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Assessment of dietary intake of manganese 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: 02
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Assessment of dietary intake of manganese in relation to tolerable upper intake

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Assessed and approved

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

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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 manganese from the diet and 1, 5 or 10 mg manganese per day in food supplements. The former maximum limit for manganese in food supplements was 5 mg per daily dose.

Manganese (Mn) is an essential dietary mineral for mammals, and is a component of metalloenzymes such as superoxide dismutase, arginase and pyruvate carboxylase. Manganese is involved in amino acid-, lipid- and carbohydrate metabolism and in proteoglycan synthesis in bone formation. In 2013, the European Food Safety Authority (EFSA) suggested 3 mg/day to represent an adequate intake (AI) of manganese because data was considered insufficient to set an average requirement (AR).

Reports of adverse effects resulting from manganese exposure in humans are associated primarily with inhalation in occupational settings. Excess oral exposure to manganese, especially from contaminated water sources, has been shown to cause permanent neurological disorder known as “manganism” which can be irreversible. The amount of manganese absorbed is inversely related to the concentration of manganese in the diet. This regulation seems to be part of the adaptive changes to the amount of dietary manganese intake, which allow the maintenance of manganese homeostasis over a wide range of intakes. Manganese is mainly absorbed as Mn(II), and absorption is reported to be below 10% of ingested manganese.

The main route of elimination of manganese from the body is via bile to the small intestine, while very little is excreted in the urine. Half-life for manganese can vary from 13 to 37 days, with a longer half-life in women than in men, but large inter-individual variation exists.

In Norway, manganese content in drinking water is low, and does not contribute to any magnitude of manganese intake. Daily dietary intake of manganese in Norway is not known, but it is proposed that manganese intake is adequate in the Scandinavian countries (NNR Project Group, 2012). Results from the Swedish Market Basket study, 2015, indicate an average daily manganese intake of 4.2 mg per person and day. Calculations based on data from Denmark, 2013 and 2015, evaluate mean dietary intake of manganese to 3.9 mg/day for adults and up to 6.9 mg/day in the higher intake groups. EFSA report on an observed mean intake in EU around 3 mg/day for adults. Main contributor to dietary manganese intake is cereals (57%) followed by fruit, vegetables, nuts and coffee/tea.

Irreversible neurotoxic adverse effects from intakes of manganese close to adequate intakes have been reported in humans (SCF, 2000). The Scientific Committee on Food (SCF) could not set a no observed adverse effect level (NOAEL), because no relevant dose-response

animal studies were found. Consequently SCF did not set a tolerable upper intake level (UL) for manganese.

VKM considers that any dose of manganese as an ingredient in food supplements may be associated with increased risk of negative health effects.

VKM emphasises that the current assessment of maximum limits for manganese in food supplements is merely based on published reports concerning upper levels from the IOM (2001, USA), SCF (2003, EU), 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, manganese, food supplement, upper level, exposure.

Sammendrag på norsk

Vitenskapskomiteen for mat og miljø (VKM) har vurdert inntaket av mangan i kosten, og dosene 1, 5 eller 10 mg mangan i kosttilskudd på oppdrag fra Mattilsynet. Den tidligere maksimumsgrensen for mangan i kosttilskudd var 5 mg/dag.

Mangan (Mn) er et essensielt mineral for pattedyr, og inngår som komponent i metalloenzymer som superoksid dismutase, arginase og pyruvat karboksylase. Mangan inngår i metabolismen av aminosyrer, fett og karbohydrater og i proteoglukansyntesen ved beindannelse. Ettersom det ikke fantes datagrunnlag for å fastsette såkalt gjennomsnittlig behov (Average Requirement=AR), foreslo European Food Safety Authority (EFSA) i 2013 at 3 mg per dag er å anse som et såkalt adekvat inntak (AI) av mangan.

De fleste rapportene om negative helseeffekter hos mennesker fra mangan er forbundet med eksponering via luftveiene i yrkesrelaterte situasjoner. Høyt oralt inntak av mangan, særlig fra kontaminerte drikkevannskilder, har vist å kunne medføre varig (og irreversibel) nevrologisk skade kalt «manganisme».

Mengden mangan som absorberes i kroppen er omvendt relatert til konsentrasjonen av mangan i kosten. Denne reguleringen ser ut til å være en del av opprettholdelsen av manganhomeostasen selv ved store variasjoner i inntak. Normalt absorberes under 10 % av mangan fra kosten, og da hovedsakelig som Mn (II).

Manganutskilling skjer hovedsakelig via gallen og tynntarmen, og svært lite skilles ut gjennom urin. Halveringstiden for mangan varierer fra 13 til 37 dager. Kvinner har generelt lengere halveringstid enn menn, men det er store individuelle variasjoner.

Mangankonsentrasjonene i drikkevann er lave i Norge, og bidrar i liten grad til det totale manganinntaket. Daglig inntak av mangan fra kosten i Norge er ikke kjent, men manganinntaket fra kosten er vurdert til å dekke behovet i de skandinaviske landene (NNR Project Group, 2012). Resultater fra en svensk såkalt «handlekurv-studie» fra 2015 antyder et gjennomsnittlig inntak av mangan på 4,2 mg/dag. Beregninger basert på danske data fra 2013 og 2015, viser et manganinntak på 3,9 mg/dag for voksne og opp til 6,9 mg/dag i grupper med høyt manganinntak.

EFSA rapporterer om et observert gjennomsnittlig inntak i EU på rundt 3 mg/dag. Matvaregrupper som bidrar mest til manganinntaket er korn og kornprodukter (57 %) etterfulgt av frukt, grønnsaker, nøtter og kaffe/te.

Det er rapportert om irreversible nevrotoksiske bivirkninger fra inntak av mangan nært såkalt adekvat inntak (AI) hos mennesker (SCF, 2000). Scientific Committee on Food (SCF) kunne ikke angi en NOAEL – det vil si et inntaksnivå der man ikke har sett noen skadelige effekter, fordi ingen relevante dyrestudier ble funnet. Mangel på muligheten for å fastsette en NOAEL og det at man har sett nevrologiske effekter på mennesker ved lave inntak resulterte i at SCF

ikke har fastsatt et tolerabelt øvre inntaksnivå (UL) for mangan. VKM konkluderer derfor med at alle mangandosene i kosttilskudd vil kunne medføre økt risiko for negative helseeffekter.

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

Abbreviations and/or glossary

Abbreviations

AI – adequate intake
AR – average requirement
ATSDR – Agency for Toxic Substances and Disease Registry, USA
BMI – body mass index
bw – body weight
CI – confidence interval
Da – Dalton
DRI – dietary reference intake
DRV – dietary reference value
DTU – Danish Technical University
EAR – estimated average requirement
EFSA – European Food Safety Authority
EVM – Expert group on Vitamins and Minerals of the Food Standard Agency, UK
IOM – Institute of Medicine, USA
LOAEL – lowest observed adverse effect level
MRL – minimal risk level
NFSA – Norwegian Food Safety Authority [*Norw.*: Mattilsynet]
NNR – Nordic Nutrition Recommendations
NOAEL – no observed adverse effect level
PRI – population reference intake
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.

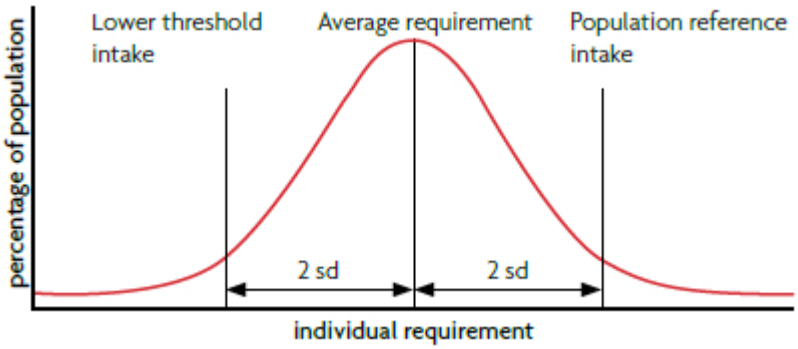

Figure 1: Population reference intake (PRI and average requirements (AR), if the requirement has a normal distribution and the inter-individual variation is known (EFSA, 2010).

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.

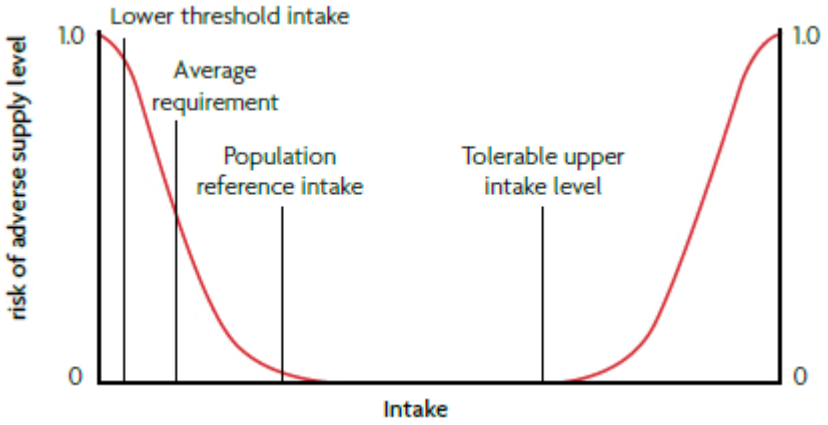

Figure 2: Relationship between individual intake and risk of adverse effects due to insufficient or excessive intake.

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.

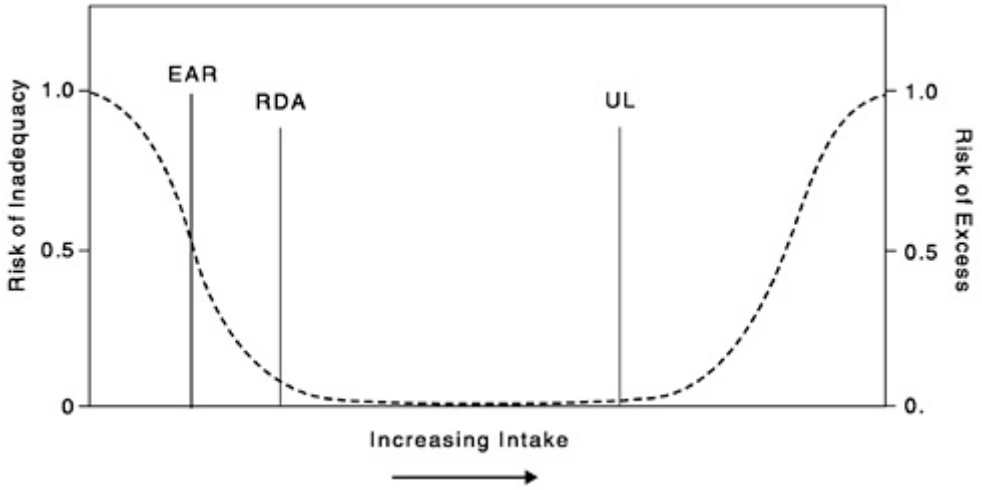

Figure 3: Dietary reference intakes.

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.

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

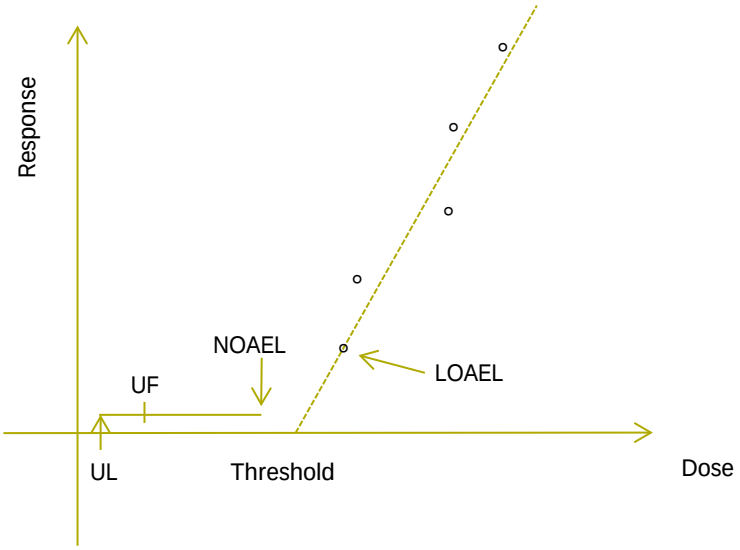

Figure 4: Derivation of Upper Intake Level (UL)

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.

Guidance Level (GL): For vitamins and minerals where a SUL could not be established due to insufficient data, EVM provided GL as an approximate indication of levels that would not be expected to cause adverse effects. As with SULs, the GLs are intended to represent the doses of vitamins and minerals that susceptible individuals could take daily on a life-long basis, without medical supervision. The EVM emphasised, however, that GLs should not be used as SULs, as they have been derived from limited data and are less secure than SULs.

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 manganese

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

The former maximum limit for manganese of 5 mg per daily dose was repealed from 30 May 2017. The minimum limit and permitted manganese 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 manganese from the diet, in all age groups in the population above 1 year.

As there is no data on manganese 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 National Food Institute in Denmark (DTU).

VKM is also requested to evaluate the consequences of establishing a maximum limit for manganese in food supplements of 1, 5 or 10 mg per daily dose, and to evaluate these scenarios against existing tolerable upper intake levels.

Assessment manganese

1 Introduction

Manganese (Mn) has an atomic mass of 54.9 Dalton (Da) and exists in a number of oxidation states ranging from -3 to +7. Mn(II) and Mn(III) are the prominent forms in biological systems (SCF, 2000). Manganese is an essential dietary mineral for mammals, and is a component of metalloenzymes such as superoxide dismutase, arginase and pyruvate carboxylase. Manganese is involved in amino acid-, lipid- and carbohydrate metabolism and in proteoglycan synthesis in bone formation (IOM, 2001; SCF, 1993).

Manganese deficient animals demonstrate impaired growth, skeletal abnormalities, reproductive deficits, ataxia of the newborn and defects in lipid and carbohydrate metabolism. Evidence of manganese deficiency in humans is poor and no specific syndrome has been described. A fleeting dermatitis, miliaria crystalline, developed in five out of seven male subjects on a purified diet with 0.11 mg/day of manganese for 39 days (Friedman et al., 1987 cited in EFSA, 2013).

Reported adverse effects of excess manganese in humans are primarily results of manganese inhalation in occupational settings. Oral exposure to manganese, especially from contaminated water sources, may also cause adverse health effects similar to those observed from inhalation exposure. The symptoms of manganese toxicity include tremors, difficulty walking, and facial muscle spasms, and may appear slowly over months and years. The final outcome can be a permanent neurological disorder known as manganism (ATSDR, 2012).

Estimated dietary daily intake of manganese in Norway is not known. Based on other European data, the main contributor to dietary manganese intake is cereals (57%) followed by fruit, vegetables, nuts and tea (EFSA, 2013).

The amount of manganese absorbed is influenced by the concentration of manganese in the diet. Low dietary manganese intake results in increased manganese absorption relative to intake (Finley, 1999; Finley et al., 2003 both cited in EFSA, 2013). Regulation at the level of absorption seems to be part of the adaptive changes to the amount of dietary manganese intake, which allow the maintenance of manganese homeostasis over a wide range of intakes.

Manganese is mainly absorbed as Mn(II), and intestinal absorption of manganese is reported to be below 10% (EFSA, 2013). Absorption of radioisotope labelled manganese from vegetable sources (lettuce, spinach, wheat, sunflower seeds) was shown to range from 1.7% to 5.2% compared with 7.7 to 10.2% absorption from a manganese chloride solution with a comparable manganese content (Johnson et al., 1991 cited in EFSA, 2013). Absorption has been suggested to take place through active transport mechanisms and passive diffusion.

High intakes of calcium, phosphorus and phytates have been reported to impair manganese absorption (ATSDR, 2012; IOM, 2001; SCF, 1993).

Absorbed manganese is transported to the liver and is further distributed to other tissues bound to transferrin, alpha2-macroglobulin and albumin. The concentration of manganese in blood of healthy adults ranges from 4-15 µg/L and with a higher concentration measured during pregnancy (15-20 µg/L). An even higher concentration is found in cord blood (30-40 µg/L) (EFSA, 2013). In plasma, manganese Mn(II) tends to be oxidised to Mn(III) and it is in this state manganese is found in several enzymes.

The main route of elimination of manganese from the body is via bile to the small intestine, while very little is excreted in the urine (ATSDR, 2012). Half-life for manganese can vary from 13 to 37 days, with a longer half-life in women than in men. However, large inter-individual variations exist.

2 Recommendations and tolerable upper intake levels

2.1 Recommendations

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

The European Food Safety Authority (EFSA) concluded that data is insufficient for deriving Average Requirements (ARs) or Population Reference Intakes (PRIs) for manganese. EFSA proposed an Adequate Intake (AI) at 3 mg/day for adults based on observed mean intake from a mixed diet in the EU as stated in Dietary Reference Values (DRVs) for manganese (EFSA, 2013). AI at 3 mg/day included pregnant and lactating women. AIs for children were calculated with use of isometric scaling. These AIs are presented in Table 2.1-1.

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

Age, both sexes	mg/day[(a)]
1-3 years	0.5
4-6 years	1.0
7-10 years	1.5
11-14 years	2.0
15-17 years	3.0
≥18 years*	3.0

(a) Calculated using isometric scaling: AI_{child} = AI_{adult} x (body weight of child/body weight of adult), where weight of adult is the average of the median body weight of 18- to 79-year-old men and women based on measured body heights of 16 500 men and 19 969 women in 13 EU Member States and assuming a body mass index (BMI) of 22 kg/m2 (see Appendix 11 in EFSA (2013)). Rounded to the nearest 0.5.
*Including pregnancy and lactation.

The U.S. Institute of Medicine (IOM) 2001 concluded that for manganese, there was not sufficient information to set Estimated Average Requirement (EAR) and Recommended Dietary Allowances (RDA), so requirements are described as estimates for Adequate Intakes (AIs) for the different age groups. The U.S. AIs for manganese for women and men from ages 19 and up are 1.8 and 2.3 mg/day, respectively. AI during pregnancy is 2.0 mg/day based on extrapolation with a weight gain of 16 kg, and for lactating women 2.6 mg/day based on median intake during lactation. For children aged 1-18 years, the AI increases with age from 1.2 to 2.2 mg/day for males, to 1.6 mg/day for females, all derived from calculated intakes.

Table 2.1-2 Adequate Intakes for manganese from IOM (2001).

Age, both sexes	mg/day male	mg/day female
1-3 years	1.2	1.2
4-8 years	1.5	1.5
9-13 years	1.9	1.6
14-18 years	2.2	1.6
>18 years	2.3	1.8
Pregnancy		2.0
Lactation		2.6

2.2 Tolerable upper intake levels

2.2.1 Scientific Committee on Food (SCF, 2000), EU

In 2000, the Scientific Committee on Food (SCF) concluded that oral intakes of manganese can cause adverse effects, both in humans and experimental animals. The critical organ is the central nervous system. Most studies on the neurotoxic effects in humans are from reports with oral intake of manganese through drinking water. Assuming a consumption of 2 litres of drinking water per day, cohorts showing neurotoxic effects were exposed to 28 mg Mn/day (Kawamura et al., 1941 cited in SCF, 2000), 0.16 – 0.5 and 3.6 – 4.4 mg Mn/day (Kondakis et al., 1989) and 0.48 – 0.69 mg Mn/day (He at al., 1994 cited in SCF, 2000) plus the contribution from food. In another study no adverse effects were found with intake from drinking water between 0.6 - 4.3 mg Mn/day plus contribution from food (Vieregge et al., 1995). However, the limitations of these studies, which also includes the uncertainty of contribution from food, make firm conclusions difficult. Similarly, SCF concluded that results from dose-response animal studies of adverse effects of Mn were too uncertain to set a no observed adverse effect level (NOAEL) for critical endpoints, mostly because all studies used high doses which consistently resulted in neurotoxic effects. The lowest dose affecting the central nervous system was found in a study with growing male rats, in which 50 µg $MnCl_2$,$4H_2O$/rat, initially equivalent to 0.28 mg Mn/kg bw, were given by stomach tube daily for 15 to 60 days (Chandra and Shukla, 1978). Furthermore, concerns were expressed of a potentially higher susceptibility of oral exposure to manganese among neonates and children who retain a much higher percentage of ingested manganese compared to adults.

SCF (2000) concluded that the margin between oral effect levels in humans and the estimated intake from food was very low. Given the findings on neurotoxicity and the potentially higher susceptibility of some subgroups in the general population, oral exposure to manganese beyond the levels normally present in food and beverages could represent a risk of adverse health effects and therefore SCF (2000) did not set a tolerable upper intake level (UL) for manganese.

2.2.2 Institute of Medicine (IOM, 2001), USA

In setting an UL for manganese, the IOM used elevated blood manganese concentration and neurotoxicity as the critical adverse effects (IOM, 2001). Animal studies were considered, but were evaluated to have poor quality and a NOAEL was not set.

A NOAEL of 11 mg/day of manganese from food was identified based on the data presented by Greger (1999) cited in IOM (2001). Greger (1999) reviewed information indicating that people eating Western-type and vegetarian diets may have intakes as high as 10.9 mg/day of manganese. Schroeder and coworkers (1966) reported that a manganese-rich vegetarian diet could contain 13 to 20 mg/day of manganese. Because no adverse effects due to manganese intake had been noted, at least not in people consuming Western diets, 11 mg/day was set as a reasonable NOAEL from food. A lowest observed adverse effect level (LOAEL) was identified on the basis of 47 women who were supplemented for 124 days with 15 mg/Mn/day Davis and Greger (1992) cited in IOM (2001). At this dose, there were significant increases in serum manganese concentrations after 25 days of supplementation and in lymphocyte manganese-dependent superoxide dismutase activity after 90 days of supplementation.

The UL for manganese for adults was set at 11 mg/day, and UL for children and adolescents were extrapolated from those established for adults based on relative body weight. The uncertainty factor (UF) was set to 1, because intake data was based on a human study.

Table 2.2.2-1 Tolerable upper intake levels for manganese in different age groups suggested by the IOM (2001).

Age (years)	UL mg/day
1-3	2
4-8	3
9-13	6
14-18	9
19 and older	11

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

The Expert Group on Vitamins and Minerals (EVM) has given a guidance level for total intake of manganese including a supplemental intake of 4 mg manganese per day. This guidance level was based on two epidemiological studies. EVM concluded that data were insufficient to establish a safe upper level (SUL) for manganese.

Kondakis et al., 1989
This was a retrospective study of three cohorts exposed to drinking water containing 0.0036-0.015, 0.08-0.25 or 1.8-2.3 mg/L manganese (Kondakis et al., 1989). The subjects were all aged over 50 years and had been exposed to manganese for more than 10 years. Assuming 2L/day water consumption, intakes for the three groups could be estimated to be 0.0072-

0.03, 0.16-0.5 and 3.6-4.6 mg manganese per day from drinking water in addition to dietary manganese. There was no difference in blood manganese levels in subjects from the three areas, but hair manganese was higher in subjects in the area with the highest level of manganese in drinking water. It has been noted (US Health and Human Services) that hair manganese is a useful measure of exposed versus unexposed populations but that it is of limited use in assessing individual exposure. Neurological signs and symptoms were elevated in subjects from the highest manganese area. The symptoms ranged from depression, fatigue and hallucinations to tremor and impaired reflexes. The authors attributed this finding to the age of the subjects, making them more susceptible to neuronal loss with ageing. The study was limited by inconsistent evidence of significant excess exposure and the subjective ascertainment of clinical effects.

Vieregge et al., 1995
This was a retrospective study based on two cohorts in which participants were exposed to water containing <0.05 mg/L or >0.3 mg/L (range 0.3-2.16 mg/L) manganese. The subjects in the two groups were aged 41-84 (mean 57.5) years and 41-86 (mean 56.9) years. Long duration of exposure (10-40 years) to manganese had taken place. Assuming 2 L/day water consumption, manganese intakes of 0.1 and 4.3 mg from water could be estimated. No significant differences in blood manganese levels or neurological scores were found between the two groups. The authors noted the conflict with the findings of Kondakis et al. (1989), which they attributed to the higher age of the participants in that study. The study of (Vieregge et al., 1995) was also limited by the lack of data on dietary manganese exposure. Animal data indicate similar neurotoxic effects and additional adverse effects on haematology and reproductive parameters.

For guidance purposes, it was reasoned that in the general population, a supplemental intake of up to 4 mg manganese/day, in addition to the dietary manganese, would be unlikely to induce adverse effects (equivalent to 0.07 mg/kg bw for a 60 kg adult) based on the NOAEL from the Vieregge study. No uncertainty factor was stated to be required as the NOAEL is based on a large epidemiological study. Using the NOAEL from the Kondakis study, it was assumed that up to 0.5 mg/day of manganese (equivalent to 0.008 mg/kg bw for a 60 kg adult) in addition to the diet would not result in adverse effects in older people. Assuming a dietary intake of 8.2 mg, acceptable total manganese intakes were estimated to be 12.2 mg/day in the general population (equivalent to 0.2 mg/kg bw in a 60 kg adult) and 8.7 mg/day (equivalent to 0.15 mg/kg bw in a 60 kg adult) for older people.

It was stated that some population groups may be exposed to higher levels of manganese as a result of tea consumption, making tea the largest contributor to manganese intake in the UK.

2.2.4 Nordic Nutrition Recommendations (NNR, 2012)

NNR Project Group (2012) has not set an UL for manganese with reference to the SCF finding data too uncertain to set an UL, and to EVM reporting data insufficient to set a SUL for manganese.

2.2.5 Summary upper intake levels

Table 2.2.5-1 summarises the evaluation of upper intake levels from the authorities mentioned above. An UL was set by the IOM based on intake data from food, while food supplement data was not used.

Table 2.2.5-1 Overview of upper intake levels in adults set by various authorities.

Authority	Upper level, mg/day	Based on	NOAEL mg/day	LOAEL mg/day	UF
IOM, 2001	11	Human studies – intake from Western diet without any neurotoxic effects	11	15	1
SCF, 2000	None				
EVM, 2003	4, from supplements only as a guidance level (GL) and assuming 8.2 from diet	Human studies on drinking water	4 suppl.		1
NNR, 2012	None (ref SCF and EVM)				

3 Intakes of manganese

3.1 Dietary intake of manganese in Norway

There are no data on habitual intake of manganese in the Norwegian population, because no available data exists for manganese in the Norwegian food composition table. Neither has there been performed evaluations with Duplicate studies, Market Baskets methods or Total Diet methods.

Water can be an important manganese source, but information from Water Works Norway shows low concentrations in drinking water in Norway (personal communication/FHI). Mean intake of manganese through water will be between 0.02 and 0.34 mg/day if intake is around 2 litre water per day.

Table 3.1-1 Concentration of manganese in drinking water in different regions in Norway.

Regions	Mean mg/L	Max mg/L	Min mg/L
Norway- East	0.02	0.05	0.01
Norway – South	0.01	0.01	0.00
Norway- West	0.01	0.04	0.01
Norway- Middle	0.02	0.02	0.01
Norway - North	0.01	0.17	0.01

3.2 Dietary intake of manganese in Europe

3.2.1 Sweden

Estimated daily intake of manganese analysed in a Market Basket study in 2015, was 4.2 mg per person and day (Livsmedelsverket, 2017), which was close to the results from a Market Basket study in 2010 (4.0 mg). Main contributor to estimated manganese intake was cereals (57%).

3.2.2 Denmark

In Denmark, the Danish Technical University (DTU) has evaluated the daily intake of manganese in 100 men by collecting duplicate portions of their regular diets for 48 hours which showed a manganese intake of 3.9 mg/day (Bro et al., 1990).

DTU has performed new dietary intake calculations of manganese based on energy intake in different age groups from Danskenes kostvaner 2013 and 2015. Danskenes kostvaner is a nationally representative survey of diet and physical activity in the Danish population aged 4-75 years and was carried out in 2011-2013 (DANSDA) (DTU, 2015). Diet was assessed

through a 4-day food record. Manganese was not part of the standard battery of minerals calculated.

Through communication with the Danish Veterinary and Food Administration, NFSA has obtained data on dietary manganese.

Table 3.2.2-1 Median and 95-percentiles of intake of manganese from the diet in various age groups in the Danish population, estimated by the DTU.

Age	50 percentile-intake (mg/day)	95 percentile-intake (mg/day)
1-3	2.1	4.3
4-6	3.2	5.4
7-10	3.4	6.7
11-14	3.0	7.2
15-17	2.8	7.2
Women 25-34	3.9	6.9
Women 55-75	3.9	6.9
Women 65-75	3.7	6.9

Accordingly, it is suggested that manganese intake is adequate in the Scandinavian countries (NNR Project Group, 2012).

3.2.3 Other EU countries

Manganese intake among Finnish children 3-18 years was in the range of 3-7 mg/day calculated from food consumption data and food contents (Bro et al., 1990)

In EFSA (2013) on DRVs for manganese, national dietary surveys among children as well as among adults in EU countries are listed. Furthermore, duplicate studies, total diet studies and market basket studies are listed. Main food contributors are cereal-based products, vegetables, fruits and beverages (coffee, tea and alcoholic beverages).

Table.3.2.3-1 Mean (SD) intakes of manganese in different age groups reported in EU calculated from different dietary surveys.

Age group	Mean (SD) (mg/day) (country) Males	Mean (SD) (mg/day) (country) Females
1-3 years	No data	No data
4-6 years	No data	No data
7-9 years	1.7 (IRL) - 3.0 (A)	1.6 (IRL) - 2.9 (A)
10-14 years	2.3 (F) - 3.2 (A)	2.0 (F) - 2.8 (A)
15-17 years	2.4 (F) - 3.9 (SLO)	2.0 (F) - 2.8 (SLO)
Adults	3.1 (F) - 3.6 (IRL)	2.7 (F) – 3.3 (IRL)

Age group	Mean (SD) (mg/day) (country) Males	Mean (SD) (mg/day) (country) Females
Adults > 60 years	2.1 (H) - 4.3 (A)	2.9 (H) - 4.4 (A)

IRL=Ireland, A=Austria, F=France, H=Hungary, SLO=Slovakia.

Table.3.2.3-2 Mean habitual manganese intakes (mg/kg bw per day) in different age groups reported in EU as evaluated by Duplicate studies, Total Diet studies or Market Basket studies.

Age group	Duplicate/total diet/ market basket studies Males	Duplicate/total diet/ market basket studies Females
1.5 -4.5 years (UK) mean mg/kg bw per day	0.168 (P97.5=0.305)	0.168 (P97.5=0.305)
4-18 years (UK) mean mg/kg bw per day	0.106 (P97.5= 0.201)	0.106 (P97.5= 0.201)
3-17 years (F) mean mg/day	1.5 (P97.5=2.6)	1.5 (P97.5=2.6)
30-34 years (DK) mean mg/day (SD)	4.5 (2.2)	
24-35 years -pregnant (SF) mean mg/day		4.45-5.49
18-79 years (F) mean mg/day	2.16 (P95=3.55)	2.16 (P95=3.55)
20-69 years (D) mean mg/day	2.7-3.4	2.1-2.8
Adults (I) mean mg/day	1.38	1.38
18-74 years (NL) mean mg/day	3.3	3.3
Adults and children (UK) mean mg/day	5.24	5.24

UK=United Kingdom, F=France, DK=Denmark, D=Deutschland, NL=the Netherlands, SF=Finland, I=Italy.

4 Assessment of the suggested maximum limits for manganese in dietary supplements

VKM supports the decision of SCF not setting an UL for manganese. SCF (2000) concluded that the margin between oral effect levels in humans and the estimated intake from food was very low. Arguments used in the decision of SCF (2000) were that given the findings on neurotoxicity and the potentially higher susceptibility of some subgroups in the general population, oral exposure to manganese beyond the levels normally present in food and beverages could represent a risk of adverse health effects. In a recent extensive report on environmental exposure to manganese by (ATSDR, 2012), it was concluded that no oral minimal risk levels could be derived for acute-, intermediate- or chronic-duration exposure to excess inorganic manganese because of inconsistencies in the dose-response relationship across studies. Furthermore, in the ATSDR report it is expressed concern about lack of information regarding all intakes of manganese (e.g. dietary intakes plus supplementation doses).

The mean dietary intakes of adults of 3.9 mg/day (Denmark) and 4 mg/day (Sweden) are within an adequate intake (AI) as suggested by EFSA (2013) (3 mg/day for adults). In (NNR Project Group, 2012) it is suggested that manganese intake in the Scandinavian countries is adequate. According to data obtained from DTU in Denmark, intake in the 95 percentiles in various age groups ranging from 1 to 75 years was 4.3 – 7.2 mg/day. Adult men were not included in these figures.

Irreversible neurotoxic adverse effects from intakes of manganese close to adequate intakes have been reported in humans. Furthermore, manganese intakes are assumed to be adequate and subsequently there is no scientific rationale for including manganese in food supplements. VKM considers that any dose of manganese as an ingredient in food supplements may be associated with increased risk of negative health effects.

5 Uncertainties

For the determinations of the ULs for manganese, SCF, IOM and EVM have not reached the same conclusions, indicating uncertainty regarding establishment of these ULs both for adults, and even more for children and adolescents. Long-term clinical studies are requested by all these scientific bodies to ascertain ULs of scientific value.

In Norway there are no data on dietary intake of manganese in the population and intake data are collected from Denmark and Sweden, as well as from other European countries. Uncertainties regarding methods for collecting intake data is also noticeable.

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 manganese from the diet, including fortified products, in all age groups in the population above 1 year. As there is no data on manganese 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 National Food Institute in Denmark (DTU).

VKM is also requested to evaluate the consequences of establishing a maximum limit for manganese in food supplements of 1, 5 or 10 mg per daily dose, and to evaluate these scenarios against existing tolerable upper intake levels.

Because no dietary intake data for manganese exists for Norway, VKM has gathered dietary information from Denmark and Sweden. These data suggest a mean dietary intake of 3.9 mg/day in Denmark and 4 mg/day of manganese in Sweden. In (NNR Project Group, 2012) manganese intake is evaluated to be adequate in the Scandinavian countries.

Irreversible neurotoxic adverse effects from intakes of manganese close to adequate intakes have been reported. Furthermore, manganese intakes are assumed to be adequate and subsequently there is no scientific rationale for including manganese in food supplements. VKM considers that any dose of manganese as an ingredient in food supplements may be associated with increased risk of negative health effects.

VKM emphasises that the current assessment of maximum limits for manganese in food supplements is merely based on published reports concerning upper levels from the IOM (2001, USA), SCF (2003, EU), 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

EFSA has not set an UL for manganese. Furthermore, no Norwegian intake data for manganese exits.

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