in food supplements.

Norwegian authorities will as soon as possible, when it exists a scientific basis, and pending establishment of common maximums limits in the EU, establish new national maximum limits for those vitamins and minerals where limits were repealed 30 May 2017.

Assessment of molybdenum

The Norwegian Food Safety Authority will consider establishing a new national maximum limit for molybdenum in the food supplement regulation.

The former maximum limit for molybdenum was 250 µg per daily dose, but this was repealed from 30 May 2017. The minimum limit and permitted molybdenum substances that may be used in the manufacture of food supplements, are listed in annex 1 and annex 2 in the food supplement regulation.

Terms of reference as provided by the Norwegian Food Safety Authority

The Norwegian Food Safety Authority (NFSA, Mattilsynet) requests the Norwegian Scientific Committee for Food and Environment (VKM) to assess the intake of molybdenum from the diet, in all age groups in the population above 1 year.

As there is no data on molybdenum in the Norwegian food composition data base (KBS), VKM is requested to evaluate if other relevant intake data can be used - included Danish intake data estimated by the Technical University of Denmark (DTU) and the EFSA Scientific Opinion on Dietary Reference Values for molybdenum (2013).

VKM is also requested to evaluate the consequences of establishing a maximum limit for molybdenum in food supplements of 100, 250, 500 or 1000 µg per daily dose, and to evaluate these scenarios against existing tolerable upper intake levels.

Assessment molybdenum

1 Introduction

Molybdenum is an essential mineral commonly found in legumes, including beans, peas and lentils, leafy vegetables, grains, nuts and liver. The molybdenum content of plant foods varies according to the soil content in which the plants are grown. Legumes, grains, and nuts are major contributors of molybdenum in the diet (Pennington and Jones, 1987; Tsongas et al., 1980). Mineral water or "hard" tap water may also contain molybdenum.

Molybdenum is a cofactor for some important enzymes. These include sulfite oxidase, which is necessary for metabolism of sulfur-containing amino acids; xanthine oxidase, which contributes to antioxidant capacity of the blood; aldehyde oxidase, which joins with xanthine oxidase in the metabolism of drugs and toxins; and mitochondrial amidoxime-reducing component, which accelerates the removal of certain toxic substances.

Molybdenum is efficiently absorbed over a large range of intakes, which suggests that molybdenum absorption is a passive process. However, the mechanism of molybdenum absorption (transcellular or paracellular transport) and the location(s) within the gastrointestinal tract responsible for absorption have not been well studied (Nielsen, 1999 cited in IOM, 2001). Molybdenum concentrations in whole blood vary widely, with an average at about 5 nmol/L (Verseick et al., 1978). Protein-bound molybdenum constitutes between 83 and 97 percent of the total molybdenum in erythrocytes. Molybdenum retention may be affected in part through formation of the molybdopterin complex. Urinary excretion is a direct reflection of the dietary molybdenum intake level (Turnlund et al., 1995a; Turnlund et al., 1995b). 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.

Clinical signs of molybdenum deficiency in otherwise healthy humans have not been observed. Symptoms suggestive of molybdenum deficiency have been observed in ruminants when subjected to molybdenum restriction, despite considerable reduction in the activity of molybdoenzymes.

2 Recommendations and tolerable upper intake levels

2.1 Recommendations

There are no Norwegian recommendations for intake of molybdenum. The Nordic Nutrition Recommendations (2012) concluded that no recommendations could be given for molybdenum due to lack of sufficient evidence (NNR Project Group, 2012).

The European Food Safety Authority (EFSA) adopted Dietary Reference Values (DRVs) for molybdenum (EFSA, 2013). EFSA concluded that data is insufficient for deriving Average Requirements (ARs) or Population Reference Intakes (PRIs). Adequate Intakes (AIs) at 65 µg/day was proposed for adults, including pregnant and lactating women. Observed molybdenum intakes from mixed diets in Europe were taken into consideration in setting this value. The AIs by age categories are presented in Table 2.1-1.

Table 2.1-1 Adequate Intakes for molybdenum from EFSA (2013).

Age, both sexes	µg/day
1-3 years	15
4-6 years	20
7-10	30
11-14 years	45
15-17 years	65
≥18 years*	65

*Including pregnancy and lactation.

2.2 Tolerable upper intake levels

In general, molybdenum compounds are considered to have low toxicity in humans. There are limited toxicity data on molybdenum in humans and most of the toxicity data are for animals, especially ruminants. Ruminants are more sensitive to molybdenum than monogastric animals, and the basis for the toxicity of molybdenum in ruminants may not be relevant for humans. Molybdenum toxicity in animals varies highly according to species, age, sex, and duration of exposure (Vyskocil and Viau, 1999). 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). None of the above-mentioned effects in animals have been observed in humans, and it is accordingly impossible to determine which ones might be considered relevant in humans.

Scientific Committee on Food (SCF, 2000), EU

In 2000, The Scientific Committee on Food (SCF) established an UL using a 9-week rat study, which was pivotal because of its design, the number of animals, demonstration of a clear dose-response relationship and clear toxicological endpoints (Fungwe et al., 1990). The no observed adverse effect level (NOAEL) in this study was found to be 0.9 mg/kg bw/day for reproductive toxicity. SCF used an uncertainty factor (UF) of 100 because the evidence base was considered to be weak. This comprised a factor of 10 for protecting human sub-populations sensitive to copper deficiencies due to high molybdenum intake (as a result of molybdenum-copper antagonism), and another factor of 10 due to the lack of knowledge about reproductive effects of molybdenum in humans and incomplete data on the toxicokinetics in man. This provided an UL of approximately 0.01 mg/kg bw/day, equivalent to 0.6 mg/person/day for adults, which also covered pregnant and lactating women. The UL for children was derived by extrapolating from the adult UL on a body weight basis using the reference body weights for Europe published by the SCF (SCF, 1993).

Table **2.2-2** Tolerable upper intake levels for molybdenum in different age groups suggested by the SCF (2000).

Age (years)	UL mg/day
1-3	0.1
4-6	0.2
7-10	0.25
11-14	0.4
15-17	0.5
Adults*	0.6

*Including lactation and pregnancy.

Institute of Medicine (IOM, 2001), USA

The U.S. Institute of Medicine (IOM) established an UL in 2001 which also was based mainly on data from animal studies.

The study by Fungwe et al. (1990) provided a dose-response relationship for adverse reproductive effects in female rats. The NOAEL from this study was 0.9 mg/kg/day and the lowest observed adverse effect level (LOAEL) was 1.6 mg/kg/day of molybdenum. This study was supported by observations of reproductive effects in mice in a three-generation study at a single dose of 1.5 mg/kg/day (Schroeder and Mitchener, 1971). Since only one dose level was used in this study, it was difficult to use this study independently to determine a LOAEL. In addition, Jeter and Davis (1954) noted decreased fertility in male rats after 13 weeks of exposure to 8 mg/kg/day of molybdenum. The NOAEL from that study was 2 mg/kg/day. IOM stated that these observations suggested that numerous adverse reproductive effects were encountered in rats and mice at dietary molybdenum levels exceeding the NOAEL of 0.9 mg/kg/day established from the study of Fungwe et al. (1990).

IOM argued that there was not sufficient data to justify lowering the degree of uncertainty from the usual UF for extrapolating from experimental animals to humans. Thus, the usual value of 10 was selected. An UF of 3 for intra-species variation was based on the expected similarity in pharmokinetics of molybdenum among humans. Although Vyskocil and Viau (1999) had argued for a larger UF for intraspecies differences, they had based their concerns on possible interactions with copper and concerns about copper-deficient humans. IOM stated that recent information suggested that molybdenum does not have any effect on copper metabolism in humans (Turnlund and Keyes, 2000 cited in IOM, 2001), and used an UF of 30.

The NOAEL of 0.9 mg/kg/day was divided by the overall UF of 30 to obtain an UL of 30 µg/kg/day for humans. The value of 30 µg/kg/day was multiplied by the average of the reference body weights for adult women, 61 kg. The resulting UL for adults was rounded to 2 mg/day (2000 µg/day).

Although adult men and women have different reference body weights, the uncertainties in the estimation of the UL were considerable and distinction of separate ULs for men and women was therefore not attempted. A common UL for both genders at 2 mg/day was also supported by limited human data from Deosthale and Gopalan (1974) who demonstrated no effect on uric acid or copper excretion in humans exposed to 1.5 mg/day for an adult. The adult UL of 2 mg/day was adjusted for children and adolescents on the basis of relative body weights.

Table 2.2-1 Tolerable upper intake levels for molybdenum in different age groups suggested by the IOM (2001).

Age (years)	UL mg/day
1-3	0.3
4-8	0.6
9-13	1.1
14-18*	1.7
19 and older*	2

*Including lactation and pregnancy

Expert Group on Vitamins and Minerals (EVM, 2003), UK

The UK Expert Group on Vitamins and Minerals (EVM) concluded: “There are insufficient data from human (Kovalsky et al., 1961) or animal studies (Fairhall et al., 1945; Arrington & Davies, 1953; Schroeder & Mitchener, 1971) to establish a safe upper level for molybdenum”, and refrained from adopting or defining any upper level for molybdenum.

Nordic Nutrition Recommendations (NNR, 2012)

The Nordic Nutrition recommendations (NNR Project Group, 2012) did not conclude on any ULs and merely cited the conclusions from the reports above.

2.2.1 Summary tolerable upper intake levels

Conclusions concerning ULs from previous reports for molybdenum from the SCF and IOM are shown in Table 2.2.1-1. The ULs are based on the same animal studies, but the SCF have argued for an UF at 100, whereas the IOM have used a lower UF at 30, and have consequently concluded on a higher UL than the SCF.

Table 2.2.1-1 Overview of ULs in adults set by various authorities.

	UL µg/day	Based on	NOAEL	LOAEL	UF
IOM, 2001	2000	Rat studies	0.9 mg/kg/day	1.6 mg/kg/day	30
SCF, 2000	600	Rat studies	0.9 mg/kg/day	1.6 mg/kg/day	100
EVM, 2003	-	-	-	-	-
NNR, 2012	-	-	-	-	-

3 Intakes and scenarios for molybdenum

There are no data on habitual intake of molybdenum in the Norwegian population, because no available data exists for molybdenum in the Norwegian food composition table. We have therefore used data from Denmark.

Through communication with the Danish Veterinary and Food Administration, NFSA has obtained data on median and 95th percentile dietary molybdenum intakes in Denmark calculated by the Technical University of Denmark (DTU).

The Danish molybdenum data are obtained from the nationally representative survey of diet and physical activity in the Danish population aged 4-75 years, carried out in 2011-2013 (DANSDA) (DTU, 2015). Diet was assessed through a 4-day food record. According to the DTU, the intake estimates for molybdenum are considered to be of high uncertainty, and the estimates of the intake of molybdenum should be interpreted with caution.

EFSA published intake data of molybdenum from several European counties in the DRV-report from 2013 (EFSA, 2013). The mean intakes in adults were mainly reported to be in the range between 75 and 157 µg/day.

Table 3-1 Estimated median and 95-percentile of dietary intake of molybdenum from food (µg/day) in age and gender groups in Denmark.

Age group	Median intakes from food	P95 from food
1-3 years	30	45
4-6 years	41	68
7-10 years	46	85
11-14 years	40	69
15-17 years	41	78
25-34 years (women)	49	79
55-75 years (women)	54	93
65-75 years (women)	52	93
25-34 years (men)	59	103
65-75 years (men)	61	103

3.1 Scenario calculations for molybdenum

For scenario calculations VKM used the intake group at P95 from food alone estimated from intake data in the Danish population to calculate molybdenum intake and added the suggested supplementation levels from NFSA (100, 250, 500 or 1000 µg molybdenum per day).

Table 3.1-1 Calculated total molybdenum intakes for various age groups in scenarios with 100, 250, 500 or 1000 µg as supplements added to the P95 of intake from food alone (µg/day).

Age group	P95 from food	Including 100 µg from suppl	Including 250 µg from suppl	Including 500 µg from suppl	Including 1000 µg from suppl
1-3 years	45	145	295	545	1045
4-6 years	68	168	318	568	1068
7-10 years	85	185	335	585	1085
11-14 years	69	169	319	569	1069
15-17 years	78	178	328	578	1078
25-34 years (women)	79	179	329	579	1079
55-75 years (women)	93	193	343	593	1093
65-75 years (women)	93	193	343	593	1093
25-34 years (men)	103	203	353	603	1103
65-75 years (men)	103	203	353	603	1103

4 Assessment of the intakes of molybdenum

For assessment of the intakes of molybdenum, VKM has used the UL from SCF of 600 µg per day for adults and bodyweight adjusted values for children and adolescents. This is the lowest of the two available ULs. VKM decided to apply the lower of the two because of the limited toxicity data on molybdenum in humans. Most of the toxicity data used to set the existing ULs are extrapolated from animal studies. This justifies use of the default uncertainty factor of 100 for extrapolation of data from animal studies to humans (10 for inter-species variability x 10 for intra-human variability). Furthermore, molybdenum deficiency is generally not observed in humans and there are no studies indicating a need for additional molybdenum from dietary supplements.

The Danish molybdenum intake data are considered to be the best available as no data are available for the Norwegian population. The mean intakes of molybdenum varies throughout Europe, and there is no scientific basis for assessing whether the Danish intake is representative of Norwegian conditions.

The Danish intakes of molybdenum in the 95th percentile from food alone are well below the ULs in all age groups. The median intakes in some adult age groups may be below the Adequate Intakes described in chapter 2. However, the Danish molybdenum estimates are considered to be of high uncertainty, and no molybdenum deficiency have been reported in human studies.

4.1 Evaluation of molybdenum intakes, including scenarios with supplementation

According to the scenario estimations in adults, the dietary molybdenum intake at the 95th percentile and additionally 100, 250 or 500 µg molybdenum from food supplements will be approximately at or below the UL while 1000 µg molybdenum from food supplements will lead to exceedance of the UL for adults. It should be noted that adding 500 µg of molybdenum slightly exceeded the UL for adult males. This is not considered to be of health concern because the lower of the two available ULs were used.

For 1-3 year old children, all the suggested maximum limits for molybdenum will lead to exceedance of the UL. In children 4-10 years, supplements with 250, 500 or 1000 µg molybdenum will lead to exceedance of the ULs, whereas for adolescents 11-17 years, the UL will be exceeded with supplemental doses at 500 or 1000 µg per day.

5 Uncertainties

For the determinations of the ULs for molybdenum, SCF and IOM arrived at different conclusions. EVM and NNR did not conclude, emphasising the uncertainty regarding establishment of these ULs for adults as well as for children and adolescents.

There are no long-term clinical studies investigating potential benefits and harms from molybdenum intake in humans. As molybdenum toxicity in animals is highly variable, extrapolation from animal studies to humans are considered to be uncertain.

There were no data for molybdenum intake from Norway. We have therefore used data from Denmark which may not reflect the situation in Norway well. The Danish data are considered to be of high uncertainty.

6 Answers to the terms of reference

The Norwegian Food Safety Authority (NFSA, Mattilsynet) has requested the Norwegian Scientific Committee for Food and Environment (VKM) to assess the intake of molybdenum from the diet, in all age groups in the population above 1 year.

VKM was also requested to evaluate the consequences of establishing a maximum limit for molybdenum in food supplements of 100, 250, 500 or 1000 µg per daily dose, and to evaluate these scenarios against existing tolerable upper intake levels.

In the assessment of molybdenum, VKM uses the tolerable upper intake level established by the SCF at 600 µg/day for adults. According to the scenario estimations in adults, the dietary molybdenum intake at the 95th percentile and additionally 100, 250 or 500 µg molybdenum from food supplements will be approximately at or below the UL. Because we are using the lower of the two ULs and because molybdenum compounds in general are considered to have low toxicity in humans, we accept an estimated intake from the 95th percentile at or slightly above the UL. Intake of 1000 µg molybdenum from food supplements will lead to exceedance of the UL for adults.

For 1-3 year old children, all the suggested maximum limits for molybdenum will lead to exceedance of the UL. In children 4-10 years, supplements with 250, 500 or 1000 µg molybdenum will lead to exceedance of the ULs, whereas for adolescents 11-17 years, the UL will be exceeded with supplemental doses at 500 or 1000 µg per day.

VKM emphasises that the current assessment of maximum limits for molybdenum in food supplements is merely based on published reports concerning upper levels from the SCF (2000, EU), IOM (2001, USA), EVM (2003, UK) and NNR (2012, Nordic countries). VKM has not conducted any systematic review of the literature for the current opinion, as this was outside the scope of the terms of reference from NFSA.

7 Data gaps

There are little data from human and animal studies on the toxicity of molybdenum from the diet or from supplements. There are also no data on the intake of molybdenum in the Norwegian population.

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