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SCIENTIFIC OPINION

Scientific Opinion on Dietary Reference Values for manganese[1]

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

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

Following a request from the European Commission, the Panel on Dietetic Products, Nutrition and Allergies (NDA) derived Dietary Reference Values (DRVs) for manganese. Manganese is an essential dietary mineral which is a component of a number of metalloenzymes involved in amino acid, lipid and carbohydrate metabolism. A specific manganese deficiency syndrome has not been described in humans. The body is able to adapt to a wide range of manganese intakes by regulating both efficiency of absorption in the intestine and the quantity excreted via bile. There are no reliable and validated biomarkers of manganese intake or status and data on manganese intakes versus health outcomes are not available for DRVs for manganese. As there is insufficient evidence available to derive an average requirement or a population reference intake, an Adequate Intake (AI) is proposed. Mean intakes of manganese in adults in the EU are around 3 mg/day. In addition, null or positive balances have consistently been observed with intakes of manganese above 2.5 mg/day. An AI of 3 mg/day is proposed for adults, including pregnant and lactating women. For infants aged from 7 to 11 months, an AI of 0.02–0.5 mg/day is proposed, which reflects the wide range of manganese intakes that appear to be adequate for this age group. The AI for children and adolescents is based on extrapolation from the adult AI using isometric scaling and reference body weights of the respective age groups.

KEY WORDS

manganese, Dietary Reference Value, Adequate Intake

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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 for the European population, including manganese.

In 1993, the Scientific Committee for Food set an Acceptable Range of Intakes for adults at 1–10 mg/day, considering observed intakes of manganese in European countries and data from balance studies. A few other authorities have set Adequate Intakes (AIs) for manganese, based on similar considerations.

Manganese is an essential dietary element for mammals. It is a component of metalloenzymes such as superoxide dismutase, arginase and pyruvate carboxylase, and is involved in amino acid, lipid and carbohydrate metabolism. A specific manganese deficiency syndrome has not been described in humans.

Absorption of manganese in the intestine is low (< 10 %). Regulation at the level of absorption appears to be one of the adaptive responses to dietary manganese intake and such regulation allows manganese homeostasis to be maintained over a wide range of intakes. A reduction in the biological half-life of manganese has been observed with increased dietary manganese intakes indicating the role of whole-body turnover rate in manganese homeostasis. Elimination of manganese is primarily via the faeces.

The assessment of manganese intake or status using biological markers is difficult owing to the rapid excretion of manganese into bile, to homeostatic mechanisms and to the lack of sensitivity of biomarkers over the normal range of intakes. Therefore, there are no reliable and validated biomarkers of manganese intake or status.

Nuts, chocolate, cereal-based products, crustaceans and molluscs, pulses, and fruits and fruit products are rich sources of manganese. The main contributors to the manganese intake of adults are cereal-based products, vegetables, fruits and fruit products and beverages. In the EU, estimated mean manganese intakes of adults range from 2 to 6 mg/day, with a majority of values around 3 mg/day. Estimated mean manganese intakes range from 1.5 to 3.5 mg/day in children, and from 2 to 6 mg/day in adolescents.

Several balance studies have been undertaken to establish manganese requirements. These studies demonstrate that the body adapts quickly to changes in manganese intake. Although balance may be maintained at intakes below 2.5 mg/day, null or positive balances have consistently been observed with manganese intakes above 2.5 mg/day. Manganese balance may be influenced by the overall diet, variations in individual rates of absorption or excretion, differences in body contents and adaptation to varying dietary levels, which make comparisons between subjects and studies difficult.

No data on manganese intakes and health outcomes were identified for the setting of DRVs.

As the evidence to derive an Average Requirement and thus a Population Reference Intake is considered insufficient, an Adequate Intake (AI) is proposed. Observed mean intakes of adults in the EU are typically around 3 mg/day. In addition, null or positive balances have consistently been observed with intakes of manganese above 2.5 mg/day. An AI of 3 mg/day for adults is, therefore, proposed. The adult AI also applies to pregnant and lactating women. For infants aged from 7 to 11 months, the Panel decides to set a range for the AI of 0.02–0.5 mg/day. This reflects the wide range of manganese intakes that appear to be adequate, based on upwards extrapolation of manganese intakes in fully breast-fed infants, observed intake of manganese in infants aged 6 and 12 months and the value estimated from extrapolation of the adult AI using isometric scaling. For children and adolescents, an AI is proposed based on extrapolation from the adult AI using isometric scaling (i.e. extrapolation based on reference body weights of the respective age groups) and rounding to the

nearest 0.5. The respective AIs vary from 0.5 mg/day in young children aged 1–3 years to 3.0 mg/day in adolescent boys and girls.

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BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

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, 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;
- Protein;

[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.

- 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

In 1993, the Scientific Committee for Food (SCF) adopted an opinion on nutrient and energy intakes for the European Community (SCF, 1993). For manganese, the SCF set an Acceptable Range of Intakes for adults at 1–10 mg/day.

2. Definition/category

2.1. Chemistry

Manganese (Mn) has an atomic mass of 54.9 Da. It can exist in a number of oxidation states ranging from −3 to +7; Mn(II) and Mn(III) are the predominant forms in biological systems (SCF, 2000; Roth, 2006).

2.2. Functions of manganese

2.2.1. Biochemical functions

Manganese is an essential dietary mineral for mammals; it is a component of metalloenzymes such as superoxide dismutase, arginase and pyruvate carboxylase, and is involved in amino acid, lipid and carbohydrate metabolism (SCF, 1993; IOM, 2001; NHMRC, 2006). Glycosyltransferases and xylosyltransferases, which are involved in proteoglycan synthesis (e.g. for bone formation), are sensitive to manganese status in animals (Nielsen, 1999).

2.2.2. Health consequences of deficiency and excess

2.2.2.1. Deficiency

Manganese-deficient animals exhibit impaired growth, skeletal abnormalities, reproductive deficits, ataxia of the newborn and defects in lipid and carbohydrate metabolism. In contrast, evidence of manganese deficiency in humans is poor. A specific deficiency syndrome has not been described in humans (SCF, 1993; WHO, 1996; SCF, 2000; IOM, 2001). In a depletion-repletion study, seven male subjects were fed a conventional diet providing 2.59 mg manganese/day for three weeks (baseline), followed by a purified diet containing 0.11 mg manganese/day for 39 days. A fleeting dermatitis, miliaria crystallina, developed in five out of the seven subjects at the end of the depletion period and disappeared as repletion began (Friedman et al., 1987).

2.2.2.2. Excess

Reports of adverse effects resulting from manganese exposure in humans are associated primarily with inhalation in occupational settings. The symptoms of manganese toxicity can result in a permanent neurological disorder known as manganism (ATSDR, 2012). Oral exposure to manganese, especially from contaminated water sources, can also cause adverse health effects, which are similar to those observed from inhalation exposure. An actual threshold level at which exposure to manganese produces neurological effects in humans has not been established (ATSDR, 2012).

For the derivation of a Tolerable Upper Intake Level (UL), the SCF (2000) noted that exposure to high levels of manganese by inhalation or oral intake of manganese may be neurotoxic. Assuming a consumption of 2 L of drinking water/day, the cohorts that showed neurological effects were exposed to estimated manganese intakes from drinking water ranging from 0.16 mg to 28 mg/day (Kawamura et al., 1941; Kondakis et al., 1989; He et al., 1994). However, the SCF noted the limitations of these studies, including the uncertainty of the contribution from food to manganese intake and the lack of information on possible confounding variables, which make firm conclusions difficult. As a no observed adverse effect level (NOAEL) for critical endpoints from animal studies was not available, and because of the limitations of the data in humans, a UL could not be set (SCF, 2000).

The US Institute of Medicine (IOM, 2001) established a NOAEL and a UL of 11 mg/day for adults, based on the fact that adverse effects in subjects ingesting up to 10.9 mg/day with Western diets have not been reported. Recently, ATSDR (2012), in its extensive report on environmental exposure to manganese, indicated that no oral minimal risk levels (MRLs) could be derived for acute-, intermediate- or chronic-duration exposure to excess inorganic manganese because of inconsistencies in the dose-response relationship information across studies, a lack of information concerning all intakes of manganese (e.g. dietary intakes plus administered doses) and uncertainties about other possible confounding exposures to neurotoxic agents in the drinking water or food.

2.3. Physiology and metabolism

2.3.1. Intestinal absorption

The amount of manganese absorbed is influenced by the concentration of manganese in the diet, with low dietary manganese intake resulting in increased manganese absorption relative to intake (Finley, 1999; Finley et al., 2003). 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. Sex differences for manganese absorption have been noted in healthy men and women (18–40 years of age), with women absorbing significantly more manganese than men. It has been hypothesised that sex differences may be related to iron status, as an inverse correlation between plasma ferritin and manganese absorption has been observed (Finley et al., 1994; Finley, 1999). The interaction between iron and manganese is further discussed in Section 2.3.7.

Absorption of radioisotopically (extrinsically or intrinsically) labelled manganese from vegetable sources (lettuce, spinach, wheat, sunflower seeds) was shown to range from 1.7 % to 5.2 % compared with 7.7–10.2 % from a manganese chloride solution with a comparable manganese content (Johnson et al., 1991). Similarly, a mean manganese absorption of 6.0–6.2 % was observed from chard (Davidsson et al., 1991b).

Absorption has been suggested to take place through active transport mechanisms (Garcia-Aranda et al., 1983) and passive diffusion (Bell et al., 1989). Some evidence indicates that manganese uptake in the intestine is mediated by high-affinity metal transporters, such as divalent metal transporter-1 (DMT1, also called DCT1), which is also involved in the transport of other metals (Chua and Morgan, 1997; Gunshin et al., 1997; Garrick et al., 2003). Manganese is mainly absorbed as Mn(II).

High intakes of calcium, phosphorus and phytates have been reported to impair manganese absorption (SCF, 1993; IOM, 2001; ATSDR, 2012), although this is probably of limited nutritional significance in the context of whole diets, as specific clinical symptoms of manganese deficiency in humans have not been reported (SCF, 1993).

The Panel notes that intestinal absorption of manganese is below 10 %.

2.3.2. Transport in blood

Manganese is taken up from the blood by the liver and is transported to extrahepatic tissues bound primarily to transferrin, alpha2-macroglobulin and albumin (IOM, 2001; Buchman, 2006; Roth, 2006).

The manganese concentration in the blood of healthy adults is reported to range from 4 to 15 µg/L (Barceloux, 1999; ATSDR, 2012). Almost all manganese in blood is associated with cells: circulating manganese is mainly found in erythrocytes (ca. 66 %), a smaller fraction is contained in leucocytes and platelets (ca. 30 %) and plasma contains about 4 % (Milne et al., 1990). Typically, manganese concentrations in whole blood have been reported to be 5–10 times higher than in serum (Pleban and Pearson, 1979).

2.3.3. Distribution to tissues

In the Mn(II) state, manganese has been described as entering cells via a number of metal transport mechanisms, including DCT1, ZIP8 and ZIP14 transporters (Gunshin et al., 1997; Himeno et al., 2002; Garrick et al., 2003; Himeno et al., 2009; Jenkitkasemwong et al., 2012). In the Mn(III) state, evidence suggests that manganese is transported via transferrin (Aschner and Aschner, 1990; Aschner and Gannon, 1994). Thus, manganese uptake into a specific cell type seems to be mediated by the uptake mechanisms expressed in that cell type and the oxidation state of manganese. There can be competition between metals using the same transport mechanisms.

In cells, manganese is mainly found in the mitochondrial and nuclear fractions (Maynard and Cotzias, 1955). Typically, the liver, pancreas and kidneys have high manganese concentrations (Aschner and Aschner, 2005). Tissues with high energy demand (e.g. brain) and high pigment content (e.g. retina, dark skin) seem to have the highest manganese concentrations, although this is not supported by all studies (ATSDR, 2012).

Average tissue concentrations are typically between 0.1 and 1 µg manganese/g wet weight (Tipton and Cook, 1963; Sumino et al., 1975). The concentration in the liver is slightly higher (1.2–1.7 µg manganese/g wet weight), and the lowest concentrations are found in bone and fat (around 0.1 µg manganese/g wet weight) (ATSDR, 2012).

Published data on maternal blood concentrations of manganese during pregnancy indicate higher concentrations (range of means: ca. 15–20 µg/L) than the values observed in the blood of the general adult population (4–15 µg/L; see Section 2.3.2) (Takser et al., 2004; Rudge et al., 2009; Zota et al., 2009; Kopp et al., 2012). Studies in mother-child pairs report manganese concentrations in cord blood which are two- to three-fold higher (range of means: ~ 30–40 µg/L) than in maternal blood (Takser et al., 2003; Takser et al., 2004; Vigeh et al., 2008; Zota et al., 2009; Kopp et al., 2012).

2.3.4. Storage

No specific storage organs or storage forms for manganese have been identified. The liver, pancreas and kidneys have been reported to contain the highest manganese concentrations (Aschner and Aschner, 2005; ATSDR, 2012).

2.3.5. Metabolism

Over time, Mn(II) in plasma is presumed to be oxidised to Mn(III) (ATSDR, 2012), although the mechanisms involved in this conversion are not fully elucidated (Roth, 2006). This is supported by the observation that the oxidation state of the manganese ion in several enzymes appears to be Mn(III) (Utter, 1976; Leach and Lilburn, 1978), whereas most manganese exposure is either as Mn(II) or Mn(IV) (ATSDR, 2012).

2.3.6. Elimination

Elimination of manganese from the body is reported to vary, with a half-life between 13 and 37 days (ATSDR, 2012). There are large inter-individual variations (Davidsson et al., 1989). Manganese has a longer half-life in men than in women (Finley et al., 1994), which has been suggested to be related to sex differences in iron status (Finley et al., 1994; Finley, 1999) (see Section 2.3.7). A reduction in biological half-life has been observed with increased dietary manganese intakes (Finley et al., 2003), indicating a role of whole-body manganese turnover rate in homeostatic response to dietary manganese levels.

Manganese is excreted into the small intestine via bile (Buchman, 2006; ATSDR, 2012). The main route of elimination is via the faeces, while very little (around 1 % of dietary intake) is excreted in the urine. Typical ranges of manganese concentrations in urine are 1–8 µg/L (ATSDR, 2012). Mean urinary excretion of manganese was shown to be 0.4 µg (7.0 nmol)/g creatinine in 10 healthy men, and

0.5 µg (9.3 nmol)/g creatinine in 47 healthy women, and was not related to oral intake of manganese (Greger et al., 1990; Davis and Greger, 1992).

Manganese secretion into breast milk was reported to be below 1 % of intake in one balance study (Schäfer et al., 2004). There is no correlation between maternal dietary intake and human milk manganese concentrations (Wünschmann et al., 2003; Leotsinidis et al., 2005; Qian et al., 2010). Data from studies published since 1990 showed that mean manganese concentrations varied from 0.8 to 30 µg/L (3–30 µg/L in Europe) (Mullee et al., 2012) (see Appendix A). The concentration is substantially higher in colostrum than in mature milk (Arnaud and Favier, 1995; Krachler et al., 1998; Leotsinidis et al., 2005). In mature milk, the manganese concentration appears to be relatively constant in the first half-year of breastfeeding (Arnaud and Favier, 1995; Aquilio et al., 1996; Krachler et al., 1998; Friel et al., 1999; Yamawaki et al., 2005), but may decrease after six months of lactation (Al-Awadi and Srikumar, 2000).

2.3.7. Interaction with iron

Some evidence suggests that iron and manganese can share common absorption and transport mechanisms, including protein transporters such as the divalent metal transporter-1 (DMT-1) or the Tf/TfR system (Fitsanakis et al., 2010). Rossander-Hulten et al. (1991) found a significant reduction of iron absorption when adding manganese to a hamburger meal and to an iron-rich solution. Davidsson et al. (1991a) found that adding iron to wheat bread did not significantly affect manganese absorption compared with wheat bread alone. Davis et al. (1992) observed that high intakes of non-haem iron, but not of haem iron, were associated with lower serum manganese concentrations and higher urinary manganese concentrations. Iron supplementation (60 mg/day as ferrous fumarate for four months) tended to decrease serum manganese concentrations and manganese superoxide dismutase (MnSOD) activity in white blood cells, but changes were statistically significant only at days 60 and 124, respectively (Davis and Greger, 1992).

Iron status may affect manganese absorption. Intestinal absorption of manganese was observed to be increased in individuals with iron deficiency anaemia (Mena et al., 1969; Thomson et al., 1971; Sandström et al., 1986). Conversely, a higher iron status (i.e. higher ferritin concentrations) has been shown to be associated with significantly lower manganese absorption (Finley, 1999) and retention (Momcilovic et al., 2009). In addition, absorption of manganese has been observed to be lower in men than in women (18–40 years), which may be related to the fact that men usually have higher iron stores than women (Finley et al., 1994). Finley (1999) found that, among women on a low-manganese diet, the biological half-life of manganese was longer in women with low serum ferritin than in women with high serum ferritin concentrations.

2.4. Biomarkers of intake and status

The IOM (2001) concluded that serum/plasma or urinary manganese concentrations may be sensitive to large variations in intake (i.e. very low or high intakes), but that they are not sensitive markers when habitual amounts of manganese are consumed. Whole blood concentration of manganese appears to be extremely variable and of limited value as a marker of intake or status (IOM, 2001). In humans, MnSOD activity has been observed to increase with high intakes of manganese (15 mg/day) (Davis and Greger, 1992), but is also influenced by other factors (Greger, 1999; IOM, 2001; NHMRC, 2006) and, therefore, lacks specificity. Greger (1999) suggested that the best measurements for detecting an inadequate supply of manganese could be a combination of serum manganese concentration and MnSOD activity, and perhaps blood arginase activity. However, no evidence is available on the effects of manganese depletion on the activity of manganese-dependent enzymes in humans.

Hope et al. (2006) determined the influence of tea drinking on manganese intake, on fasting manganese concentrations in plasma and whole blood and on leucocyte expression of MnSOD and aminopeptidase P in 24 tea drinkers and 28 controls. Mean manganese intake as assessed by a food frequency questionnaire (FFQ) was significantly lower in non-tea drinkers (3.2 mg/day) than in tea drinkers (5.5 or 10 mg/day, depending on the value used for the manganese content of black tea).

There was no correlation between manganese intake and any of the parameters measured and no differences between groups were observed, which confirms that these are not sensitive and reliable markers of intake or status at usual levels of manganese intake.

As the major route of excretion is through faeces and as less than 10 % of dietary manganese is absorbed (see Section 2.3.1), faecal manganese could, in theory, provide a useful marker of recent dietary intake (Hambidge, 2003). Faecal manganese concentration has been observed to be sensitive to various levels of intake under controlled conditions (Freeland-Graves et al., 1988). However, because faecal manganese is composed of unabsorbed dietary manganese and manganese excreted in bile, it is influenced by a variety of factors (e.g. diet composition, previous intake) and may thus be of limited use in practice.

The manganese concentration of hair and toenails, as well as magnetic resonance imaging measurements to detect the presence of increased concentrations of manganese in the brain, have also been investigated as potential markers of chronic manganese exposure (Laohaudomchok et al., 2011; ATSDR, 2012). This was mainly in the context of studies assessing occupational or environmental exposure, and there is a lack of data on the association between usual dietary manganese intake and these measurements.

Overall, the assessment of manganese intake or status using biological markers is difficult owing to rapid excretion of manganese into bile, to homeostatic control and to the lack of sensitivity of biomarkers over the normal range of intakes.

The Panel concludes that there are no reliable and validated biomarkers of manganese intake or status.

3. Dietary sources and intake data

3.1. Dietary sources

Nuts, chocolate, cereal-based products, crustaceans and molluscs, pulses, and fruits and fruit products are rich sources of manganese (Rose et al., 2010; Anses, 2011) (Table 1).

The main food contributors (> 5 %) to manganese intake are cereal-based products, vegetables, fruits/fruit products and beverages (coffee, tea, alcoholic beverages) (Rose et al., 2010; Anses, 2011) (Appendix B). The EU legislation sets a parametric value of 50 µg/L for manganese in drinking water.[5]

Manganese salts permitted for use in foods[6] and food supplements[7] are manganese carbonate, manganese chloride, manganese citrate, manganese gluconate, manganese glycerophosphate and manganese sulphate (all as Mn(II)); in addition, manganese ascorbate, manganese L-aspartate, manganese bisglycinate, and manganese pidolate (all as Mn(II)) are permitted for use in food supplements.[6]

Manganese in infant formula and follow-on formula is regulated by Directive 2006/141/EC[8] in the EU.

[5] Council Directive 98/83/EC of 3 November 1998 on the quality of water intended for human consumption, OJ L 330, 5.12.1998, p. 23.
[6] 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.
[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] Commission Directive 2006/141/EC of 22 December 2006 on infant formulae and follow-on formulae and amending Directive 1999/21/EC, OJ L 401, 30.12.2006, p. 1.

Table 1: Rich sources of manganese in the French and British total diet studies (Rose et al., 2010; Anses, 2011)

	Mean manganese concentration (mg/kg)	Country
Nuts	24.9	UK
Dried fruits, nuts and seeds	11.9	France
Chocolate	8.9	France
Bread	8.0	UK
Miscellaneous cereals	8.0	UK
Bread and dried bread products	7.2	France
Sweet and savoury biscuits and bars	4.3	France
Crustaceans and molluscs	4.9	France
Pulses	4.7	France
Fruit products	4.6	UK

3.2. Dietary intake

Data from national dietary surveys, as well as results from duplicate diet studies,[9] total diet studies[10] (TDSs) and market basket studies,[11] provide information on manganese intake in European countries.

National dietary surveys combine individual consumption data collected from dietary records, diet history, 24-hour recall, or food frequancy questionnaires (FFQs) with analytical data from food composition tables (EFSA, 2009). Duplicate diet studies, TDSs and market basket studies involve analysis of manganese content in foods. TDSs and market basket studies are usually used to estimate average intake among the general population (EFSA/FAO/WHO, 2011), whereas duplicate diet studies allow individual intakes in selected (small) sub-groups of the population to be estimated.

Data on manganese intakes of infants, children and adolescents are presented in Appendix C (10 studies from eight EU countries), and data for adults are presented in Appendix D (17 studies from 12 EU countries).

3.2.1. Infants, children and adolescents

A Finnish study undertaken in infants aged 1–3 months showed mean intakes ranging from 0.5 to 0.9 µg/kg body weight per day (i.e. 3–4 µg/day) (Vuori, 1979). In seven studies analysing the breast milk of women residing in the EU, mean manganese concentrations in milk varied from 3 to 30 µg/L (Parr et al., 1991; Arnaud and Favier, 1995; Aquilio et al., 1996; Krachler et al., 1998; Bocca et al., 2000; Wünschmann et al., 2003; Leotsinidis et al., 2005). Based on this information, and assuming an average milk intake of 0.8 L/day (Butte et al., 2002; FAO/WHO/UNU, 2004; EFSA NDA Panel, 2009), the estimated mean intake of infants fed human milk as the principal food during the first six months of life ranges from 2.4 to 24 µg/day.

National dietary surveys in children (3–14 years) showed that average daily manganese intakes varied between 1.4 and 3.4 mg/day in boys and between 1.3 and 3.3 mg/day in girls. In adolescents (older

[9] Duplicate diet studies require the provision, for subsequent analyses, of an exact duplicate of a 24-hour food intake by an individual. It is usually done in a home setting, over a period of time (usually 3-7 days). Foods are collected as consumed, homogenised and analysed.

[10] Total diet studies (TDSs) consist of selecting, collecting and analysing commonly consumed food purchased at a retail level, processing the food as for consumption, pooling the prepared food items into representative food groups and analysing them for substances of interest. They are designed to cover the whole diet and to measure the amount of each substance ingested by the population living in a country over their lifetime, using representative consumption data such as data from national consumption surveys (chronic dietary intake) (EFSA/FAO/WHO, 2011).

[11] Market basket studies are TDS-like studies where the foods are not or only minimally processed before analysis. They are restricted to a predetermined set of foods.

than 14 years), average manganese intakes were between 2.4 and 6.2 mg/day in males and between 1.9 and 5.4 mg/day in females (SCF, 2003; Mensink GB et al., 2007; Afssa, 2009).

Data from the French and British TDSs (Rose et al., 2010; Anses, 2011) indicate that French children aged 3–17 years had a mean manganese intake of 1.5 mg/day, whereas the British data showed mean intakes of 0.168 and 0.106 mg/kg body weight/day for children aged 1.5–4.5 years and 4–18 years, respectively.

Overall, the Panel notes that mean manganese intakes in various EU countries range from around 1.5 to 3.5 mg/day in children, and from 2 to 6 mg/day in adolescents.

3.2.2. Adults

National dietary surveys from Austria (Elmadfa et al., 2009a), France (Afssa, 2009), Germany (Mensink and Beitz, 2004), Hungary (Bíró et al., 2007), Ireland (IUNA, 2011) and the UK (Henderson et al., 2003) reported mean daily intake estimates for manganese ranging from 2.5 to 6.6 mg in men and from 2.0 to 5.5 mg in women, with most values around 3 mg/day.

Two national TDSs conducted in France (Anses, 2011) and the UK (Rose et al., 2010), which were representative of the average diet of the population in these countries and covered most relevant sources of manganese in the diet, estimated mean manganese intakes of 2.2 mg/day[12] for French adults and 5.2 mg/day[13] for British adults and children, respectively.

Small TDSs conducted in Finland (Vuori et al., 1980) and Italy (Turconi et al., 2009), and market basket studies carried out in Spain (Marti-Cid et al., 2009; Rubio et al., 2009) and Sweden (NFA, 2012), provided mean manganese intakes between 1.4 and 5.5 mg/day. Because they involved specific population groups (e.g. breastfeeding women), limited food sampling methods and/or sales statistics or local surveys as the source of consumption data, the Panel notes that these results may not be representative of the average manganese intakes in these countries.

Mean manganese intakes estimated from duplicate diet studies in Belgium (Buchet et al., 1983), Germany (Anke et al., 1991; Schäfer et al., 2004), Denmark (Bro et al., 1990) and the Netherlands (Ellen et al., 1990) ranged from 2.0 mg (n = 104; Anke et al., 1991) to 2.8 mg/day (n = 28; Schäfer et al., 2004) in women, and from 3.0 mg (n = 104; Anke et al., 1991) to 4.5 mg/day (n = 100; Bro et al., 1990) in men.

Overall, the Panel notes that estimated mean manganese intakes of adults in the EU range from 2 to 6 mg/day, with the majority of values around 3 mg/day. Wide inter-individual variation may occur, depending on individual characteristics and dietary habits (e.g. vegetarian vs. mixed diet).

4. Overview of Dietary Reference Values and recommendations

4.1. Adults

The German-speaking countries (D-A-CH, 2013) estimated that a manganese intake of 2–5 mg/day is associated with neither deficiency nor toxicity. Owing to insufficient scientific evidence for deriving a manganese requirement, an intake of 2–5 mg/day was derived as the Adequate Intake (AI).

The US Institute of Medicine (IOM, 2001) did not have sufficient data to set an Estimated Average Requirement (EAR) for manganese. Because a wide range of manganese intakes can result in manganese balance, balance data could not be used to set an EAR. In addition, IOM considered that

[12] From the 41 food groups constituting the diet, the main contributors were bread and dried bread products (29 %), vegetables (including potatoes; 8 %), coffee (5 %), other hot beverages (5 %), pasta (5 %), fruit (5 %) and alcoholic beverages (5 %).
[13] From the 20 food groups constituting the diet, the main contributors were beverages (41 %), miscellaneous cereals (20 %), bread (16 %) and fruit products (5 %).

because overt symptoms of manganese deficiency are not apparent in the North American population, a recommended dietary allowance (RDA) based on balance data (Friedman et al., 1987; Freeland-Graves and Turnlund, 1996; Hunt et al., 1998) would be most likely to overestimate the requirement for most North American individuals. Based on the US TDS (1991–1997), the median dietary manganese intake was 2.1–2.3 mg/day for men and 1.6–1.8 mg/day for women. IOM considered that dietary intake assessment methods tend to underestimate the actual daily intake of foods and, therefore, considered the highest intake value reported for the four adult age groups (19–30 years, 31–50 years, 51–70 years, 71 years and over) to set the AI for each sex. The AI was set as 2.3 mg/day for men and 1.8 mg/day for women.

Afssa (2001) stated that the requirement was estimated to be between 1 and 2.5 mg/day in adults (Freeland-Graves and Turnlund, 1996), and that dietary intakes were between 2 and 9 mg/day, but could be above 10 mg/day in vegetarians (Freeland-Graves and Turnlund, 1996; Nielsen, 1996). Afssa considered that setting a Population Reference Intake (PRI) for manganese for adults of all ages or for pregnant and lactating women was not justified, as requirements were largely met by dietary intakes, although a reference value might be in the order of 2–3 mg/day for adults.

The SCF (1993) set an Acceptable Range of Intakes for adults at 1–10 mg/day, considering that most intakes were around 2–3 mg/day, that some reached 8.3 mg/day (Friedman et al., 1987; Hurley and Keen, 1987), that a basal average requirement of 0.74 mg/day had been derived from balance studies (Freeland-Graves et al., 1988) and that negative balances observed on dietary intakes between 1.21 and 2.89 mg/day could represent homeostasis (Freeland-Graves et al., 1988).

The UK Committee on Medical Aspects of Food Policy (COMA) (DH, 1991) considered that observed population intakes were adequate (Anonymous, 1988), and derived Safe Intakes above 1.4 mg/day for adults.

The Nordic countries (NNR, 2012), the Health Council of the Netherlands (2009) and WHO/FAO (2004) did not derive DRVs for manganese for adults.

Table 2: Overview of Dietary Reference Values (DRVs) for manganese for adults

	D-A-CH (2013)	IOM (2001)	SCF (1993)	DH (1991)
Type of DRV	**AI [(a)] (mg/day)**	**AI [(a)] (mg/day)**	**ARI [(b)] (mg/day)**	**SI [(c)] (mg/day)**
Age (years)	≥ 15	≥ 19	All	Adults
DRV	2–5	2.3 (men) 1.8 (women)	1–10	> 1.4

(a): AI, Adequate Intake
(b): ARI, Acceptable Range of Intakes.
(c): SI, Safe Intake; the Safe Intake was judged to be a level or range of intake at which there is no risk of deficiency, and below a level where there is a risk of undesirable effects.

4.2. Infants and children

The German-speaking countries (D-A-CH, 2013) estimated AIs for infants aged 4 to < 12 months from observed intakes of 71 and 80 µg/kg body weight per day in Canadian infants aged 6 and 12 months, respectively (Gibson and DeWolfe, 1980). AIs for children and adolescents were extrapolated, taking into account body weight and estimated food intake.

For infants, IOM (2001) derived an AI reflecting the observed mean manganese intake of infants principally fed human milk. For breast-fed infants from birth to six months of age, the AI was set at 0.003 mg/day (after rounding), according to an average milk consumption of 0.78 L/day and an average manganese concentration in human milk of 3.5 µg/L (Casey et al., 1985; Casey et al., 1989;

Aquilio et al., 1996). For older infants aged 7–12 months, two approaches were considered that provided coherent results: the first one was based on the average manganese intake of infants aged 6-12 months (71-80 µg/kg body weight per day) (Gibson and DeWolfe, 1980) and the reference weights of 7 and 9 kg for these two population groups; the second approach was based on extrapolation from the value for adults using reference body weights. The AI was set at 0.6 mg/day. For children, IOM (2001) considered that the few balance studies available could not be used to set an EAR. Therefore, for children aged 1–18 years, AIs were set using the median intake for each of the age groups from the US TDS: 1.22 mg/day (1–3 years), 1.48 mg/day (4–8 years), 1.57 mg/day (girls 9–13 years), 1.91 mg/day (boys 9–13 years), 1.55 mg/day (girls 14–18 years) and 2.17 mg/day (boys 14–18 years).

The Nordic countries (NNR, 2012), the Health Council of the Netherlands (2009), WHO/FAO (2004), Afssa (2001), the SCF (1993) and the UK COMA (DH, 1991) did not derive DRVs for manganese for infants and children. However, the UK COMA (DH, 1991) considered that the observed population intakes were adequate, and that Safe Intakes would lie above 16 µg/kg body weight per day for infants and children.

Table 3: Overview of Dietary Reference Values (DRVs) for manganese for children

	D-A-CH (2013)	IOM (2001)
Age (months)		0–6
AI [(a)] (mg/day)		0.003
Age (months)	4–<12	7–12
AI (mg/day)	0.6–1.0	0.6
Age (years)	1-<4	1–3
AI (mg/day)	1.0–1.5	1.2
Age (years)	4–<7	4–8
AI (mg/day)	1.5–2.0	1.5
Age (years)	7–<10	9–13
AI (mg/day)	2–3	1.9 (boys) 1.6 (girls)
Age (years)	10–<15	14–18
AI (mg/day)	2–5	2.2 (boys) 1.6 (girls)
Age (years)	≥ 15	
AI (mg/day)	2–5	

(a): AI, Adequate Intake.

4.3. Pregnancy and lactation

IOM (2001) derived an AI of 2 mg/day (after rounding) for pregnant adolescent girls aged 14–18 years and for pregnant women aged 19–50 years. The value was extrapolated from the AI of non-pregnant women considering a median weight gain of 16 kg during pregnancy (Carmichael et al., 1997), and was also coherent with intake data from the US TDS.

For lactating women, an AI of 2.6 mg/day (after rounding) was derived based on the median manganese intake of lactating women from the US TDS and considering that manganese deficiency has not been observed in North America (IOM, 2001). IOM also noted that approximately 3 µg manganese per day is secreted in human milk.

5. Criteria (endpoints) on which to base Dietary Reference Values

5.1. Biomarkers as endpoints

The Panel considers there are no suitable biomarkers of manganese status which can be used to estimate manganese requirements (see Section 2.4).

5.2. Balance studies on manganese

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 intake, balance studies enable the quantification of basal or 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 a new steady state is reached (Young, 1986), or they might reflect only the conditions for maintenance of nutrient stores in the context of a given diet and, consequently, the relevance of the pool size for health still needs to be established for each nutrient (Mertz, 1987).

Two trials studied balances at various manganese intakes under controlled conditions and measured manganese balances over consecutive periods of time.

In a depletion-repletion study by Friedman et al. (1987), seven healthy males (aged 19–22 years) received a controlled purified diet containing 2.59 mg/day of manganese for three weeks, followed by a manganese-depleted purified diet containing 0.11 mg/day for 39 days, and repleted diets containing 1.53 mg/day for five days and then 2.55 mg/day for a further five days. During depletion, mean balance was negative during the first two seven-day periods (−1.78 ± 1.12 and −0.16 ± 0.13 mg/day), whereas it became close to zero for the four following periods (0.01 ± 0.03, 0.01 ± 0.02, −0.01 ± 0.03 and −0.02 ± 0.03 mg/day). Mean balance was positive during the two repletion periods (0.84 ± 1.33 and 1.02 ± 0.63 mg/day). The authors observed alterations in concentrations of cholesterol, calcium, phosphorus and alkaline phosphatase in the blood, and the appearance of dermatitis in five out of the seven subjects at the end of the depletion period, which disappeared as repletion began.

Freeland-Graves et al. (1988) provided five healthy males (aged 19–20 years) with controlled diets of conventional foods supplemented with five levels of manganese. The study was divided into five periods of 21, 21, 38, 11 and 14 days, in which the mean daily intakes of manganese were 2.89, 2.06, 1.21, 3.79, and 2.65 mg, respectively. Mean balances were slightly negative during the first three periods (−0.08 ± 0.06 mg/day, three subjects in negative balance and two subjects in positive balance; −0.02 ± 0.03 mg/day, two subjects in negative balance and three subjects in positive balance; −0.09 ± 0.03 mg/day, all subjects in negative balance) and became positive during the last two periods (0.66 ± 0.05 and 0.14 ± 0.05 mg/day, all subjects in positive balance). During the initial dietary period, the two subjects who were in positive balance had the lowest pre-study dietary manganese intakes, whereas the subjects who had the greatest negative balance had the highest pre-study intakes, which indicates that initial body pools of manganese may have influenced the results of the first balance period.

Two cross-over studies were designed to measure balance at two levels of manganese intake. Hunt et al. (1998) reported mean balances to be positive in 21 women (20–42 years) consuming controlled lacto-ovo-vegetarian or omnivorous diets for eight weeks providing mean manganese intakes of 5.9 mg/day and 2.5 mg/day, respectively. In a study by Finley (1999) involving women with low-ferritin (LF) or high-ferritin (HF) status (n = 11 in LF group vs. n = 16 in HF group) for two periods of 60 days, a low-manganese diet of ca. 0.7 mg/day resulted in slightly negative mean manganese

balances (LF group: −0.01 ± 0.37 mg/day; HF group: −0.12 ± 0.49 mg/day), whereas mean balances were positive with a high-manganese diet of 9.5 mg/day (LF group, 1.53 ± 0.37 mg/day; HF group, 0.59 ± 0.49 mg/day). Dietary manganese intake was not significantly associated with other clinical measures (including platelet manganese concentration, arginase activity and GSH-Px activity in erythrocytes).

Positive balances were observed in two women with respective mean manganese intakes of 2.48 mg/day and 2.62 mg/day for 27 days (McLeod and Robinson, 1978). In another study with 20 men and 20 women, balances did not differ significantly from zero (0.27 ± 1.07 mg/day in men vs. −0.12 ± 0.49 mg/day in women: not statistically different) when subjects consumed a controlled diet providing 3.51 mg/day of manganese (at an energy intake of 2 000 kcal/day) for four weeks (Finley et al., 1994).

Two seven-day balance studies by Patterson et al. (1984) and Schäfer et al. (2004), using duplicate diet techniques to estimate subjects' manganese intake through self-selected diets, reported negative balances with manganese intakes ranging from 2.4 to 5.9 mg/day. The Panel notes that subjects' usual diet was modified during the collection period in the study by Patterson et al. (1984) and that the time was likely to have been too short for a new equilibrium to have been reached, given the half-life of manganese (13–37 days; see Section 2.3.6).

A number of other balance studies instead investigated the influence of different dietary factors (e.g. other minerals and various types of fibre or macronutrient sources) on manganese balance (Greger et al., 1978; Spencer et al., 1979; Johnson et al., 1982; Behall et al., 1987; Hallfrisch et al., 1987; Holbrook et al., 1989; Johnson and Lykken, 1991; Ivaturi and Kies, 1992; Randhawa and Kawatra, 1993; Hunt et al., 1995; Finley et al., 2003; Nielsen, 2004). Some of these studies used relatively low amounts of manganese (around 1 mg/day) for five to six weeks and found mean balances to be close to zero when manganese was provided in combination with high or low levels of calcium (Johnson and Lykken, 1991) and high or low levels of magnesium and boron (Nielsen, 2004).

Overall, the Panel notes that these studies indicate that the body adapts rather quickly to varying manganese intakes and that balance can be achieved across a range of intakes. Whereas intakes below 2.5 mg/day may also be associated with null manganese balance, null or positive balances have consistently been observed with manganese intakes over 2.5 mg/day in balance studies lasting 11–60 days.

The Panel concludes that there are large variations in manganese intakes that result in null manganese balance. Manganese balance may be influenced by the overall diet, variation in individual rates of absorption or excretion, differences in body contents and adaptation to varying levels of dietary manganese intake, which make comparisons between subjects and studies difficult.

5.3. Manganese intake and health consequences

Other criteria based on health consequences of manganese intake may also be considered in order to derive DRVs for manganese.

A comprehensive search of the literature which had been published between January 1990 and October 2011 was performed as preparatory work to this assessment in order to identify relevant health outcomes upon which DRVs may potentially be based for manganese (Mullee et al., 2012). Two studies were retrieved which investigated the relationship of manganese intake or whole blood concentrations with neurological and psychological functions (Finley et al., 2003; Henn et al., 2010). One small cross-over study in healthy young women, which used diets containing low or high amounts of manganese combined with two sources of fat (corn oil or cocoa butter) for eight weeks, reported a lack of response of neurological and psychological variables to changes in manganese intakes (Finley et al., 2003).

The relationship between manganese whole blood/serum concentrations, manganese concentration in toenails or hair and health outcomes has been examined in observational studies, where associations might be confounded by the effect of dietary, lifestyle, environmental or other factors on the outcomes investigated (Takser et al., 2004; Vigeh et al., 2008; Zota et al., 2009; Henn et al., 2010; Mordukhovich et al., 2012). The Panel notes that in none of these studies was manganese intake estimated, and that manganese blood/serum concentrations and manganese content of toenails or hair are not reliable and validated markers of manganese intake or status.

The Panel considers that the data available from these studies cannot be used to derive DRVs for manganese.

6. Data on which to base Dietary Reference Values

The Panel considers that the available data are insufficient to derive ARs and PRIs for manganese and, therefore, the Panel proposes to set an AI for all population groups. There is no indication that the AI should be different according to sex.

6.1. Adults

The setting of an AI for manganese is based on observed manganese intakes with a mixed diet and the apparent absence of signs of deficiency in Europe, suggesting that current intake levels are adequate.

Intake data from national dietary surveys, as well as total diet and duplicate diet studies, have shown that mean intakes of adult men and women range from 2 to 6 mg/day in the EU, with a majority of values around 3 mg/day (Section 3.2.2).

In addition, the Panel notes that null or positive balances have consistently been observed with intakes of manganese above 2.5 mg/day, in balance studies lasting 11–60 days (Section 5.2).

On the basis of the available evidence, the Panel concludes that an AI can be set at 3 mg/day for adults.

6.2. Infants

Assuming a mean manganese concentration in breast milk over the first six months of lactation of 15 µg/L (i.e. at the approximate midpoint of the observed range of concentrations) (see Appendix A) and an average breast milk consumption of infants aged zero to six months of 0.8 L/day (Butte and King, 2002; FAO/WHO/UNU, 2004; EFSA NDA Panel, 2009), the estimated manganese intake of infants in the first half-year of life is 12 µg/day. Extrapolation from this figure, using isometric scaling (i.e. linear with body weight), results in an estimated intake of 17 µg/day for infants aged 7–11 months.

Gibson and DeWolfe (1980) reported an average daily manganese intake of 71 and 80 µg/kg body weight at 6 and 12 months, respectively, in apparently healthy Canadian infants. Friel et al. (1984) reported mean intakes of 110 and 140 µg/kg body weight per day (0.89 and 1.46 mg/day) at 6 and 12 months, respectively, in Canadian infants born at term. The Panel notes that these figures include the use of infant formulae, which may have been fortified with manganese.

Considering a mean of 75 µg/kg body weight per day derived from the values reported by Gibson and DeWolfe (1980), an intake of 0.65 mg/day is calculated for infants aged 7–11 months, using reference body weights of infants aged nine months (WHO Multicentre Growth Reference Study Group (2006)). This is slightly higher than, but in line with, the value estimated from extrapolation of the adult AI by isometric scaling, which results in a value of 0.4 mg/day.

The Panel notes the wide range of manganese intakes estimated with these approaches. There is no evidence that such intakes would be inadequate. Therefore, the Panel decides to set a range for the AI of infants. The lower value is chosen as the estimated intake resulting from upwards extrapolation of

manganese intakes in fully breast-fed infants, which is rounded to 0.02 mg/day. The higher value of the range is chosen at the intermediate level of 0.5 mg/day, between the observed intake of manganese in infants aged 6 and 12 months of 0.65 mg/day and the value of 0.4 mg/day estimated from extrapolation of the adult AI by isometric scaling.

6.3. Children and adolescents

The AI for children and adolescents is extrapolated from the AI for adults using isometric scaling and rounding to the nearest 0.5 (Table 4).

Table 4: Summary of Adequate Intakes for manganese for infants and children

Age	Reference body weight (kg)	Adequate intake (mg/day) [(a)]
7–11 months	8.6 [(b)]	0.02–0.5 [(c)]
1–3 years	11.9 [(d)]	0.5
4–6 years	19.0 [(e)]	1.0
7–10 years	28.7 [(f)]	1.5
11–14 years	44.6 [(g)]	2.0
15–17 years	60.3 [(h)]	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 BMI of 22 kg/m^2 (see Appendix 11 in EFSA NDA Panel (2013)). Rounded to the nearest 0.5.
(b): Mean body weight-for-age at 50th percentile of male and female infants aged nine months (WHO Multicentre Growth Reference Study Group, 2006).
(c): In view of the wide range of manganese intakes that appear to be adequate, a range is set for the AI of this age group (see Section 6.2).
(d): Mean of body weight-for-age at 50th percentile of boys and girls aged 24 months (WHO Multicentre Growth Reference Study Group, 2006).
(e): Mean body weight at 50th percentile of boys and girls aged 5 years (van Buuren et al., 2012).
(f): Mean body weight at 50th percentile of boys and girls aged 8.5 years (van Buuren et al., 2012).
(g): Mean body weight at 50th percentile of boys and girls aged 12.5 years (van Buuren et al., 2012).
(h): Mean body weight at 50th percentile of boys and girls aged 16 years (van Buuren et al., 2012).

6.4. Pregnancy and lactation

No data on observed manganese intakes in pregnant women are available to the Panel. The Panel considers that the gain in body weight during pregnancy does not need to be accounted for given the homeostatic control of manganese. For lactating women, data on mean manganese intakes from small samples of Finnish and German breastfeeding women were in the range 2.3 to 5.5 mg/day (Vuori et al., 1980; Schäfer et al., 2004) and only small amounts of manganese have been shown to be secreted in breast milk (Section 2.3.7).

Thus, for pregnant and lactating women, the Panel proposes the same AI as for non-pregnant and non-lactating women of 3 mg/day.

CONCLUSIONS

The Panel concludes that there is insufficient evidence to derive an Average Requirement (AR) and a Population Reference Intake (PRI) for manganese. Data on manganese intake or status and health outcomes were not available for the setting of DRVs for manganese. Thus, the Panel proposes an Adequate Intake (AI) for adults based on observed mean manganese intakes from mixed diets in the EU. It was considered unnecessary to give sex-specific values. The Panel proposes that the adult AI also applies to pregnant and lactating women. An AI is also proposed for infants and children based on extrapolation from the adult AI using isometric scaling and body weights of the respective age groups.

Table 5: Summary of Adequate Intakes for manganese

Age	Adequate intake (mg/day)
7–11 months	0.02–0.5 [(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 [(b)]	3.0

(a): In view of the wide range of manganese intakes that appear to be adequate, a range is set for the AI of this age group (see Section 6.2).
(b): Including pregnancy and lactation.

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APPENDICES

Appendix A. Manganese concentration in human milk of mothers of term infants

Reference[14]	Number of women (number of samples)	Country	Maternal intake (mg/day)	Stage of lactation	Manganese concentration (µg/L)			
					Mean ± SD		Median	Range
Abdulrazzaq et al. (2008)	205 (205)	United Arab Emirates	Not reported	Infants aged up to 80 weeks	0.93 ± 1.20		0.29	0.002–9.1
Al-Awadi and Srikumar (2000)	34 (34)	Kuwait	Not reported	0–6 months	Kuwaitis:	6.0 ± 0.04		
					Non-Kuwaitis:	5.7 ± 0.02		
				6–12 months	Kuwaitis:	4.2 ± 0.2		
					Non-Kuwaitis:	3.7 ± 0.3		
				12–18 months	Kuwaitis:	3.8 ± 0.2		
					Non-Kuwaitis:	3.1 ± 0.1		
Anderson (1992)	7 (84)	USA	Not reported	Up to 5 months	7.0			
Aquilio et al. (1996)	8	Italy	Not reported	2–6 days	3.9 ± 0.1			
				12–16 days	3.9 ± 0.3			
				21 days	4.1 ± 0.1			
Arnaud and Favier (1995)	82 (143)	France	Not reported	day 1	6.04 ± 3.29			
				day 2	11.81 ± 5.77			
				day 3	7.14 ± 4.12			
				day 4	5.49 ± 2.75			
				day 5	3.29 ± 1.10			
				day 6	3.02 ± 1.65			
				day 7	4.12 ± 1.10			
Bocca et al. (2000)	60 (60)	Italy	Not reported	Not reported	30 ± 2		10	
Friel et al. (1999)	19 (136)	Canada	Not reported	Week 1			Median (MAD[(a)]) 17.00 (10.38)	10–17 (median values)
				Week 2			13.00 (7.41)	
				Week 3			11.50 (7.41)	
				Week 4			14.00 (8.90)	
				Week 5			14.00 (7.41)	

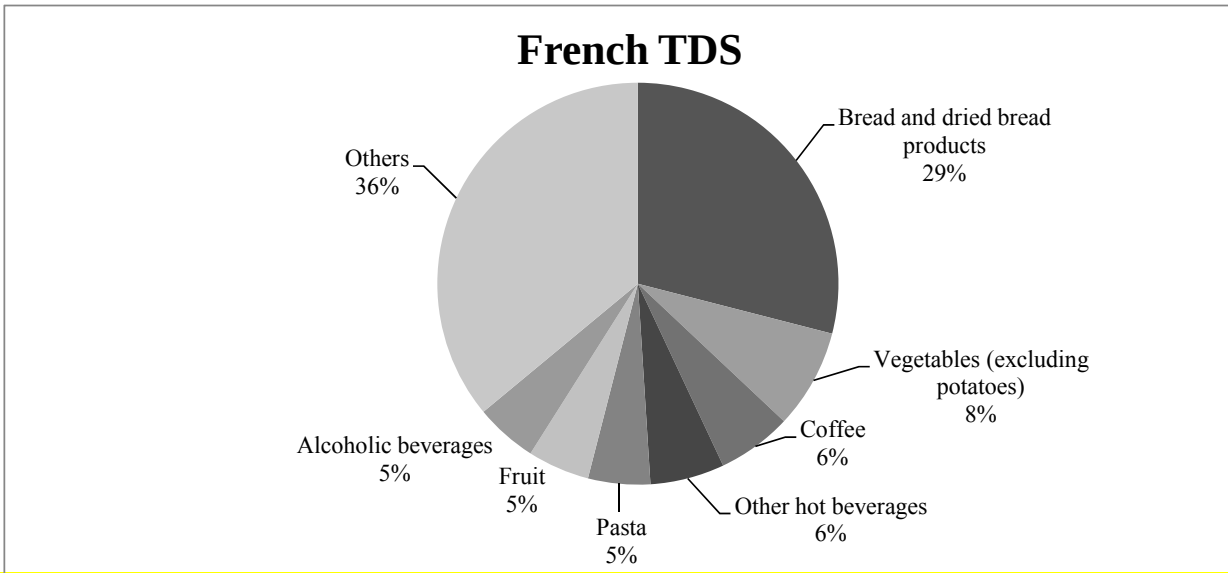
[14] Studies published since 1990.

Reference[14]	Number of women (number of samples)	Country	Maternal intake (mg/day)	Stage of lactation	Manganese concentration (µg/L)		
					Mean ± SD	Median	Range
				Week 6		14.00 (16.31)	
				Week 7		11.00 (10.38)	
				Week 8		10.00 (10.38)	
				Week 12		13.00 (13.34)	
Krachler et al. (1998)	46 (55)	Austria	Not reported	1–3 days	9.4	7.2	3.6–22
				4–17 days	5.3	5.5	1.3–9.1
				42–60 days	4.2	3.9	1.6–6.5
				66–90 days	4.3	4.5	3.1–5.5
				97–293 days	4.5	4.0	2.6–6.7
				Overall	5.9	4.9	1.3–22
Leotsinidis et al. (2005)	180 (275)	Greece	Non-significant correlation of Mn intake (FFQ) with breast milk levels	day 3	4.79 ± 3.23	3.58	1.01–15.70
				day 17	3.13 ± 2.00	2.56	0.17–9.89
Ljung et al. (2009)	68 (67)	Bangladesh	Mean of 720 µg Mn/L in water samples	2 months	9.2	6.6	2.4–59
Parr et al. (1991)	(84)	Guatemala	Not reported	3 months		Median (SD[b])	
						3.79 (0.29)	
	(71)	Hungary				4.00 (0.45)	
	(18)	Nigeria				15.84 (4.10)	
	(63)	Philippines				39.55 (3.54)	
	(31)	Sweden				3.23 (0.27)	
	(68)	Zaire				11.21 (2.45)	
Qian et al. (2010)	120 (120)	China:	Median (IR[c])	8–10 days		Median (IR[c])	
		Yangpu	7.9 (7.0, 9.4)			19 (16, 21)	
		Hongkou	7.2 (6.1, 7.9)			19 (17, 21)	
		Jingan	8.8 (6.2, 12.9)			18 (16, 21)	
		Chongming	8.5 (7.4, 9.0)			7 (5, 13)	
Sharma and Pervez (2005)	35 (35) maternal age: 20–25 years	India	Not reported	Up to 1 week	Below detection		

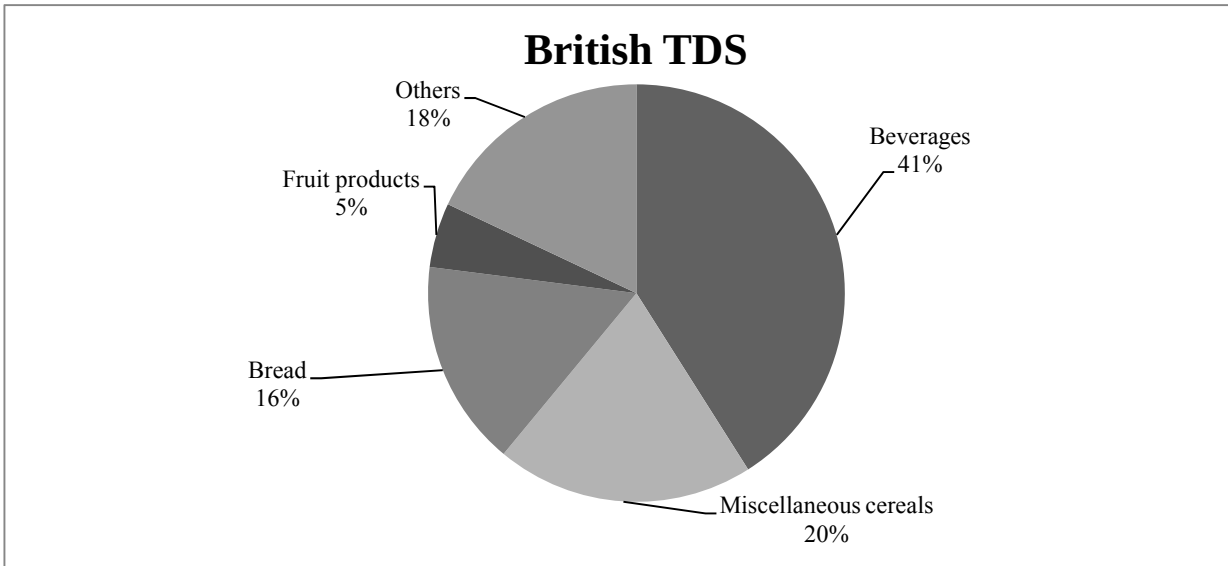
Reference[14]	Number of women (number of samples)	Country	Maternal intake (mg/day)	Stage of lactation	Manganese concentration (µg/L)		
					Mean ± SD	Median	Range
	25–30 years				Below detection		
	30–35 years				Below detection		
	35–40 years				0.8 ± 0.1		
	40–45 years				1.5 ± 0.8		
Ljung and Vahter (2007)	(25)	India	2.21 (range: 0.67–4.99)	Not reported	1.0		0.69–1.8
Wünschmann et al. (2003)	(23)	Germany	Mean (SD) 3.5 ± 1.61	2–71.2 weeks	4.6 ± 1.3		1.5–290
Yamawaki et al. (2005)	(1167)	Japan	Not reported	Summer	9 ± 16		
				Winter	12 ± 29		
				1–5 days	12 ± 8		
				6–10 days	18 ± 53		
				11–20 days	25 ± 66		
				21–89 days	8 ± 22		
				90–180 days	12 ± 11		
				181–365 days	9 ± 11		
				Overall	11 ± 23		

(a): median absolute deviation.
(b): standard deviation of the median defined as $0.926R/\sqrt{N}$, where R is its interquartile range and N is the number of samples.
(c): interquartile range.

Appendix B. Main food contributors to manganese intake in the French and British total diet studies



Based on Anses (2011)



Based on Rose et al. (2010)

Appendix C. Manganese intake among infants and children in European countries

Table 6: National dietary surveys (mg Mn/day)

Country	Data source	Method	Year of survey	Age (years)	Sex	n	Mean (mg/day)	SD (mg/day)	P5 (mg/day)	P95 (mg/day)
Austria	Elmadfa et al. (2009b)	3-day record	2007	7–9	Boys	146	3.0	1.3		
					Girls	146	2.9	1.2		
				10–14	Boys	248	3.2	1.5		
					Girls	248	2.8	1.1		
France	Afssa (2009)	7-day record	2006–2007	3–10	Boys	n.a.	1.8	0.7		
					Girls	n.a.	1.7	0.7		
				11–14	Boys	n.a.	2.3	0.7		
					Girls	n.a.	2.0	0.6		
				15–17	Boys	n.a.	2.4	0.8		
					Girls	n.a.	2.0	0.7		
Germany	Mensink GBM et al. (2007)	Dietary history	1998	6–11	Boys	626	3.4		1.6	6.1
					Girls	608	3.3		1.7	5.9
				12–17	Boys	622	6.2		2.5	12.7
					Girls	650	5.4		2.2	11.9
Ireland	Elmadfa et al. (2009b)	7-day weighed record	2005–2008	5–6	Boys	72	1.4	0.5		
					Girls	72	1.3	0.5		
				7–9	Boys	110	1.7	0.8		
					Girls	110	1.6	0.6		
				10–12	Boys	109	1.8	0.8		
					Girls	109	1.7	0.6		
				13–17	Boys	224	2.5	1.5		
					Girls	217	1.9	0.8		
Portugal	Elmadfa et al. (2009b)	Food frequency questionnaire	n.a.	13	Boys	987	3.8	1.5		
					Girls	987	3.7	1.6		
Slovenia	Elmadfa et al. (2009b)	Food frequency questionnaire	n.a.	15–18	Boys	1 010	5.6	3.9		
					Girls	1 214	4.2	2.8		

Table 7: Duplicate diet studies, total diet studies, market basket studies (mg Mn/day)

Country	Data source	Method	Population	Age	Sex	n	Mean (mg/day)	P5 (mg/day)	P95 (mg/day)
Finland	Vuori (1979)	Concentration of breast milk samples multiplied by average intake of energy at 1, 2 and 3 months: 464, 406, 393 kJ/kg bw per day for girls; 485, 418, 402 kJ/kg bw per day for boys	Full-term healthy infants (initially n = 27), studied from birth, exclusively breast-fed apart from water, vitamin D concentrate and diluted fruit juice	1 month	Boys and girls	23	0.004		
				2 months	Boys and girls	18	0.003		
				3 months	Boys and girls	14	0.003		
France	Anses (2011)	2nd TDS. Analysed food samples. Food consumption data from French INCA2	Under-reporters excluded	3–17 year	Boys and girls	1 444	1.5	0.7	2.6

bw, body weight ; INCA, Enquête Individuelle et Nationale sur les Consommations Alimentaires ; TDS, total diet study.

Table 8: Duplicate diet studies, total diet studies, market basket studies (mg Mn/kg bw per day)

Country	Data source	Method	Population	Age	Sex	n	Mean (mg/kg bw per day)	Median (mg/kg bw per day)	P97.5 (mg/kg bw per day)
Finland	Vuori (1979)	Concentration of breast milk samples multiplied by average intake of energy at 1, 2 and 3 months: 464, 406, 393 kJ/kg bw per day for girls; 485, 418, 402 kJ/kg bw per day for boys	Full-term healthy infants (at birth, n = 27, lower number afterwards), studied from birth, exclusively breast-fed apart from water, vitamin D concentrate and diluted fruit juice	1 month	Boys	12		0.0009	
					Girls	11		0.0009	
					Boys and girls	23	0.0009		
				2 months	Boys	9		0.0006	
					Girls	9		0.0005	
					Boys and girls	18	0.0006		
				3 months	Boys	7		0.0006	
					Girls	7		0.0004	
					Boys and girls	14	0.0005		
United Kingdom	Rose et al. (2010)	2006 UK TDS. Composite samples: 20 food groups (combined from 119 food categories) collected from 24 randomly selected towns, prepared and analysed. Proportions of the foods within a group: representative of the average UK household diet. Consumption data: UK NDNS study	Toddlers	1.5–4.5 years	Boys and girls	n.a.	0.168		0.305
			Older children	4–18 years	Boys and girls	n.a.	0.106		0.201

bw, body weight ; NDNS, National Diet and Nutrition Survey ; TDS, total diet study.

Appendix D. Manganese intake among adults in European countries

Table 9: National dietary surveys (mg Mn/day)

Country	Data source	Method	Year of survey	Age (years)	Sex	n	Mean (mg/day)	SD (mg/day)	P2.5 (mg/day)	P97.5 (mg/day)
Austria	Elmadfa et al. (2009a)	3-day record		≥ 65	Men	147	4.3	1.7		
					Women	202	4.4	2.0		
France	Afssa (2009)	7-day record	2006–2007	18–79	Men	776	3.1	1.2		
					Women	1 142	2.7	1.2		
Germany	Mensink and Beitz (2004)	Food frequency questionnaire	1998	18–79	Men (West Germany)	581	5.9 (95 % CI: 5.6–6.2)			
					Women (West Germany)	815	5.1 (95 % CI: 4.8–5.3)			
					Men (East Germany)	1 182	6.6 (95 % CI: 6.4–6.7)			
					Women (East Germany)	1 452	5.5 (95 % CI: 5.4–5.6)			
Hungary	Bíró et al. (2007)	3-day record	2003–2004	18–34	Men	136	2.6	5.7		
					Women	176	2.0	2.8		
				35–59	Men	199	3.8	11.2		
					Women	295	2.4	4.6		
				≥ 60	Men	138	2.1	0.8		
					Women	235	2.9	12.6		
Ireland	IUNA (2011)	4-day record	2008–2010	18–64	Men	634	3.6	1.7		
					Women	640	3.3	3.3		
				≥ 65	Men	106	4.0	1.6		
					Women	120	3.6	1.9		
United Kingdom	Henderson et al. (2003)	7-day weighed record	2000–2001	19–64	Men	833	3.32	1.42	1.33	6.83
					Women	891	2.69	1.10	0.95	5.31

Table 10: Duplicate diet studies, total diet studies, market basket studies (mg Mn/day)

Country	Data source	Method	Additional methodological information	Population/location/year of survey	Age (years)	Sex	n	Mean (mg/day)	SD (mg/day)	Median (mg/day)	P5 (mg/day)	P95 (mg/day)
Denmark	Bro et al. (1990)	Duplicate diet study	48-hour duplicate food portions (self-selected diets). Subjects were asked to record all food and beverages consumed in a four-day period including one week-end day, in March-May 1988. During two of the four days, they were asked to collect an exact duplicate of each item of food or beverage that had been consumed	Random sample among men in one urban (Odense) and two rural areas	30–34	Men	100	4.5	2.2	3.9		
Finland	Vuori et al. (1980)	Total diet study	Primipara, volunteers from a maternity ward in Helsinki. Dietary data were obtained from two seven-day food records. The first record (1st survey week) was kept between 6 and 8 weeks and the 2nd record (2nd survey week) between 17 and 22 weeks post partum. A mixture representing the calculated average daily food consumption for both survey weeks separately was prepared from the foodstuffs bought from supermarkets in the Helsinki area and analysed	1st survey week	24–35	Women	15	4.45	1.13			
				2nd survey week	24–35	Women	15	5.49	1.75			

Country	Data source	Method	Additional methodological information	Population/location/year of survey	Age (years)	Sex	n	Mean (mg/day)	SD (mg/day)	Median (mg/day)	P5 (mg/day)	P95 (mg/day)
France	Anses (2011)	Total diet study	A total of 41 food groups, subdivided into 212 different food items, were selected, covering around 90 % of dietary consumption in the adult and child populations. Approximately 20 000 foods were purchased in ~ 30 towns across France, combined into 1 319 composite samples representative of French shopping baskets and consumer purchases. 'As consumed' food samples were analysed by ICP-MS. Analytical results were combined with food consumption data from INCA2	Under-reporters excluded	18–79	Men and women	1 918	2.16			1.07	3.55
Germany	Anke et al. (1991)	Duplicate diet study	24-hour duplicates of all meals and beverages, as well as fruit, sweets and beverages consumed outside meals, over seven consecutive days. Two areas in Brandenburg (Wusterhausen, Vetschau) and two in Thuringia (Jena, Bad Langensalza)	Bad Langensalza	20–60	Men	28	2.9	0.94			
						Women	28	2.1	0.74			
				Jena	20–60	Men	28	2.8	0.98			
						Women	28	2.0	0.53			
				Vetschau	20–60	Men	28	2.5	0.98			
						Women	28	2.3	1.1			
				Wusterhausen	20–60	Men	28	3.8	1.6			
						Women	28	2.2	1.2			
Germany	Schäfer et al. (2004)	Duplicate diet study	Subjects of 21 test groups (17 of which consisted of at least seven men and seven women) collected the exact 24-hour duplicate portions of all foods and beverages including water consumed on seven consecutive days	1988	20–69	Men	28	3.0	1.2			
						Women	28	2.1	0.91			
				1996	20–69	Men	31	2.7	1.2			
						Women	31	2.4	1.2			
				1992	20–69	Men	42	3.4	1.4			
						Women	42	2.8	1.3			
Germany	Schäfer et al. (2004)	Duplicate diet study	Subjects of 21 test groups (17 of which consisted of at least seven men and seven women) collected the exact 24-hour	Breastfeeding, without supplementation	21–25	Women	14	2.307	1.044			

Country	Data source	Method	Additional methodological information	Population/location/year of survey	Age (years)	Sex	n	Mean (mg/day)	SD (mg/day)	Median (mg/day)	P5 (mg/day)	P95 (mg/day)
			duplicate portions of all foods and beverages including water consumed on seven consecutive days. Non-breast-feeding young women ingested a Mn supplementation (300 µg/day) or a placebo over a period of 21 days, duplicate samples were collected from the 15th to the 21st experimental day. Breast-feeding women were supplemented with Mn (300 µg/day) from month 8 of pregnancy until day 35 of lactation, duplicate samples were collected from day 29 to day 35 of lactation	Non-breastfeeding, without supplementation	21–25	Women	14	2.955	1.342			
Italy	Turconi et al. (2009)	Modified total diet study	Choice of foods from the Italian Household National Survey (IHNS) 1994-1996. Foods aggregated into six main groups. Most samples collected in a university cafeteria (raw, cooked, ready-to-eat), over two consecutive weeks in July 2004 (n = 226 samples). Some traditional breakfast foods and a few foods included in the IHNS that were not served at the cafeteria were purchased at three local supermarkets (n = 22 samples). Samples were pooled and analysed, and the content was multiplied by the average consumption by the north-west Italian adult population	Pavia (Northern Italy)		Men and women		1.38				
Netherlands	Ellen et al. (1990)	Duplicate diet study	Duplicate portions of 24-hour diets. Two groups (n = 56 each) in two periods of one week each, in October 1984 and March 1985. On each day of these two weeks, weekends included, eight persons collected a duplicate portion of all their foods and drinks as consumed	Bilthoven	18–74	Men and women	110	3.3		3.2		

Country	Data source	Method	Additional methodological information	Population/location/year of survey	Age (years)	Sex	n	Mean (mg/day)	SD (mg/day)	Median (mg/day)	P5 (mg/day)	P95 (mg/day)
Spain	Marti-Cid et al. (2009)	Market basket study	In July 2006, food samples were randomly purchased from local markets, supermarkets and grocery stores from Tarragona county, Catalonia, near a waste incinerator. For each of the 24 kinds of food selected, 15 samples were collected and analysed (360 samples). Food consumption data from a regional nutritional survey (ENCAT) were used	Estimated intake for a man (70 kg bw)		Men		2.23				
Spain	Rubio et al. (2009)	Market basket study	420 food and drink samples collected in local markets, supermarkets and grocery stores from January 2001 to June 2002. Several brands of each product, representing the most frequently consumed in the Canary Islands, were analysed. Food consumption data from a regional nutritional survey (ENCA) were used, based on 24-hour recall administered on two non-consecutive days, and a food frequency questionnaire of 77 food items	Canary Islands	Adults and teenagers			2.37				
Sweden	NFA (2012)	Market basket study	Food baskets were collected in Uppsala in May-June 2010 (and in autumn for fruits, vegetables and potatoes) from five Swedish major grocery chains by using a shopping list based on per capita food consumption data derived from production and trade statistics; supplementary purchase statistics for fish and fats for 2009/2010). Market baskets were divided into 12 food groups and analysed as purchased (n = 123 samples)		Adults and children			4				

Country	Data source	Method	Additional methodological information	Population/location/year of survey	Age (years)	Sex	n	Mean (mg/day)	SD (mg/day)	Median (mg/day)	P5 (mg/day)	P95 (mg/day)
United Kingdom	Rose et al. (2010)	Total diet study	Composite samples for 20 food groups (combined from 119 food categories) collected from 24 randomly selected towns, prepared and analysed by ICP-MS. Relative proportion of each food within a group reflected its importance in the average UK household diet. Consumption data of the food groups from the NDNS study were used		Adults and children			5.24				

bw, body weight.

Table 11: Duplicate diet studies, total diet studies, market basket studies (mg Mn/kg bw per day)

Country	Data source	Method	Additional methodological information	Population and other information	Age (years)	Mean (mg/kg bw per day)	P97.5 (mg/kg bw per day)
United Kingdom	Rose et al. (2010)	Total diet study	Composite samples for 20 food groups (combined from 119 food categories) collected from 24 randomly selected towns, prepared and analysed by ICP-MS. Proportions of the foods within a group were representative of the average UK household diet. Consumption data from the NDNS study were used		16–64	0.067	0.124
				Elderly, free living	≥ 65	0.056	0.112
				Elderly, institutional	≥ 65	0.05	0.121

bw, body weight.

ABBREVIATIONS

Afssa	Agence française de sécurité sanitaire des aliments
AI	Adequate Intake
Anses	Agence nationale de la sécurité sanitaire de l'alimentation, de l'environnement et du travail
AR	Average Requirement
ATSDR	Agency for Toxic Substances and Disease Registry
Bw	Body weight
COMA	Committee on Medical Aspects of Food Policy
D-A-CH	Deutschland-Austria-Confoederatio Helvetica
DCT	Divalent cation transporter
DMT	Divalent metal transporter
DH	Department of Health
DRV	Dietary Reference Value
EAR	Estimated Average Requirement
EC	European Commission
EFSA	European Food Safety Authority
ENCAT	Evaluation of Nutritional Status in Catalonia
EU	European Union
FAO	Food and Agriculture Organization
FFQ	Food Frequency Questionnaire
INCA	Enquête Individuelle et Nationale sur les Consommations Alimentaires
ICP-MS	Inductively Coupled Plasma Mass Spectrometry
IOM	US Institute of Medicine of the National Academy of Sciences
IR	Interquartile range
IUNA	Irish Universities Nutrition Alliance
HF	High ferritin
LF	Low ferritin

Mn	Manganese
MnSOD	Manganese superoxide dismutase
NDNS	National Diet and Nutrition Survey
NHMRC	National Health and Medical Research Council
NNR	Nordic Nutrition Recommendations
NOAEL	No observed adverse effect level
PRI	Population Reference Intake
RDA	Recommended Dietary Allowance
SCF	Scientific Committee for Food
SI	Safe Intake
TDS	Total diet study
UK	United Kingdom
UL	Tolerable upper intake level
WHO	World Health Organization
ZIP	Zrt/IRT-like protein