DRAFT SCIENTIFIC OPINION

Scientific Opinion on Dietary Reference Values for molybdenum[1]

EFSA Panel on Dietetic Products, Nutrition, and Allergies (NDA)[2, 3]

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ABSTRACT

Following a request from the European Commission, the Panel on Dietetic Products, Nutrition and Allergies (NDA) derived dietary reference values (DRVs) for molybdenum. Molybdenum is efficiently and rapidly absorbed at a wide range of intakes, and the body is able to maintain homeostasis through the regulation of excretion via the urine. Molybdenum deficiency in otherwise healthy humans has not been observed and there are no biomarkers of molybdenum status. Various metabolic balance studies have been performed to establish molybdenum requirements. However, only one balance study in adult men, performed with a constant diet and under controlled conditions, was considered to be of sufficient duration. In this small study, balance was reported to be near zero when molybdenum intakes were 22 µg/day. Biochemical changes or symptoms suggestive of molybdenum deficiency were not observed, and it is possible that humans may be able to achieve molybdenum balance at even lower intakes. Data on molybdenum intakes and health outcomes were unavailable for the setting of DRVs for molybdenum. As the evidence required to derive an Average Requirement and a Population Reference Intake was considered insufficient, an Adequate Intake (AI) is proposed. Observed molybdenum intakes from mixed diets in Europe were taken into consideration in setting this value. An AI of 65 µg/day is proposed for adults, a figure that is based on molybdenum intakes at the lower end of the wide range of observed intakes. It is suggested that the adult AI also applies to pregnant and lactating women. An AI is also proposed for infants from seven months and for children based on extrapolation from the adult AI using allometric scaling and the reference body weights of the respective age groups. © European Food Safety Authority, 20YY

KEY WORDS

Molybdenum, Adequate Intake, Dietary Reference Value

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SUMMARY

Following a request from the European Commission, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver a scientific opinion on Dietary Reference Values (DRVs) for the European population, including molybdenum.

Molybdenum is an essential component of certain flavin- and iron-containing enzymes. In humans, sulphite oxidase, xanthine oxidoreductase, aldehyde oxidase and mitochondrial amidoxime reducing component require molybdenum linked with a pterin (molybdopterin) as the cofactor. These enzymes are involved in the metabolism of aromatic aldehydes and the catabolism of sulphur-containing amino acids and heterocyclic compounds, including purines, pyrimidines, pteridins and pyridines.

In humans, a single case report of a syndrome suggestive of dietary molybdenum deficiency in a patient on total parenteral nutrition for several months has been reported, but clinical signs of molybdenum deficiency in otherwise healthy humans have not been observed. A distinct molybdenum deficiency syndrome has not been observed in animals when subjected to molybdenum restriction, despite considerable reduction in the activity of molybdoenzymes.

Water-soluble molybdates are efficiently and rapidly absorbed from the digestive tract at a wide range of intakes, and the body is able to adapt to this wide intake range by regulating excretion via the urine. Storage of molybdenum in mammals is low, and most tissue molybdenum is thought to be associated with molybdoenzymes.

There are no suitable biomarkers of molybdenum status. Biochemical changes observed in subjects with molybdopterin cofactor deficiency, a genetic disorder, or in the one subject reported with possible molybdenum deficiency, have not been observed in healthy individuals on varying levels of molybdenum intake. Low activity of molybdoenzymes in tissues, or changes in substrate/product relationships, are considered as insufficiently specific to be used as biomarkers of status.

Molybdenum is present in nearly all foods in trace amounts as soluble molybdates. Foods high in molybdenum are pulses, cereal grains and grain products, offal (liver, kidney) and nuts. Cereals and cereal-based products including bread are the major food contributors to the dietary molybdenum intake of adults. Mean molybdenum intakes of adults in various European countries as assessed in duplicate diet or food portion studies, total diet studies and market basket studies vary over a wide range, i.e. 58 µg/day to 157 µg/day. Mean intakes are at or above 100 µg/day in five of the eight European countries for which data are available. Molybdenum intakes of children are only available from two European countries.

In 1993, the Scientific Committee for Food did not publish DRVs for molybdenum. More recently, other authorities have set DRVs for molybdenum and these are based on the maintenance of molybdenum homeostasis as measured in balance studies, taking into account molybdenum bioavailability from various food sources, or are based on observed molybdenum intakes with a mixed diet.

Various balance studies have been performed to establish molybdenum requirements. However, only one balance study in adults was considered to be of sufficient duration, and was performed with a constant diet and under controlled conditions. In this study carried out in four men, balance was reported to be near zero from day 49 until day 102 of the depletion period when intakes were as low as 22 µg/day. Biochemical changes or symptoms suggestive of molybdenum deficiency were not observed and the possibility that humans may be able to achieve molybdenum balance at even lower intakes cannot be excluded. Results of two balance studies with some methodological limitations were reported in children, but these studies cannot be used to derive an average molybdenum requirement for children. Data on molybdenum intakes and health outcomes were unavailable for the setting of DRVs for molybdenum.

As the evidence to derive an Average Requirement (AR), and thus a Population Reference Intake, was considered insufficient, an Adequate Intake (AI) is proposed. An AI of 65 µg/day is proposed for adult men and women based on mean molybdenum intakes at the lower end of the wide range of observed intakes from mixed diets in Europe. Due to the scarcity of data on molybdenum intakes in pregnant and lactating women, it is suggested that the adult AI also applies to pregnant and lactating women. For infants from seven months and children, it was decided that an AR could not be established, and an AI is proposed based on extrapolation from the adult AI using allometric scaling, i.e. extrapolation based on metabolic weight and reference body weights of the respective age groups. The respective AIs vary between 15 µg molybdenum/day in infants aged 7-11 months and 65 µg/day in adolescent boys and girls.

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BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

The scientific advice on nutrient intakes is important as the basis of Community action in the field of nutrition, for example such advice has in the past been used as the basis of nutrition labelling. The Scientific Committee for Food (SCF) report on nutrient and energy intakes for the European Community dates from 1993. There is a need to review and if necessary to update these earlier recommendations to ensure that the Community action in the area of nutrition is underpinned by the latest scientific advice.

In 1993, the SCF adopted an opinion on the nutrient and energy intakes for the European Community[4]. The report provided Reference Intakes for energy, certain macronutrients and micronutrients, but it did not include certain substances of physiological importance, for example dietary fibre.

Since then new scientific data have become available for some of the nutrients, and scientific advisory bodies in many European Union Member States and in the United States have reported on recommended dietary intakes. For a number of nutrients these newly established (national) recommendations differ from the reference intakes in the SCF (1993) report. Although there is considerable consensus between these newly derived (national) recommendations, differing opinions remain on some of the recommendations. Therefore, there is a need to review the existing EU Reference Intakes in the light of new scientific evidence, and taking into account the more recently reported national recommendations. There is also a need to include dietary components that were not covered in the SCF opinion of 1993, such as dietary fibre, and to consider whether it might be appropriate to establish reference intakes for other (essential) substances with a physiological effect.

In this context, EFSA is requested to consider the existing Population Reference Intakes for energy, micro- and macronutrients and certain other dietary components, to review and complete the SCF recommendations, in the light of new evidence, and in addition advise on a Population Reference Intake for dietary fibre.

For communication of nutrition and healthy eating messages to the public it is generally more appropriate to express recommendations for the intake of individual nutrients or substances in food-based terms. In this context, EFSA is asked to provide assistance on the translation of nutrient based recommendations for a healthy diet into food based recommendations intended for the population as a whole.

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

In accordance with Article 29 (1)(a) and Article 31 of Regulation (EC) No. 178/2002, the Commission requests EFSA to review the existing advice of the Scientific Committee for Food on population reference intakes for energy, nutrients and other substances with a nutritional or physiological effect in the context of a balanced diet which, when part of an overall healthy lifestyle, contribute to good health through optimal nutrition.

In the first instance the EFSA is asked to provide advice on energy, macronutrients and dietary fibre. Specifically, advice is requested on the following dietary components:

- Carbohydrates, including sugars;
- Fats, including saturated fatty acids, polyunsaturated fatty acids and monounsaturated fatty acids, *trans* fatty acids;

[4] Scientific Committee for Food, Nutrient and energy intakes for the European Community, Reports of the Scientific Committee for Food 31st series, Office for Official Publication of the European Communities, Luxembourg, 1993.

- Protein;
- Dietary fibre.

Following on from the first part of the task, EFSA is asked to advise on population reference intakes of micronutrients in the diet and, if considered appropriate, other essential substances with a nutritional or physiological effect in the context of a balanced diet which, when part of an overall healthy lifestyle, contribute to good health through optimal nutrition.

Finally, EFSA is asked to provide guidance on the translation of nutrient-based dietary advice into guidance, intended for the European population as a whole, on the contribution of different foods or categories of foods to an overall diet that would help to maintain good health through optimal nutrition (food-based dietary guidelines).

ASSESSMENT

1. Introduction

Molybdenum is required as a component of enzymes involved in the catabolism of sulphur amino acids and heterocyclic compounds, as well as in the metabolism of aromatic aldehydes. Because of its role in metabolism, molybdenum is considered an essential dietary element for mammals, though clinical signs of dietary molybdenum deficiency in otherwise healthy humans have not been described. In 1993, the Scientific Committee for Food did not publish Dietary Reference Values (DRVs) for molybdenum (SCF, 1993), but more recently other authorities have set DRVs for molybdenum.

2. Definition/category

2.1. Chemistry

Molybdenum (Mo) is a Periodic Group 6 element (transition metal) existing in several valence states, the most stable being (+IV) and (+VI). Molybdenum is widely distributed in nature, the abundance in the earth's crust being about 1-1.5 mg molybdenum/kg (SCF, 2000; Eckhert, 2006). It is ubiquitous in food and water as soluble molybdates ($Mo(VI)O_4^{2-}$).

2.2. Functions of molybdenum

2.2.1. Biochemical functions

Molybdenum-containing enzymes are found in many plants and animal organisms. Due to the redox potential of Mo(IV)/Mo(VI), the most important function in mammals is the transfer of oxygen to a two-electron substrate using electron-transferring compounds such as flavin adenine dinucleotide. Molybdenum is an essential component of some flavin- and iron-containing enzymes (Rajagopalan, 1988). In humans, sulphite oxidase, xanthine oxidoreductase, aldehyde oxidase and mitochondrial amidoxime reducing component require molybdenum linked with a pterin (molybdopterin) as cofactor (Reiss and Hahnewald, 2011). These enzymes are involved in the catabolism of sulphur-containing amino acids and heterocyclic compounds, including purines, pyrimidines, pteridins and pyridines, and in the metabolism of aromatic aldehydes.

2.2.2. Health consequences of deficiency and excess

2.2.2.1. Deficiency

A distinct molybdenum deficiency syndrome has not been described in animals when subjected to molybdenum restriction, despite considerable reduction in the activity of molybdoenzymes. For example, using low-molybdenum diets and administration of tungsten in drinking water, the activity of rat liver xanthine oxidase was decreased to 10 % of its normal value without changing the excretion of uric acid or allantoin or otherwise affecting the health of the animals. Likewise, adult rats with less than 3 % residual liver sulphite oxidase activity remained healthy and showed no signs of neurological damage (Cohen et al., 1973; Johnson et al., 1974).

In humans, there is one published case report of a syndrome suggestive of dietary molybdenum deficiency. A 24-year-old male patient with Crohn's disease and short bowel syndrome was on total parenteral nutrition (TPN) lacking in molybdenum for 12 months, at which point he developed a syndrome characterised by tachycardia, tachypnea, severe headache, nausea and vomiting, night

blindness, and central scotomas, which progressed to oedema, lethargy, disorientation and coma. These symptoms were associated with high plasma methionine and low serum uric acid concentrations, as well as reduced urinary concentrations of sulphate, thiosulphate, and uric acid. Whilst modification of the TPN solution by lowering the sulphur load was ineffective, treatment with ammonium molybdate (300 µg/day)[5] resulted in considerable improvement of the clinical symptoms and progressive reversal of the biochemical abnormalities within 30 days (Abumrad et al., 1981). Clinical signs of molybdenum deficiency in otherwise healthy humans have not been observed.

Molybdenum cofactor deficiency, a rare autosomal recessive syndrome with a defective hepatic synthesis of molybdenum cofactor, results in deficiency of all molybdoenzymes in humans. This genetic defect, for which three subtypes are known according to the gene affected, has been found in a variety of ethnic groups and all over the world (Reiss and Hahnewald, 2011). It is associated with feeding difficulties and seizures starting shortly after birth, neurological and developmental abnormalities, mental retardation, encephalopathy, ectopy of the lens and usually death at an early age, though the successful treatment of one affected child with molybdenum cofactor deficiency type A using the first detectable intermediate substance in the biosynthesis pathway of molybdenum cofactor has recently been reported (Veldman et al., 2010; Mendel and Kruse, 2012). In untreated patients, plasma concentrations of urate are low, urinary concentrations of sulphite, thiosulphate and S-sulpho-L-cysteine are increased, and urinary urate and sulphate concentrations are decreased.

2.2.2.2. Excess

The Scientific Committee on Food (SCF) has set a Tolerable Upper Intake Level (UL) of 0.6 mg/day for adults, including pregnant and lactating women, based on a No Observed Adverse Effect Level (NOAEL) for reproductive toxicity derived in a study with rats. For children from one year of age onwards, the UL was extrapolated from the adult UL on a body weight basis, and was set at between 0.1 and 0.5 mg/day (SCF, 2000).

2.3. Physiology and metabolism of molybdenum

2.3.1. Intestinal absorption

Water-soluble molybdates are readily absorbed from the digestive tract. Balance studies with stable isotopes have shown that molybdenum is efficiently and rapidly absorbed at a wide range of intakes, indicating that molybdenum absorption is passive and not saturable, and that it is not regulated at the level of intestinal absorption (Turnlund et al., 1995a).

At doses up to about 1 mg, molybdenum dissolved in water is completely absorbed into the systemic circulation. Molybdenum absorption in the presence of solid foods (cress, green salad, tomatoes, bean soup) is lower compared to administration with water (Giussani et al., 2006; Giussani et al., 2007). When added to a beverage containing starch, dextrimaltose, oil, sucrose, α-cellulose and minerals, the absorption efficiency of increasing doses of ^{100}Mo ranging from 24 to 1 378 µg was between 90 and 94 % in healthy men (Novotny and Turnlund, 2006, 2007). Black tea has been shown to considerably reduce molybdenum absorption upon ingestion of relatively high amounts of molybdenum (0.5-1 mg as a single dose of stable isotope) (Giussani et al., 2006; Giussani et al., 2007). In ten premature infants, absorption of the stable isotope ^{100}Mo from infant formula was 97.5 % (96.3-99.1 %) after receiving 25 µg molybdenum/kg body weight (Sievers et al., 2001).

[5] Reported as such by Abumrad et al. (1981), without additional information (e.g. molecular weight) of the compound used. Others have interpreted this as a molybdenum dose of 147 µg/day (WHO, 1996) or 300 µg/day (Rajagopalan, 1988).

Studies using kale or soy intrinsically labeled with stable isotopes of molybdenum have shown that molybdenum absorption was 86.1 % and 56.7 %, respectively, from meals with either kale or soy casseroles containing about 100 µg molybdenum. Molybdenum absorption from an extrinsic label also added to the meals was 87.5 %. When the molybdenum content of the meal was increased to about 310 µg in a subsequent study, molybdenum absorption from soy amounted to 58.3 %, and molybdenum absorption from the extrinsic label was 92.8 % (Turnlund et al., 1999).

Using a compartmental model based on a molybdenum depletion-repletion study in four men, the mean bioavailability of molybdenum from the experimental diet was predicted to be 76 % (Novotny and Turnlund, 2006). A slightly higher bioavailability of 83 % for food-bound molybdenum was predicted with the compartmental model, based on a study which gave the same three-day rotating diet regimen but with five different molybdenum contents consecutively for 24 days each to four men (Novotny and Turnlund, 2007).

Little is known about the mechanism of molybdenum absorption and the site of absorption in the gastrointestinal tract. In animals, Mo(VI) but not Mo(IV) is readily absorbed from the duodenum and proximal jejunum (SCF, 2000). Recently, a family of proteins probably related to molybdate transport in animals and humans has been described, though the exact location of this high-affinity transporter within the cell has not yet been identified (Tejada-Jimenez et al., 2011; Mendel and Kruse, 2012). It is assumed that in addition to a possible high-affinity uptake system, molybdate may also enter the cell nonspecifically through the sulphate uptake system, which has been shown to be present in plants (Fitzpatrick et al., 2008).

Tungsten is known to inhibit molybdenum uptake, and this inhibitory effect has been used in animal studies to induce molybdenum deficiency, but it is not considered relevant for humans because of the rare occurrence of tungsten in the environment and consequently in the food chain (Cohen et al., 1973; Johnson et al., 1974; Rajagopalan, 1988; Eckhert, 2006). In sheep and rats, high sulphate intakes have been shown to inhibit molybdenum absorption, suggesting that both sulphate and molybdenum share a common transport mechanism (Eckhert, 2006). An interaction with copper has been observed leading to copper deficiency in sheep exposed to high molybdenum intake. In ruminants, excessive intakes of molybdenum lead to formation of thiomolybdate in the sulphide-rich environment of the rumen; thiomolybdate (a molecule where sulphur groups surround a molybdenum centre) is a chelator of copper ions, thereby inhibiting copper absorption (Nederbragt et al., 1984). By contrast, in humans, clinical symptoms of copper deficiency are largely confined to individuals with rare genetic defects in copper metabolism (Suttle, 2012). In four adult males on two sorghum diets providing daily 2.4 mg of copper and 166 µg or 540 µg of molybdenum, respectively, faecal copper excretion was comparable and apparent copper absorption unaffected by molybdenum intake (Deosthale and Gopalan, 1974).

2.3.2. Transport in blood

In animals and humans, little is known about proteins involved in molybdenum transport (Llamas et al., 2011). Specific binding to α-2-macroglobulin, but not to albumin, has been shown in *in vitro* studies after incubation of human serum with ^{99}Mo (Kselikova et al., 1977), though it is thought that the fraction bound to α-2-macroglobulin is small and that most molybdenum remains in the blood as molybdate (MoVI) which does not bind to α-2-macroglobulin (Bibr et al., 1985). Part of the molybdenum in the blood is transported in erythrocytes after uptake through a membrane anion exchanger (Gimenez et al., 1993). In erythrocytes, most molybdenum is protein-bound (IoM, 2001).

Molybdenum concentrations in plasma measured with more sensitive and accurate techniques (ICP-MS) have been reported to range between 3-11 nmol/L in people with usual molybdenum intakes (Turnlund and Keyes, 2004).

Intravenously infused molybdenum disappears rapidly from the blood; depending on the tracer dose given, the plasma tracer concentration was approximately halved or even lower within two hours after injection (Cantone et al., 1995; Giussani et al., 2006).

2.3.3. Distribution to tissues

The highest molybdenum concentrations are found in the liver and kidney. In adults, the liver contains 1.3-2.9 mg molybdenum/kg dry matter, the kidney 1.6 mg/kg dry matter, the lung 0.15 mg/kg dry matter, the brain and muscle 0.14 mg/kg dry matter (WHO, 1996), and for hair concentrations of 0.03 mg/kg (Ochi et al., 2011) have been reported. Total body molybdenum of a "standard man" was calculated to be about 2.3 mg after analysis of tissues from 150 accidental deaths (Schroeder et al., 1970), and about 2.2 mg with the use of a compartmental model and fractional transfer coefficients observed at a molybdenum intake of 121 µg/day given for 24 days, and which was considered to be in line with the habitual molybdenum intake of participants prior to the study (Novotny and Turnlund, 2007).

2.3.4. Storage

Storage of molybdenum in mammals is low. Most tissue molybdenum is thought to be associated with molybdoenzymes, as indicated by the reported absence of detectable molybdenum in the liver tissue of molybdenum cofactor-deficient patients (Rajagopalan, 1988).

In the liver of fetuses (age: 23 weeks of gestation to term), molybdenum concentrations were more than seven-fold lower compared to adults (Meinel et al., 1979), and such differences have subsequently been interpreted as the absence of molybdenum stores and a low fetal molybdenum requirement (Abramovich et al., 2011).

2.3.5. Metabolism

In order to fulfill its biological role, molybdenum must enter the cell and be assembled into a molybdenum cofactor. In eukaryotes, the molybdate transport process and the proteins involved are not fully understood (Llamas et al., 2011).

Molybdenum cofactor is synthesised in the cytosol by a conserved biosynthetic pathway that can be divided into four main steps. In the final step of molybdenum cofactor biosynthesis, a single molybdenum ion is bound to one or two molybdopterin dithiolates. After completion of biosynthesis, mature molybdenum cofactor has to be inserted into molybdoenzymes. A molybdenum cofactor carrier protein has been described in the green alga *Chlamydomonas rheinhardtii*, but information is lacking for other eukaryotes (Llamas et al., 2006). The formation of active molybdoenzymes depends not only on the availability of molybdenum but also on the presence of iron, zinc and copper (Llamas et al., 2011).

2.3.6. Elimination

2.3.6.1. Kidney

Absorbed molybdenum is rapidly excreted via the kidney, and whole body retention is regulated primarily by urinary excretion. Depending on the dose of stable isotope (^{95}Mo or ^{96}Mo) injected, 34 % to about 60 % of the injected tracer was excreted in the urine within one day, and between 42 and about 70 % within five days, following its injection (Werner et al., 2000). Studies using different doses of molybdenum intake have shown that about 60 % of the total amount of molybdenum excreted was via the urine when dietary molybdenum intake was very low (22 µg/day), whereas the

proportion excreted via the urine increased to more than 90 % when dietary molybdenum intake was high (467 µg/day or up to 1 488 µg/day) (Turnlund et al., 1995a; Turnlund et al., 1995b). When dietary molybdenum intake is low, mechanisms such as an increased fractional transfer from plasma to tissues act to reduce urinary molybdenum excretion and to conserve body molybdenum (Turnlund et al., 1995a; Novotny and Turnlund, 2006, 2007).

2.3.6.2. Faeces

Molybdenum excretion via the faeces is low. Upon oral ingestion of the stable isotope ^{100}Mo (at doses increasing from 23.8 µg to 1 378 µg) by four young men, an average of between 7.3 and 12.3 % of the dose fed was excreted in their faeces in the 12 days after each dose (Turnlund et al., 1995a).

2.3.6.3. Breast milk

Molybdenum concentrations in human milk sampled at various stages of lactation are shown in Appendix A and these include seven studies on human milk molybdenum concentrations from women residing in the EU. Only one study measured maternal molybdenum intake (132 ± 60 µg/day). This study on 19 women did not find a correlation between maternal molybdenum intake and breast milk concentration (Wappelhorst et al., 2002). For all studies shown in Appendix A and including colostrum, transitory and mature human milk, the concentration of molybdenum was highly variable ranging from 0.001 to 63 µg/L, with mean values from 0.348 to 24 µg/L.

Molybdenum concentrations of human milk appear to be highest during the first few days of breastfeeding, and decrease during the course of lactation (Dang et al., 1984; Casey and Neville, 1987; Bouglé et al., 1988; Aquilio et al., 1996; Krachler et al., 1998; Friel et al., 1999) (Appendix A). In mature human milk[6] from women in Europe, mean molybdenum concentrations were reported to range from 0.72 to 4 µg/L.

2.4. Biomarkers

2.4.1. Biomarkers of intake

Plasma molybdenum concentrations reflect longer-term molybdenum intake, but 24-hour urinary excretion is more directly related to recent intake and appears to be a suitable biomarker of short term molybdenum intake (Turnlund and Keyes, 2004).

2.4.2. Biomarkers of status

Biochemical changes observed in subjects with genetic molybdopterin cofactor deficiency or in the one subject with molybdenum deficiency (low urinary and serum uric acid, elevated plasma methionine, high urinary excretion of hypoxanthine and xanthine, abnormal excretion of sulphur metabolites) have not been observed in healthy individuals on varying levels of molybdenum intake (Turnlund et al., 1995a; Turnlund et al., 1995b).

Low activity of molybdoenzymes in tissues (e.g. of xanthine dehydrogenase) or changes in substrate/product relationships are considered as insufficiently specific to be used as biomarkers of status, as they are also influenced by the intake of other dietary components such as protein/amino acids (WHO, 1996).

The Panel concludes that there is no useful biomarker of molybdenum status.

[6] Mature human milk is usually defined as human milk obtained after 14 days of lactation (Montagne et al., 2001).

3. Dietary sources and intake data

3.1. Dietary molybdenum sources

Molybdenum is present in nearly all foods in trace amounts as soluble molybdates. Foods high in molybdenum are pulses, cereal grains and grain products, offal (liver, kidney) and nuts (Pennington and Jones, 1987; Rajagopalan, 1988; Rose et al., 2010; ANSES, 2011). Molybdenum is an essential micronutrient required by plants (Fitzpatrick et al., 2008). The molybdenum content in plant-based foods varies greatly and depends on the properties of the soil where the foods are grown; molybdenum uptake by plants is promoted by neutral or alkaline soils (WHO, 1996). Molybdenum concentrations in drinking water are usually below 10 µg/L, although concentrations as high as 200 µg/L have been reported in areas near mining sites (WHO, 2008).

Currently, potassium molybdate (MoVI) may be added to food supplements[7], whereas ammonium molybdate (MoVI) and sodium molybdate (MoVI) may be added to both foods[8] and food supplements[7].

Results from Total Diet Studies (TDS) in Western countries including France and the UK have shown that cereals and cereal-based products including bread are the major food contributors to dietary molybdenum intake of adults and such sources contribute about one third to one half of total molybdenum intake. Further contributors to molybdenum intake are dairy products and vegetables (Pennington and Jones, 1987; Rose et al., 2010; ANSES, 2011; National Food Agency, 2012; FSANZ, online). Foods contributing to molybdenum intake in France, UK and Sweden are shown in Appendix B.

3.1.1. Infant and follow-on formula

In a report on the essential requirements of infant and follow-on formulae, the SCF did not define a minimum or maximum content of molybdenum for either type of formulae (SCF, 2003). Compared to mature human milk, cow's milk has a higher molybdenum concentration (34 µg/kg as reported by Rose et al. (2010), mean of 46 µg/kg as reported by ANSES (2011)). Hence, the molybdenum content of cow's milk based-infant formula is higher compared to mature human milk. For 81 powdered cow's milk-based or soy-based infant formulae from the US and Canada, molybdenum concentrations ranged from 15.4 to 80.3 µg/L (mean ± SE, 37.7 ± 1.7 µg/L) (Abramovich et al., 2011).

3.2. Dietary molybdenum intake in children and adults

Reports of usual dietary molybdenum intakes vary widely because of differences in analytical methods and in the molybdenum content of the soils in which foods are grown. National food consumption surveys usually do not report on molybdenum intake because of lack of information on molybdenum in food composition databases.

Appendix C shows dietary molybdenum intakes of adults, children or the total population in various European countries where molybdenum intakes have been assessed using duplicate diet/portion sampling, the total diet approach or the market basket approach to provide information about total dietary exposure. Results show that mean molybdenum intakes of adults vary over a wide range, i.e. from 58 µg/day (German women in four regions of Eastern Germany) to 157 µg/day (Sweden). Mean intakes are at or above 100 µg/day in five of the eight European countries for which data are available. Average molybdenum intakes assessed in duplicate diet or food portion studies range

[7] Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements, OJ L 183, 12.7.2002, p. 51

[8] Regulation (EC) No 1925/2006 of the European Parliament and of the Council of 20 December 2006 on the addition of vitamins and minerals and of certain other substances to foods, OJ L 404, 30.12.2006, p. 26

between 58 µg/day (Germany) and 112 µg/day (Denmark), while they are between 79.6 and 125 µg/day in three total diet studies (Italy, France, UK). The Italian study used a modified TDS approach in which analysed molybdenum contents of local foods of only one region in Northern Italy were used in the calculations. Minimum intakes range between 20 µg/day (Denmark) and 86 µg/day (Finland), with the intake at the 5th percentile being 49.1 µg/day in France. Maximum intakes range between 89.1 µg/day (Belgium) to 560 µg/day (Denmark), with the intake at the 95th percentile being 155 µg/day in France.

Data on molybdenum intakes in pregnant women are not available. In lactating women, there is only one study on 19 women, which reported a mean molybdenum intake of 132 ± 60 µg/day (see Section 2.3.6.3).

In children, mean intakes were reported to be 74.9 µg in France (3-17 years), and about 3 µg/kg body weight per day (4-18 years) and 4.8 µg/kg body weight per day (1.5-4.5 years) in the UK. Intakes at the lower (P5) and upper (P95) end were 40.3 µg/day and 130 µg/day, respectively, in French children (3-17 years).

4. Overview of dietary reference values and recommendations

4.1. Adults

The German-speaking countries (D-A-CH, 2012) set an Adequate Intake (AI) of 50-100 µg/day based on molybdenum intakes with a mixed diet.

The US Institute of Medicine (IoM, 2001) derived an average requirement based on a molybdenum balance study with four young males by Turnlund et al. (1995b). Average molybdenum balance was achieved with an intake of 22 µg/day, and no clinical signs of deficiency or biochemical changes associated with molybdenum deficiency were observed. The average minimum molybdenum requirement for maintaining adequate molybdenum status was estimated to be 22 µg/day, to which an additional 3 µg/day was added to allow for miscellaneous losses. In addition, it was assumed that molybdenum bioavailability from some diets may be lower than from the diet provided in the study. Thus, an average bioavailability of 75 % was used to set an Estimated Average Requirement (EAR) of34 µg/day. Because of the use of only two different molybdenum intake levels and the small size of the study, IoM used a coefficient of variation (CV) of 15 % and derived a Recommended Dietary Allowance (RDA) of 45 µg/day as the EAR plus twice the CV to cover the needs of 97 to 98 % of the individuals in the group. As no data on which to base an EAR were found for women or older adults, the same values were given for these population groups (IoM, 2001).

The UK COMA (Committee on Medical Aspects of Food Policy) did not derive a Recommended Nutrient Intake (RNI) for molybdenum but set a safe intake range of 50-400 µg/day. The range is based on intakes of apparently healthy subjects in various Western countries (COMA, 1991).

The Nordic countries (NNR, 2004), WHO/FAO (2004), the Scientific Committee for Food (SCF, 1993), the Health Council of the Netherlands (Health Council of the Netherlands, 2009) and Agence Française de Sécurité Sanitaire des Aliments (AFSSA, 2001) did not derive DRVs for molybdenum for adults. AFSSA considered it premature to set DRVs for molybdenum, but considered that the daily requirement for molybdenum could be of the order of 25 µg/day (Turnlund et al., 1995b), and that the Population Reference Intake (PRI) could be around 30 to 50 µg/day, for adults.

4.2. Infants and children

The German speaking countries (D-A-CH, 2012) set adequate molybdenum intakes for infants and children by extrapolating from the AI for adults and taking into account age-specific reference values for energy.

For children from 7 to 12 months, the IoM (2001) set an AI of 3 µg/day using the weight ratio method and extrapolating from the AI for infants aged 0 through 6 months (2 µg/day) exclusively fed human milk, as data on the molybdenum content of complementary food consumed in addition to human milk were not available. For children and adolescents from 1 to 18 years, IoM extrapolated an EAR from the adult EAR using metabolic weight owing to the role of molybdenum as cofactor of several enzymes and because this approach resulted in a higher AR compared to using body weight. The same CV as in adults of 15 % was used.

UK COMA derived a safe intake range based on evidence from breastfed infants. In the absence of other evidence, they suggested similar safe intakes of 0.5-1.5 µg/kg body weight per day for children up to 18 years of age (COMA, 1991).

The Nordic countries (NNR, 2004), WHO/FAO (2004), the Scientific Committee for Food (SCF, 1993), the Health Council of the Netherlands (Health Council of the Netherlands, 2009) and Agence Française de Sécurité Sanitaire des Aliments (AFSSA, 2001) did not derive DRVs for molybdenum for infants and children.

Table 1: Overview of Dietary Reference Values (DRVs) for molybdenum for infants, children and adults

	D-A-CH (2012) [a]	IoM (2001) [b]	UK (1991)
Age (months)	4-<12	7-12	-
DRV (µg/day)	20-40	3 [a]	-
Age (years)	1-<4	1-3	0-18
DRV (µg/day)	25-50	17	0.5-1.5 [c]
Age (years)	4-<7	4-8	-
DRV (µg/day)	30-75	22	-
Age (years)	7-<10	9-13	-
DRV (µg/day)	40-80	34	-
Age (years)	10-<19	14-18	-
DRV (µg/day)	50-100	43	-
Age (years)	19+	19+	19+
DRV (µg/day)	50-100	45	50-400 [d]

(a): Adequate Intake
(b): Recommended Dietary Allowance
(c): Safe intake (range), given as µg/kg body weight per day
(d): Safe intake (range)

4.3. Pregnancy

The IoM (2001) concluded that no direct data are available for determining the additional daily requirement for molybdenum during pregnancy. A weight gain of 16 kg observed in women with good pregnancy outcomes was added to the reference weight for non-pregnant adolescent girls and adult women, and an EAR was extrapolated using isometric scaling (linear with body weight). Applying a

CV of 15 % to the EAR of 40 µg/day and rounding to the nearest 10 µg, the RDA was set at 50 µg/day.

4.4. Lactation

The IoM (2001) derived an EAR for lactation as the sum of the molybdenum intake necessary to replace the molybdenum secreted daily in human milk and the EAR for adolescent girls and adult women. Based on a daily excretion of 2 µg/day and using a CV of 15 % as well as rounding to the nearest 10 µg, the RDA was set at 50 µg/day.

5. Criteria (endpoints) on which to base dietary reference values

Current DRVs for molybdenum are based on maintenance of molybdenum homeostasis as measured in balance studies, and taking into account molybdenum bioavailability from various food sources, or on estimated intakes in adults or exclusively breastfed infants. For other age and life-stage groups, reference values were then extrapolated. For lactating women, losses via secretion of milk were also taken into account when the average requirement was estimated factorially.

5.1. Biomarkers of status

Clinical signs of molybdenum deficiency in otherwise healthy humans have not been observed. There are no suitable biomarkers of molybdenum status (see Section 2.3.2) which can be used to estimate molybdenum requirements.

5.2. Molybdenum balance

Balance studies are based on the assumption that a healthy subject on an adequate diet maintains an equilibrium or a null balance between nutrient intakes and nutrient losses: at this null balance, the intake matches the requirement determined by the given physiological state of the individual. When intakes exceed losses (positive balance), there is nutrient accretion that may be attributable to growth or to weight gain, anabolism or repletion of stores; when losses exceed intakes (negative balance), nutrient stores are progressively depleted resulting, in the long term, in clinical symptoms of deficiency. When performed at different levels of intakes, balance studies enable the quantification of obligatory losses by regression to zero. In addition to numerous methodological concerns about accuracy and precision in the determination of intakes and losses (Baer et al., 1999), the validity of balance studies for addressing requirements has been questioned: they might possibly reflect only adaptive changes before reaching a new steady-state (Young, 1986) or only the conditions for maintenance of nutrient stores (Mertz, 1987), or, in the absence of such stores, only activities of molybdenum-containing enzymes in the context of a given diet. The relevance of the level of these activities for health remains to be established since they can be very low without overt clinical signs (see Section 2.2.2.1).

5.2.1. Balance studies in adults

Various balance studies have been performed to establish the molybdenum requirements of adults (Tipton et al., 1969; Robinson et al., 1973; Jacobson and Wester, 1977; Turnlund et al., 1995a; Turnlund et al., 1995b; Yoshida et al., 2006). However, only a few of these studies were of sufficient duration to allow the body to adapt to the level of dietary intake before collecting balance data (at least 12 days according to IoM (2001), possibly longer than 24 days (especially for high intakes after low intakes) as indicated in the study by Turnlund et al. (1995a), and were performed with constant diets and under controlled conditions.

One such study was a depletion-repletion study, in which four healthy adult men aged 22-29 years received a diet containing 22 µg molybdenum/day for 102 days followed by 18 days on the same diet but supplemented with ammonium molybdate to provide 467 µg molybdenum/day (Turnlund et al., 1995b). During the dietary periods, stable molybdenum isotopes were administered intravenously (^{97}Mo) or orally (^{100}Mo) to participants to investigate absorption, retention and excretion. Blood and urinary uric acid and urinary sulphite concentrations were periodically measured and no clinical symptoms or biochemical changes linked to molybdenum deficiency were observed. Molybdenum concentrations were monitored in urine and faeces. Losses via sweat, saliva and skin could not be analysed reliably and were not taken into account. For the first 48 days of the depletion period, mean balance based on dietary, urinary and faecal molybdenum was negative. For the following 54 days, the average was near zero (0.3 µg/day). After administration of the high dose (467 µg/day) during the repletion phase, mean balances were positive for the first two 6-day-periods but had returned to around baseline (-6.6 µg/day) for the third 6-day-period. The Panel notes that despite the careful performance of this balance study, part of the molybdenum losses could not be quantified and, considering the small scale of the study (n=4) and the fact that biochemical changes or symptoms indicative of molybdenum deficiency were not observed during the depletion period, the possibility that humans may be able to achieve molybdenum balance at even lower intakes cannot be excluded.

When plasma molybdenum concentrations could be reliably measured (see Section 2.2.4), the data from this depletion-repletion study were also used in a compartmental model of molybdenum kinetics (Novotny and Turnlund, 2006). In order to model ^{100}Mo ingested from foods and total molybdenum in plasma, urine and faeces, the model required four compartments, i.e. a stomach, gastro-intestinal, plasma, and tissue compartment. For ^{97}Mo injected intravenously, two further plasma compartments were needed to fit the data. Using the fractional transfer and flow rates observed during the molybdenum depletion state, which differed from those observed in the repletion state, an intake of 43 µg/day was estimated for maintaining the mean plasma molybdenum concentration at baseline (9.4 nmol/L). The Panel notes that fractional transfer and flow rates estimated under molybdenum-sparing conditions were used to predict an intake for a plasma molybdenum concentration that may have been the result of a (much) higher intake, and concurrently would have required the use of other fractional transfer and flow rates.

Another balance study used five diets, varying only in molybdenum content. These were given consecutively for 24 days each, with total molybdenum intakes starting with 24 µg/day, followed by 72 µg/day, 122 µg/day, 466 µg/day, and lastly 1 488 µg/day, to four adult men aged 22-33 years (Turnlund et al., 1995a). During the first six days of the period with the lowest molybdenum intake (24 µg molybdenum/day), balance was highly negative (-46.9 µg/day) but became closer to zero for the remaining three 6-day-balances of this molybdenum intake level (highest mean balance for 6-day interval, -5.3 µg/day). Thereafter, mean balances were positive for all dietary levels given (balances of 1.8 µg/day, 1.3 µg/day, 9.1 µg/day and 103 µg/day, respectively). When dietary molybdenum was increased, balances went from positive early in the period to negative by the end of the 24-day-period, except in the fourth period. The Panel concludes that the results from this small scale study indicate that 24 days were not long enough for the subjects to adapt to the low level of molybdenum intake and to conserve tissue molybdenum. The Panel also notes that subjects in this study adapted relatively rapidly to ingestion of increasing amounts of molybdenum intakes over a wide range, by increasing excretion.

5.2.2. Molybdenum balance in children

Two balance studies in children have been published. However, these studies lacked an adaptation period, used various diets differing in composition, or measured balances after habitual molybdenum intake.

Alexander et al. (1974) estimated molybdenum balances in eight healthy children aged between three months and eight years. Over three days, molybdenum intakes with the habitual diet were estimated after analysis of duplicate portions, and urine and faeces were analysed for molybdenum. At individual molybdenum intakes between 12 and 65 µg/day and mean intakes of 3.0 ± 0.88 µg/kg body weight per day, mean retention was positive (1.27 ± 0.59 µg/kg body weight per day or 42 %).

Engel et al. (1967) reported on molybdenum balance in girls, aged 6-10 years who were given various diets differing in amount and type of protein for 6 to 56 days. For each dietary regimen, 3-12 girls were studied. Mean molybdenum intake with the different diets ranged from 43.2 to 80.8 µg/day, and all diets resulted in positive molybdenum balances (mean balances for intakes from 43.2 to 47.7 µg/day were between 7.8 and 12.1 µg/24 hours, for intakes from 71.2 to 80.8 µg/day between 2.9 and 32.6 µg/24 hours; range of individual balances 0.3-36.4 µg/24 hours).

In addition to the methodological limitations discussed above, these studies did not cover a range of molybdenum balances (from negative, through zero or null, to positive) correlated to dietary molybdenum intake. Thus, the Panel concludes that these balance studies cannot be used to derive an average molybdenum requirement for children.

5.3. Molybdenum intake and health consequences

Other criteria based on the functional and health consequences of molybdenum intake may also be considered in order to derive DRVs for molybdenum. However, no studies on health outcomes in relation to molybdenum intake (from foods or from single-nutrient supplements) were identified during the literature review as preparatory work for these DRVs (Mullee et al., 2012).

6. Data on which to base dietary reference values

6.1. Adults

For the reasons outlined in Sections 5.1 and 5.2, the Panel decided that there is insufficient evidence to derive an average molybdenum requirement for adults and thus to set a PRI. Therefore, the Panel proposes to set an AI.

For the setting of an adequate molybdenum intake, the Panel considered the observed molybdenum intakes from mixed diets in Europe (Appendix C), which were found to vary over a wide range. At the lower end of the range, mean molybdenum intakes of 58 µg/day and 74 µg/day were observed in women and men, respectively, with the use of the duplicate diet method. Taking into account reference body weights of adult men and women as shown in Table 2, an approximate intake of 1 µg/kg body weight per day can be inferred. Therefore, an AI of 65 µg/day is proposed for all adults. This approach to setting an AI based on molybdenum intakes at the lower end of what has been observed in the EU is supported by evidence from a balance study in men on zero molybdenum balance and absence of biochemical changes or symptoms indicative of molybdenum deficiency at intakes as low as 22 µg/day for three months (see Section 5.2.1).

Due to the scarcity of data on molybdenum intakes in pregnant and lactating women, the Panel proposes that the AI of 65 µg/day derived for adults should also apply to pregnant and lactating women.

6.2. Infants and children

No data are available on which to base an average molybdenum requirement for infants and children. The Panel decided that an AR cannot be established and proposes an AI extrapolated from the adult AI using metabolic weight, i.e. body weight to the power of 0.75 (EFSA NDA Panel (EFSA Panel on

Dietetic Products Nutrition and Allergies), 2010). This mode of extrapolation is chosen because of the role of molybdenum as a cofactor of several enzymes, and to reflect that basal metabolic rate, which in mammals is mainly determined by the visceral organs (Makarieva et al., 2005), is an exponential function of body mass. The heart, kidneys, liver and brain have high specific basal metabolic rates when compared with the remaining less-active tissues, such as skeletal muscle, adipose tissue, bone and skin (Wang et al., 2001), and two of these metabolically active organs, i.e. liver and kidneys, are the tissues with the highest molybdenum concentrations in the (adult) body (see Section 2.3.3).

For infants aged 7 to 11 months, scaling down from an adult AI results in an AI of 15 µg/day, which is well above the value that would result from upward extrapolation based on mean molybdenum intakes from mature human milk in exclusively breastfed infants in the first half year of life.

CONCLUSIONS

The Panel concluded that there is insufficient evidence to derive an Average Requirement (AR) and a Population Reference Intake (PRI) for molybdenum. Data on the relationship between molybdenum intakes and health outcomes were unavailable for the setting of DRVs for molybdenum. Thus, the Panel proposes an Adequate Intake (AI) for adults based on mean molybdenum intakes at the lower end of the range of observed intakes with mixed diets in the EU. It was considered unnecessary to give sex-specific values. The Panel suggests that the adult AI can be applied to pregnant and lactating women. An AI is also proposed for infants and children based on extrapolation from the adult AI using allometric scaling and the body weights of the respective age groups (Table 2).

Table 2: Summary of Dietary Reference Values (DRVs) for molybdenum for infants, children and adults

Age	Reference weight (kg)		Adequate Intake (µg/day)
	Males	Females	
7-11 months	8.9 [(a)]	8.2 [(a)]	15
1-3 years	12.2 [(b)]	11.5 [(b)]	20
4-6 years	19.2 [(c)]	18.7 [(c)]	25
7-10 years	29.0 [(d)]	28.4 [(d)]	35
11-14 years	44.0 [(e)]	45.1 [(e)]	50
15-17 years	64.1 [(f)]	56.4 [(f)]	65
≥ 18 years [(g)]	68.1 [(h)]	58.5 [(h)]	65

(a): Median weight-for-age of male or female infants, respectively, aged 9 months according to the WHO Growth Standards (WHO Multicentre Growth Reference Study Group, 2006)
(b): Median weight-for-age of male or female children, respectively, aged 24 months according to the WHO Growth Standards (WHO Multicentre Growth Reference Study Group, 2006)
(c): Median weight of male or female children, respectively, aged 5 years according to van Buuren et al. (2012)
(d): Median weight of male or female children, respectively, aged 8.5 years according to van Buuren et al. (2012)
(e): Median weight of male or female children, respectively, aged 12.5 years according to van Buuren et al. (2012)
(f): Median weight of male or female children, respectively, aged 16 years according to van Buuren et al. (2012)
(g): Including pregnancy and lactation
(h): Median body weight of 18 to 79-year-old men and women, respectively, based on measured body heights of 16 500 men and 19 969 women in 13 EU Member States and assuming a BMI of 22 kg/m^2 (see Appendix 11 in EFSA NDA Panel (EFSA Panel on Dietetic Products Nutrition and Allergies) (2013)).

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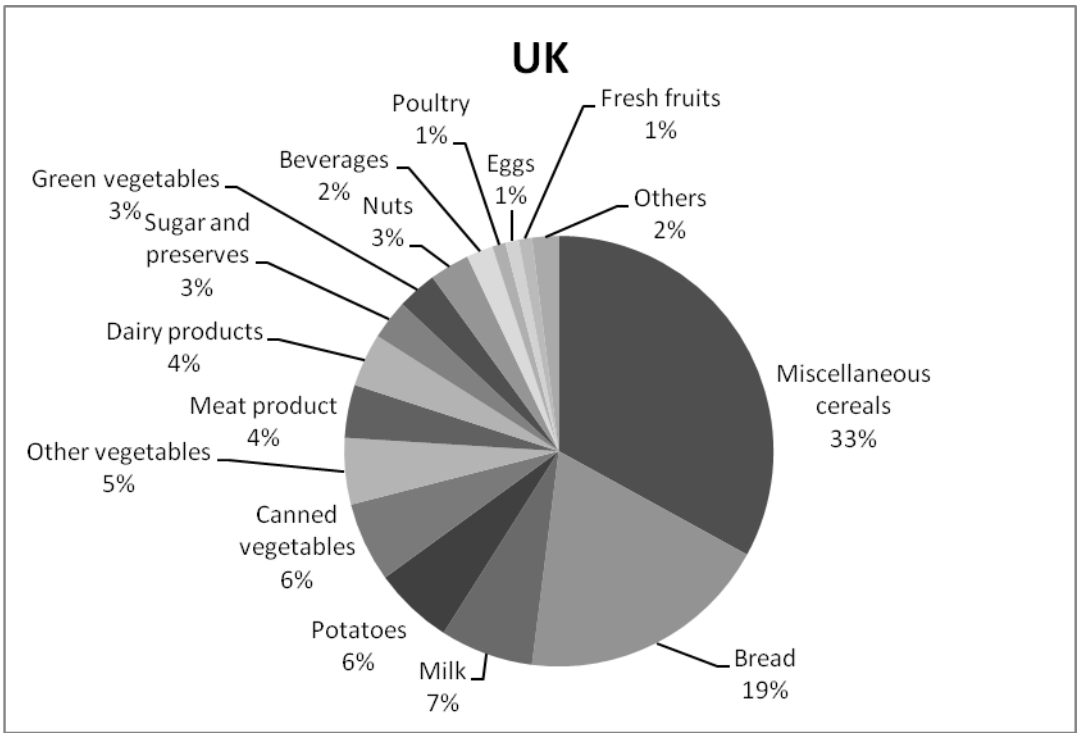
APPENDICES

A. MOLYBDENUM CONCENTRATION IN HUMAN MILK

Reference	n (Number of samples)	Country	Maternal intake (µg/day; mean ± SD)	Stage of lactation	Mo concentration (µg/L)		
					Mean ± SD	Median	Range (µg/L)
Abdulrazzaq et al. (2008)	205	United Arab Emirates	Not reported	4-80 weeks	0.348	0.061	0.001-1.9
Anderson (1992)	7 (84)	USA	Not reported	Various times up to 5 months	16.98 ± 0.97 (mean ± SE)		
Aquilio et al. (1996)	8 (mothers of term infants)	Italy	Not reported	2-6 days 12-16 days 21 days	6.8 ± 2.5 5.7 ± 2.3 3.6 ± 1.4		
Biego et al. (1998)	17	France	Not reported	'Mature'	4 ± 3		
Bougle et al. (1988)	6 (mothers of term infants)	France	Not reported	3-5 days 7-10 days 14 days 1 month 2 months	10.2 ± 3.7 4.8 ± 3.9 1.5 ± 1.4 2.6 ± 2.2 0.2 (n=1)		
Casey and Neville (1987)	13 (62)	USA	Not reported	1st day 14 days 1 month	15.0 ± 6.1 4.5 ± 2.9 ~2		Day 2: 4.1-26.7 Overall: 0.69-26.7
Dang et al. (1984)	6 9 8 8	India	Not reported	3-5 days 4-6 weeks	12.1 ± 5.5 (middle income) 10.8 ± 5.5 (low income) 10.7 ± 3.4 (middle income) 7.2 ± 5.4 (low income)		
Friel et al. (1999)	19 (152)	Canada	Not reported	1 week 2 weeks 4 weeks 5-7 weeks		4 3 2 1	

Reference	n (Number of samples)	Country	Maternal intake (µg/day; mean ± SD)	Stage of lactation	Mo concentration (µg/L)		
					Mean ± SD	Median	Range (µg/L)
Gunshin et al. (1985)	24	Japan	Not reported	19-384 days	24		5-63
Hattori et al. (2004)	3 (17)	Japan	Not reported	96-327 days		4.5	2.0-8.8
Krachler et al. (1998); Rossipal and Krachler (1998)	46 (55)	Austria	Not reported	1-3 days 4-17 days 42-60 days 66-90 days 97-293 days	8.88 ± 3.74 5.1 1.43 ± 1.77 1.3 1.78 ± 1.62	9.00 6.1 1.02 0.6 1.56	4.3-16 1.2-27 < 0.50-4.9 < 0.50-3.5 < 0.50-5.3
Lopez-Garcia et al. (2007)	3 (15)	Spain	Not reported	Not reported	2.9 ± 0.1 (volunteer 1) 4.1 ± 0.1 (volunteer 2) 0.7 ± 0.1 (volunteer 3)		
Pandey et al. (2003)	241	India	Not reported	'Mature'	18 ± 4		7-60
Sievers et al. (2004)	19 (43)	Germany	Not reported	3.6 weeks (2.6-4.7) 8.4 weeks (7.3-10.1) 15.9 weeks (15.3-16.6)	1.1 ± 2.5 3.9 ± 2.9 2.1 ± 2.6		
Wappelhorst et al. (2002)	19 (536)	Germany, Poland, Czech Republic	132 ± 60 (Median: 125, analysis of food duplicates)	3-68 weeks	0.72	0.53	0.27-1.62
WHO/IAEA (1989); Parr et al. (1991)	(335)	Guatemala Hungary Nigeria Philippines Sweden Zaire	Not reported	3 months		2.12 < 0.3 2.65 16.36 0.40 1.39	< 0.3-9.0 < 0.3-3.9 0.34-9.7 6.75-35.4 < 0.3-5.9 < 0.3-5.8
Yoshida et al. (2008)	79 (79)	Japan	Not reported	5-191 days	5.42 ± 5.33	3.18	< 0.1-25.9

916 **B. FOODS CONTRIBUTING TO MOLYBDENUM INTAKE IN THE UK, FRANCE, AND SWEDEN**



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918 Based on data from Rose et al. (2010)

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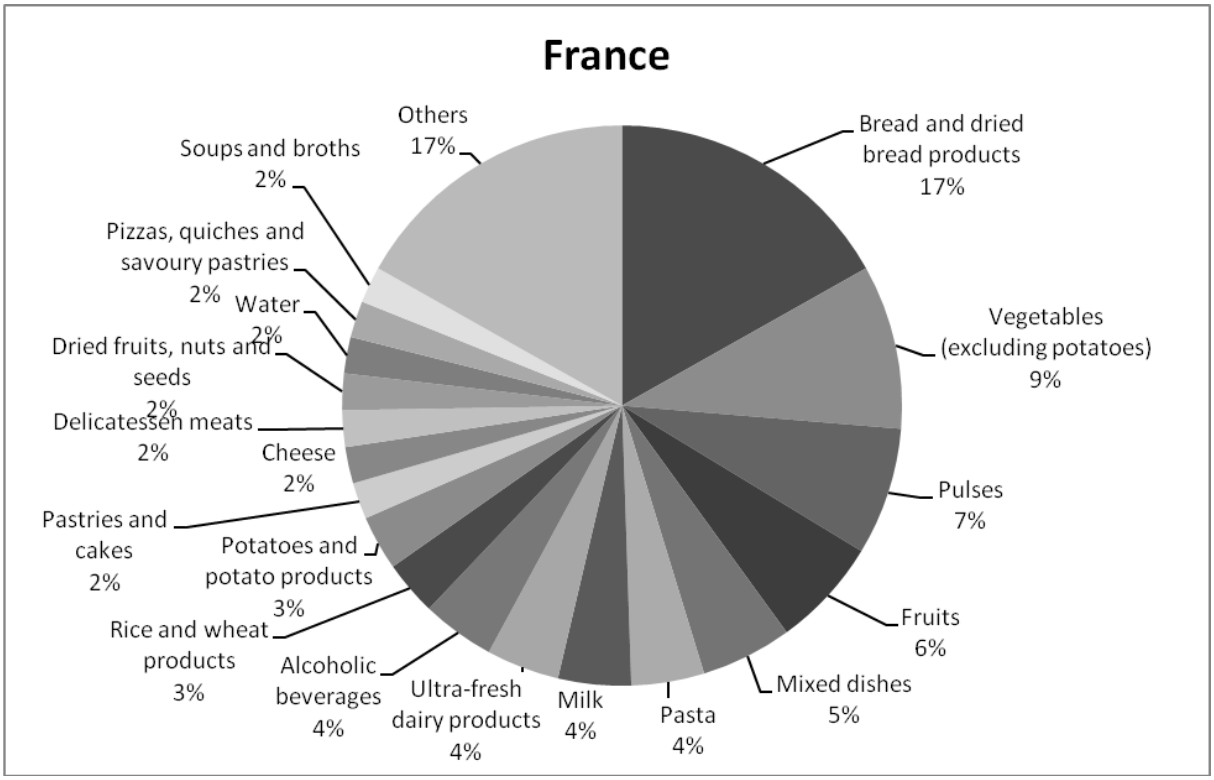

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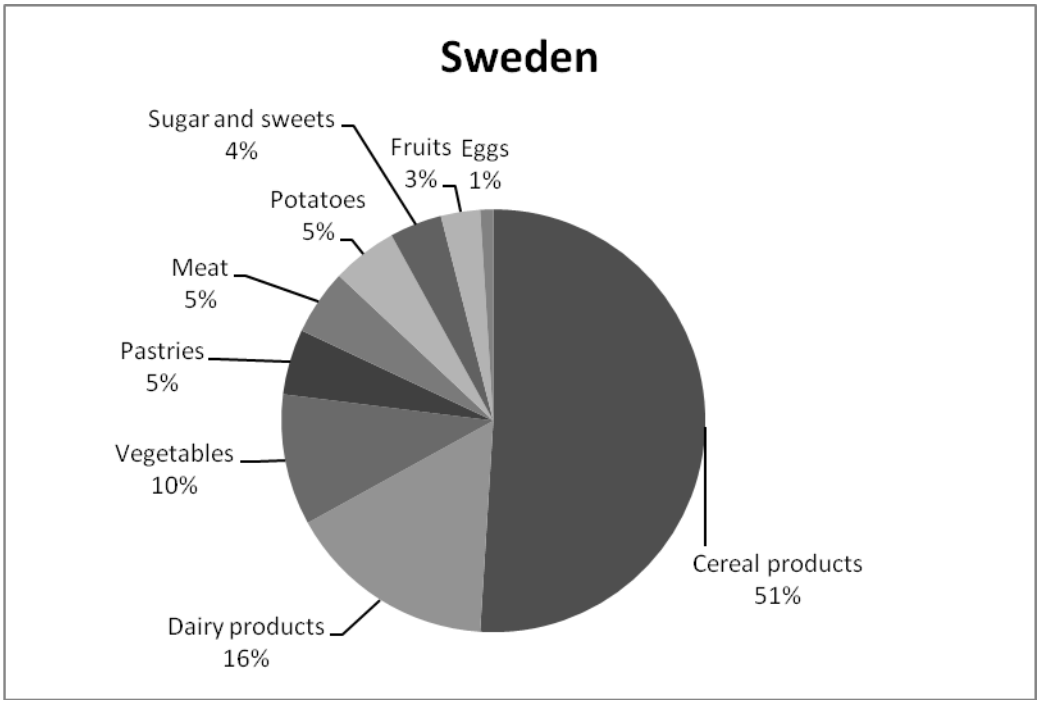
921 Based on data from ANSES (2011)



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923 Based on data from NFA (2012)

924 **C. MOLYBDENUM INTAKE IN CHILDREN AND ADULTS IN VARIOUS EUROPEAN COUNTRIES**

Country	Age (years)	Sex/ group	n	Method	Additional information	Population/location	Data source	Mean	SD	Median	Min	P5	P95	P97.5	Max
In µg/day															
Belgium		Adults		Duplicate portion study	Duplicate meals, beverages and provision for between meals were collected over 24-h periods in four different settings in Belgium: Brussels (military academy), Antwerp (hospital), Vilvoorde (military service quarter), Liège (hospital). Sampling carried out for seven days consecutively between February and October 1992.	Mean+/- SD of the four sites	Van Cauwenbergh et al. (1997)	87.0	11.0						
						Antwerp		75.0	10.1		56.9				89.1
						Brussels		99.0	15.6		74.9				125.3
						Liège		79.0	14.4		66.4				110.2
						Vilvoorde		93.1	74.3		45.6				257.6
Denmark	30-34	Men	100	Duplicate diet study	48-hour duplicate food portions (self-selected diets, in March-May 1988). Subjects were asked to make records of all food and beverages consumed in a four-day period including one week-end day. During two of the four days, they were asked also to collect an exact duplicate of each item of food or beverage that had been consumed.	Random sample among the population of 30-34 year old men in one urban (Odense, the third largest city in Denmark) and two rural areas	Bro et al. (1990)	112.0	63.0	99.0	20.0				560.0
Finland		Adults		Duplicate portion study	Duplicated meals served in 11 hospitals throughout Finland. Over seven consecutive days, diet duplicates included all meals, and meals were served to provide 2 150 kcal/day.		Sinisalo et al. (1989)	100.0	10.0		86.0				130.0
Finland		Adults and children		Market Basket study	For 450 foods (raw, semi-processed or ready-made) commonly consumed in Finland, representative samples were analysed. No food preparation, processing or cooking before analyses. Method used to derive daily intake estimate not mentioned in this reference.		Varo and Koivistoinen (1980)	120.0							

Country	Age (years)	Sex/ group	n	Method	Additional information	Population/location	Data source	Mean	SD	Median	Min	P5	P95	P97.5	Max
France	3-17	Children		Total Diet Study	2nd TDS (2007-2008). Analysed food samples from all the administrative regions of mainland France. 787 food items, one national list of 116 foods and eight regional lists. 212 different types of foods were selected and sampled in at least one region, or at the national level. 19 830 products were purchased and prepared 'as consumed', making up the 1 319 composite samples. Analysed content multiplied by food consumption data from INCA2 (n=1 444 children, n=1 918 adults)	Children, under-reporters excluded	ANSES (2011)	74.7				40.3	130.0		
	18-79	Adults				Adults, under-reporters excluded		93.9				49.1	154.9		
Germany	20-60	Men	28 (n=7 per location)	Duplicate diet study	In 1988, 1992 and 1996, the Mo consumption of healthy adults on mixed diets was investigated in different locations in Eastern Germany by means of duplicate portions studies at 11 regions in Eastern Germany. Each test group consisted of at least seven women and seven men. Recruited volunteers recorded all foods and beverages consumed during a three-day preliminary study to assess dietary habits. Seven women and seven men were randomly selected to participate in the study and collected a duplicate of each item of food or beverage that had been consumed during 24 hours, over seven subsequent days.	Year 1988, in the following locations: Bad Langensalza and Jena in Thuringia, Vetschau and Wusterhausen in Brandenburg.	(Holzinger et al., 1998)	74.0	62.0						
			42 (n=7 per location)			Year 1992, in the following locations: Bad Langensalza and Bad Liebenstein in Thuringia, Chemnitz and Freiberg in Saxony, Greifswald in Mecklenburg-Western Pomerania, Wusterhausen in Brandenburg.		81.0	63.0					
			31			Year 1996, in the following locations: Jena, Ronneburg, Rositz, and Steudnitz in Thuringia.		100.0	66.0					
		Women	28 (n=7 per location)			Year 1988, in the following locations: Bad Langensalza and Jena in Thuringia, Vetschau and Wusterhausen in Brandenburg.		58.0	36.0					

Country	Age (years)	Sex/ group	n	Method	Additional information	Population/location	Data source	Mean	SD	Median	Min	P5	P95	P97.5	Max
			42 (n=7 per location)			Year 1992, in the following locations: Bad Langensalza and Bad Liebenstein in Thuringia, Chemnitz and Freiberg in Saxony, Greifswald in Mecklenburg-Western Pomerania, Wusterhausen in Brandenburg.		69.0	58.0						
			31			Year 1996, in the following locations: Jena, Ronneburg, Rositz, and Steudnitz in Thuringia.		89.0	98.0						
Italy		Adults		Modified Total Diet Study	Choice of foods from the Italian Household National Survey 1994-1996 (1 978 randomly selected subjects representative of the four main areas in Italy (North-West, North-East, Centre, South). Foods aggregated into six main food groups. Most samples collected in a cafeteria (raw, cooked, ready-to-eat), over two consecutive weeks in July 2004 from a university cafeteria (n=226 samples). A sample of each food that was prepared daily was collected. Some traditional breakfast foods not served at the cafeteria were purchased at three local supermarkets, as well as a few foods included in the Italian Household national Survey but not served at the cafeteria (n=22 samples). Food samples were pooled, and analysed. Analysed content multiplied by the average consumption by the NW Italian adult population (entire population, i.e. consumer and non-consumers).	Pavia (Northern Italy)	Turconi et al. (2009)	79.6			32.6				106.2

Country	Age (years)	Sex/ group	n	Method	Additional information	Population/location	Data source	Mean	SD	Median	Min	P5	P95	P97.5	Max
Sweden		Adults and children		Market Basket study	Collection of food baskets, in Uppsala in May-June 2010 (and in autumn for fruits, vegetables and potatoes), from five major Swedish grocery chains by using a shopping list based on per capita food consumption data derived from production and trade statistics (Swedish Board of Agriculture, 2007); supplementary purchase statistics for fish and fats for 2009/2010). Market baskets divided into 12 food groups and analysed as purchased (n=123 samples).		National Food Agency (2012)	157.0							
United Kingdom		Adults and children		Total Diet Study	Composite samples for 20 food groups (combined from 119 food categories) collected from 24 randomly selected UK towns, prepared and analysed. Proportions of the foods within a group: representative of the average UK household diet. Consumption data from NDNS study (Henderson et al., 2002; Gregory et al., 1990). Exposures were estimated for the lower- and upper-bound concentrations and these have been included as ranges.	2006 UK Total Diet Study.	Rose et al. (2010)	123-125							
In µg/kg body weight per day															
United Kingdom	1.5-4.5	Children		Total Diet Study	Composite samples for 20 food groups (combined from 119 food categories) collected from 24 randomly selected UK towns, prepared and analysed. Proportions of the foods within a group: representative of the average UK household diet. Consumption data from NDNS study (Henderson et al., 2002; Gregory et al., 1990). Exposures were estimated for the lower- and upper-bound concentrations and these have been included as ranges.	2006 UK Total Diet Study.	Rose et al. (2010)	4.80-4.87						7.54-8.32	
	4-18	Children				2006 UK Total Diet Study.		3.01-3.05						5.77-5.82	
	16-64	Adults				2006 UK Total Diet Study.		1.61-1.64						3.03-3.08	
	≥ 65	Adults (free living)				2006 UK Total Diet Study. Elderly		1.43-1.46						3.00-3.03	
	≥ 65	Adults (institu-tional)				2006 UK Total Diet Study. Elderly		1.33-1.36						3.46-3.54	

925 **GLOSSARY AND ABBREVIATIONS**

AFSSA	Agence Française de Sécurité Sanitaire des Aliments
AI	Adequate intake
AR	Average requirement
COMA	Committee on Medical Aspects of Food Policy
CV	Coefficient of variation
D-A-CH	Deutschland- Austria- Confoederatio Helvetica
DRV	Dietary Reference Values
EAR	Estimated Average Requirement
EC	European Commission
EFSA	European Food Safety Authority
EU	European Union
FAO	Food and Agriculture Organization
FNB	U.S. Food and Nutrition Board
IoM	U.S. Institute of Medicine of the National Academy of Sciences
ICP-MS	Inductively coupled plasma mass spectrometry
NNR	Nordic Nutrition Recommendations
PRI	Population Reference Intake
RDA	Recommended Dietary Allowance
SCF	Scientific Committee for Food
SD	Standard deviation
SE	Standard error
TDS	Total Diet Study
TPN	Total Parenteral Nutrition
UNU	United Nations University
USDA	United States Department of Agriculture
WHO	World Health Organization

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