DRAFT 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 the setting of DRVs for manganese. As there is insufficient evidence available to derive an Average Requirement and a Population Reference Intake, an Adequate Intake (AI) is proposed. Mean intakes of manganese in 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 is proposed for adults, including pregnant and lactating women. The AI proposed for older infants (7-11 months), 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

[1] On request from the European Commission, Question No EFSA-Q-2011-01216, endorsed for public consultation on 12 July 2013.

[2] Panel members: Carlo Agostoni, Roberto Berni Canani, Susan Fairweather-Tait, Marina Heinonen, Hannu Korhonen, Sébastien La Vieille, Rosangela Marchelli, Ambroise Martin, Androniki Naska, Monika Neuhäuser-Berthold, Grażyna Nowicka, Yolanda Sanz, Alfonso Siani, Anders Sjödin, Martin Stern, Sean (J.J.) Strain, Inge Tetens, Daniel Tomé, Dominique Turck and Hans Verhagen. Correspondence: nda@efsa.europa.eu

[3] Acknowledgement: The Panel wishes to thank the members of the Working Group on Dietary Reference Values for minerals: Carlo Agostoni, Susan Fairweather-Tait, Marianne Geleijnse, Michael Hambidge, Ambroise Martin, Androniki Naska, Hildegard Przyrembel, Alfonso Siani, and Hans Verhagen for the preparatory work on this scientific opinion.

Suggested citation: EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 20YY. Draft Scientific Opinion on Dietary Reference Values for manganese. EFSA Journal 20YY; volume(issue):NNNN, 43 pp. doi:10.2903/j.efsa.20YY.NNNN

Available online: www.efsa.europa.eu/efsajournal

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, fruits and fruit products are rich sources of manganese. 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 (AR) 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 from seven months, children and adolescents, an AI is proposed and is 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 between 0.5 mg/day in infants aged 7-11 months and 3.0 mg/day in adolescent boys and girls.

TABLE OF CONTENTS

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 54.93805 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 man 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 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 showing the 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 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 via 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 part of the adaptive changes to the amount of dietary manganese intake allowing 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), 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 to 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., 1991a).

Absorption has been suggested to take place through active transport mechanism (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 amounts 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 the absorption of manganese in the intestine 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 leukocytes 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 to enter 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 lowest concentrations are found in bone and fat (around 0.1 µg manganese/g wet weight) (ATSDR, 2012). Mean concentrations of manganese in scalp hair are in the range 1-10 µg/g (Afridi et al., 2011).

Published data on maternal blood concentrations of manganese during pregnancy indicate higher concentrations (means range: ca. 15-20 µg/L) than the values observed in blood of the general adult population (4 to 15 µg/L; 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 (mean range: ~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), while most manganese intake 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-related differences in iron status (Finley et al., 1994; Finley, 1999) (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) (Appendix A). The concentration is substantially higher in colostrum compared to mature milk (Arnaud and Favier, 1995; Krachler et al., 1998; Leotsinidis et al., 2005). In mature milk, the manganese concentration appears 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. (1991b) found that adding iron to wheat bread did not significantly affect manganese absorption compared to 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 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 as compared to women (18-40 years), which may be related to the fact that men usually have higher iron stores than women (Finley et al., 1994). On a low manganese diet, Finley (1999) found that the biological half-life of manganese was longer in women with low serum ferritin compared to 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 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, fasting manganese concentrations in plasma and whole blood, and leukocyte expression of MnSOD and aminopeptidase P, in 24 tea drinkers and 28 controls. Mean manganese intake as assessed by 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 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 faeces is the major route of excretion and less than 10 % of dietary manganese is absorbed (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.

No correlation has been observed between manganese intake and the manganese concentration of breast milk (Wünschmann et al., 2003; Leotsinidis et al., 2005; Ljung et al., 2009; Qian et al., 2010).

The manganese concentration of hair and toenails, as well as magnetic resonance imaging measurements to detect the presence of increased amounts 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, fruits and fruit products are rich sources of manganese (Rose et al., 2010; Anses, 2011) (Table 1).

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].

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

[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.

386

387 **Table 1:** Rich sources of manganese in the French and British Total Diet Studies (Rose et al., 2010;
388 Anses, 2011)

	Mean manganese content (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

389

390 ### 3.2. Dietary intake

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

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

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

402 #### 3.2.1. Infants, children and adolescents

403 A Finnish study undertaken in infants aged 1-3 months showed mean intakes ranging from 0.5 to
404 0.9 µg/kg body weight per day, i.e. 3 to 4 µg/day (Vuori, 1979). In seven studies analysing the breast
405 milk of women residing in the EU, mean manganese concentrations in milk varied from 3 to 30 µg/L
406 (Parr et al., 1991; Arnaud and Favier, 1995; Aquilio et al., 1996; Krachler et al., 1998; Bocca et al.,
407 2000; Wünschmann et al., 2003; Leotsinidis et al., 2005). Based on this information and assuming an
408 average milk intake of 0.8 L/day (Butte et al., 2002; FAO/WHO/UNU, 2004; EFSA NDA Panel,
409 2009), the estimated mean intake of infants fed human milk as the principal food during the first six
410 months of life ranges from 2.4 to 24 µg/day.

[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 provided as consumed, homogenised and analysed.

[10] Total Diet Studies (TDSs) consist of selecting, collecting and analysing commonly consumed food purchased at 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 minimally processed before analysis. They are restricted to a predetermined set of foods.

National dietary surveys in children (3-14 years) showed that average daily manganese intakes vary between 1.4 and 3.4 mg/day in boys and between 1.3 and 3.3 mg/day in girls. In adolescents (older 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 (Mensink et al., 2007; Afssa, 2009; Elmadfa et al., 2009b).

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, while the British data showed mean intakes of 0.168 and 0.106 mg/kg body weight per 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 adult men and from 2.0 to 5.5 mg in adult 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 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 a 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, 2012) estimated that a manganese intake of 2-5 mg/day is associated with neither deficiency nor toxicity. Due 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

[12] From the 41 food groups composing the diet, 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 composing the diet, main contributors were beverages (41 %), miscellaneous cereals (20 %), bread (16 %) and fruit products (5 %).

manganese balance, balance data could not be used to set an EAR. In addition, IoM considered that 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 most likely overestimate the requirement for most North American individuals. Based on the US TDS (1991-1997), the median dietary manganese intake was 2.1 to 2.3 mg/day for men and 1.6 to 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 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 COMA (DoH, 1991) considered that observed population intakes were adequate (Anonymous, 1988), and derived safe intakes above 1.4 mg/day for adults.

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

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

	D-A-CH (2012)	IoM (2001)	SCF (1993)	UK COMA (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, 2012) estimated AIs for infants aged 4-<12 months from observed intakes of 71 and 80 µg/kg body weight per day in Canadian infants aged six 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, 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 populations; 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 UK COMA (DoH, 1991), the World Health Organization (WHO/FAO, 2004), the Nordic countries (NNR, 2012), the Scientific Committee for Food (SCF, 1993), Afssa (2001) and the Health Council of the Netherlands (2009) did not derive DRVs for manganese for infants and children. However, the UK COMA (DoH, 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 (2012)	IoM (2001)
Age (months)	0-<4	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 also noted that approximately 3 µg manganese/day is secreted in human milk.

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

5.1. Biomarkers as endpoints

The Panel considers there are no suitable biomarkers of manganese status which can be used to estimate manganese requirements (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 intakes, balance studies enable the quantification of obligatory losses by regression to zero. In addition to numerous methodological concerns about accuracy and precision in the determination of intakes and losses (Baer et al., 1999), the validity of balance studies for addressing requirements has been questioned: they might possibly reflect only adaptive changes before reaching a new steady-state (Young, 1986) or only the conditions for maintenance of nutrient stores 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 and 2.55 mg/day, respectively, for two consecutive five-day periods. During depletion, mean balance was negative during the first two seven-day periods (- 1.78 ± 1.12 and - 0.16 ± 0.13 mg/day, respectively), while 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, respectively). 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, 3 subjects in negative balance and 2 subjects in positive balance; - 0.02 ± 0.03 mg/day, 2 subjects in negative balance and 3 subjects in positive balance; - 0.09 ± 0.03 mg/day, all subjects in negative balance) and became positive during the two last 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 (LF group, n = 11 vs. HF group, n = 16) 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), while 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, arginase activity, 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 (McLoed 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 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 time was likely too short for a new equilibrium to be reached given the half-life of manganese (13 to 37 days; Section 2.3.6.).

A number of other balance studies rather 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 5-6 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 rather quickly adapts 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 to 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 functional and health consequences of manganese intake may also be considered in order to derive DRVs for manganese.

The relationship between manganese blood/serum concentrations, manganese content of 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. The Panel notes that in none of these studies (e.g. Takser et al. (2004), Vigeh et al. (2008), Zota et al. (2009), Henn et al. (2010) and Mordukhovich et al. (2012)) 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 an AR and a PRI 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, 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 (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

The bases for setting an AI are observed intakes of manganese together with absence of evidence of signs of deficiency.

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 Canadian infants. Friel et al. (1984) reported estimated 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. The Panel notes that these estimations include the use of infant milk 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 to 11 months, using reference body weights of infants aged 9 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 0.4 mg/day.

The Panel sets an AI for infants aged 7 to 11 months at the intermediate level of 0.5 mg/day.

6.3. Children and adolescents

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

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

Age	Reference weight (kg)	Adequate Intake (mg/day) [(a)]
7-11 months	8.6 [(b)]	0.5
1-3 years	11.9 [(c)]	0.5
4-6 years	19.0 [(d)]	1.0
7-10 years	28.7 [(e)]	1.5
11-14 years	44.6 [(f)]	2.0
15-17 years	60.3 [(g)]	3.0

644 (a): Calculated using isometric scaling : $AI_{child} = AI_{adult}$ * (weight of child/weight of adult), where weight for adult is the
645 average of the median body weight of 18 to 79-year-old men and women based on measured body heights of 16 500
646 men and 19 969 women in 13 EU Member States and assuming a BMI of 22 kg/m^2 (see Appendix 11 in EFSA
647 NDAPanel (2013)). Rounded to the nearest 0.5.
648 (b): Mean of body weight-for-age at 50th percentile of male and female infants aged 9 months, according to the WHO
649 Multicentre Growth Reference Study Group (2006)
650 (c): Mean of body weight-for-age at 50th percentile of boys and girls aged 24 months, according to the WHO Multicentre
651 Growth Reference Study Group (2006)
652 (d): Mean of body weight at 50th percentile of boys and girls aged 5 years, according to van Buuren et al. (2012)
653 (e): Mean of body weight at 50th percentile of boys and girls aged 8.5 years, according to van Buuren et al. (2012)
654 (f): Mean of body weight at 50th percentile of boys and girls aged 12.5 years, according to van Buuren et al. (2012)
655 (g): Mean of body weight at 50th percentile of boys and girls aged 16 years, according to van Buuren et al. (2012)

656 ## 6.4. Pregnancy and lactation

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

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

665

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	0.5
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 [(a)]	3.0

(a): Including pregnancy and lactation

677 **REFERENCES**

678 Abdulrazzaq YM, Osman N, Nagelkerke N, Kosanovic M and Adem A, 2008. Trace element
679 composition of plasma and breast milk of well-nourished women. Journal of Environmental
680 Science and Health. Part A, Toxic/Hazardous Substances and Environmental Engineering, 43, 329-
681 334.

682 Afridi HI, Kazi TG, Brabazon D and Naher S, 2011. Association between essential trace and toxic
683 elements in scalp hair samples of smokers rheumatoid arthritis subjects. Science of the Total
684 Environment, 412-413, 93-100.

685 Afssa (Agence française de sécurité sanitaire des aliments), 2001. Apports nutritionnels conseillés
686 pour la population française [Nutritional recommendations for the French population]. Editions
687 Tec&Doc, Paris, France, 605 pp.

688 Afssa (Agence française de sécurité sanitaire des aliments), 2009. Étude Individuelle Nationale des
689 Consommations Alimentaires 2 (INCA 2) 2006-2007 [Individual and National Study on Food
690 Consumption 2 (INCA 2) 2006-2007]. 228 pp.

691 Al-Awadi FM and Srikumar TS, 2000. Trace-element status in milk and plasma of Kuwaiti and non-
692 Kuwaiti lactating mothers. Nutrition, 16, 1069-1073.

693 Anderson RR, 1992. Comparison of trace elements in milk of four species. Journal of Dairy Science,
694 75, 3050-3055.

695 Anke M, Groppel B, Krause U, Arnhold W and Langer M, 1991. Trace element intake (zinc,
696 manganese, copper, molybdenum, iodine and nickel) of humans in Thuringia and Brandenburg of
697 the Fed. Rep. of Germany. Journal of Trace Elements and Electrolytes in Health and Disease, 5,
698 69-74.

699 Anonymous, 1988. Manganese deficiency in humans: fact or fiction? Nutrition Reviews, 46, 348-352.

700 Anses (French Agency for Food, Environmental and Occupational Health & Safety), 2011. Total Diet
701 Study 2 - Report 1 - Inorganic contaminants, minerals, persistent organic pollutants, mycotoxins
702 and phytoestrogens. 304 pp.

703 Aquilio E, Spagnoli R, Seri S, Bottone G and Spennati G, 1996. Trace element content in human milk
704 during lactation of preterm newborns. Biological Trace Element Research, 51, 63-70.

705 Arnaud J and Favier A, 1995. Copper, iron, manganese and zinc contents in human colostrum and
706 transitory milk of French women. Science of the Total Environment, 159, 9-15.

707 Aschner JL and Aschner M, 2005. Nutritional aspects of manganese homeostasis. Molecular Aspects
708 of Medicine, 26, 353-362.

709 Aschner M and Aschner JL, 1990. Manganese transport across the blood-brain barrier: relationship to
710 iron homeostasis. Brain Research Bulletin, 24, 857-860.

711 Aschner M and Gannon M, 1994. Manganese (Mn) transport across the rat blood-brain barrier:
712 saturable and transferrin-dependent transport mechanisms. Brain Research Bulletin, 33, 345-349.

713 ATSDR (Agency for Toxic Substances and Disease Registry, US Department of Health and Human
714 Services), 2012. Toxicological profile for manganese. 556 pp.

715 Baer J, Fong A, Novotny J and Oexmann M, 1999. Compartmental modeling, stable isotopes, and
716 balance studies. In: Well-controlled diet studies in humans: A practical guide to design and
717 management. Eds Dennis BH, Ershow AG, Obarzanek E, Clevidence BA. American Dietetic
718 Association, Chicago, USA, 238-254.

719 Barceloux DG, 1999. Manganese. Journal of Toxicology. Clinical Toxicology, 37, 293-307.

720 Behall KM, Scholfield DJ, Lee K, Powell AS and Moser PB, 1987. Mineral balance in adult men:
721 effect of four refined fibers. American Journal of Clinical Nutrition, 46, 307-314.

722 Bell JG, Keen CL and Lonnerdal B, 1989. Higher retention of manganese in suckling than in adult rats
723 is not due to maturational differences in manganese uptake by rat small intestine. Journal of
724 Toxicology and Environmental Health, 26, 387-398.

725 Bíró L, Zajkás G, Greiner E, Szórád I, Varga A, Domonkos A, Ágoston H, Balázs A, ., Mozsáry E,
726 Vitrai J, Hermann D, Boros J, Németh R, Kéki Z and Martos É, 2007. Táplálkozási vizsgálat
727 Magyarországon, 2003–2004. Mikro-tápanyagbevitel: ásványi sók [Dietary survey in Hungary,
728 2003–2004. Micro-nutrient intake: minerals]. Orvosi Hetilap [Hungarian Medical Journal] 148,
729 703-708.

730 Bocca B, Alimonti A, Giglio L, Di Pasquale M, Caroli S, Ambruzzi MA, Bocca AP and Coni E, 2000.
731 Nutritive significance of element speciation in breast milk. The case of calcium, copper, iron,
732 magnesium, manganese, and zinc. Advances in Experimental Medicine and Biology, 478, 385-386.

733 Bro S, Sandstrom B and Heydorn K, 1990. Intake of essential and toxic trace elements in a random
734 sample of Danish men as determined by the duplicate portion sampling technique. Journal of Trace
735 Elements and Electrolytes in Health and Disease, 4, 147-155.

736 Buchet JP, Lauwerys R, Vandevoorde A and Pycke JM, 1983. Oral daily intake of cadmium, lead,
737 manganese, copper, chromium, mercury, calcium, zinc and arsenic in Belgium: a duplicate meal
738 study. Food and Chemical Toxicology, 21, 19-24.

739 Buchman AL, 2006. Manganese. In: Modern Nutrition in Health and Disease. Eds Shils ME, Shike M,
740 Ross AC, Caballero B, Cousins RJ. Lippincott Williams & Wilkins, Philadelphia, USA, 326-331
741 pp.

742 Butte NF, Lopez-Alarcon MG and Garza C, 2002. Nutrient adequacy of exclusive breastfeeding for
743 the term infant during the first six months of life. World Health Organization, 55 pp.

744 Carmichael S, Abrams B and Selvin S, 1997. The pattern of maternal weight gain in women with good
745 pregnancy outcomes. American Journal of Public Health, 87, 1984-1988.

746 Casey CE, Hambidge KM and Neville MC, 1985. Studies in human lactation: zinc, copper, manganese
747 and chromium in human milk in the first month of lactation. American Journal of Clinical
748 Nutrition, 41, 1193-1200.

749 Casey CE, Neville MC and Hambidge KM, 1989. Studies in human lactation: secretion of zinc,
750 copper, and manganese in human milk. American Journal of Clinical Nutrition, 49, 773-785.

751 Chua AC and Morgan EH, 1997. Manganese metabolism is impaired in the Belgrade laboratory rat.
752 Journal of Comparative Physiology. B, Biochemical, Systemic, and Environmental Physiology,
753 167, 361-369.

754 D-A-CH (Deutsche Gesellschaft für Ernährung - Österreichische Gesellschaft für Ernährung -
755 Schweizerische Gesellschaft für Ernährungsforschung - Schweizerische Vereinigung für
756 Ernährung), 2012. Referenzwerte für die Nährstoffzufuhr. 1st edition, 4th corrected reprint.
757 Umschau Braus Verlag, Frankfurt am Main, Germany, 251 pp.

758 Davidsson L, Cederblad A, Lonnerdal B and Sandstrom B, 1989. Manganese retention in man: a
759 method for estimating manganese absorption in man. American Journal of Clinical Nutrition, 49,
760 170-179.

761 Davidsson L, Cederblad A, Lonnerdal B and Sandstrom B, 1991a. Manganese absorption from
762 mangold (Beta vulgaris): Comparison of intrinsic and extrinsic labels. Journal of Nutritional
763 Biochemistry, 2, 323-328.

764 Davidsson L, Cederblad A, Lonnerdal B and Sandstrom B, 1991b. The effect of individual dietary
765 components on manganese absorption in humans. American Journal of Clinical Nutrition, 54,
766 1065-1070.

767 Davis CD, Malecki EA and Greger JL, 1992. Interactions among dietary manganese, heme iron, and
768 nonheme iron in women. American Journal of Clinical Nutrition, 56, 926-932.

Davis CD and Greger JL, 1992. Longitudinal changes of manganese-dependent superoxide dismutase and other indexes of manganese and iron status in women. American Journal of Clinical Nutrition, 55, 747-752.

DoH (Department of Health), 1991. Dietary reference values for food energy and nutrients for the United Kingdom. Report of the Panel on Dietary Reference Values of the Committee on Medical Aspects of Food Policy. HM Stationary Office, London, UK, 210 pp.

EFSA (European Food Safety Authority), 2009. General principles for the collection of national food consumption data in the view of a pan-European dietary survey. EFSA Journal, 7(12):1435, 51 pp.

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2009. Scientific Opinion on the appropriate age for introduction of complementary feeding of infants. EFSA Journal, 7(12): 1423, 38 pp.

EFSA NDA Panel (EFSA Panel on Dietetic Products Nutrition and Allergies), 2013. Scientific Opinion on Dietary Reference Values for energy. EFSA Journal, 11(1):3005, 112 pp.

EFSA/FAO/WHO (European Food Safety Authority/Food and Agriculture Organization/World Health Organization), 2011. Towards a harmonised Total Diet Study approach: a guidance document. EFSA Journal, 9(11):2450, 66 pp.

Ellen G, Egmond E, Van Loon JW, Sahertian ET and Tolsma K, 1990. Dietary intakes of some essential and non-essential trace elements, nitrate, nitrite and N-nitrosamines, by Dutch adults: estimated via a 24-hour duplicate portion study. Food Additives and Contaminants, 7, 207-221.

Elmadfa I, Freisling H, Nowak V, Hofstädter D, Hasenegger V, Ferge M, Fröhler M, Fritz K, Meyer AL, Putz P, Rust P, Grossgut R, Mischek D, Kiefer I, Schätzer M, Spanblöchel J, Sturtzel B, Wagner K-H, Zilberszac A, Vojir F and Plsek K, 2009a. Österreichischer Ernährungsbericht 2008 [Austrian Nutrition Report 2008]. Institut für Ernährungswissenschaften der Universität Wien, Bundesministerium für Gesundheit, 454 pp.

Elmadfa I, Meyer A, Nowak V, Hasenegger V, Putz P, Verstraeten R, Remaut-DeWinter AM, Kolsteren P, Dostalova J, Dlouhy P, Trolle E, Fagt S, Biltoft-Jensen A, Mathiessen J, Velsing Groth M, Kambek L, Gluskova N, Voutilainen N, Erkkila A, Vernay M, Krems C, Strassburg A, Vasquez-Caicedo AL, Urban C, Naska A, Efstathopoulou E, Oikonomou E, Tsiotas K, Bountziouka V, Benetou V, Trichopoulou A, Zajkas G, Kovacs V, Martos E, Heavey P, Kelleher C, Kennedy J, Turrini A, Selga G, Sauka M, Petkeviciene J, Klumbiene J, Holm Totland T, Andersen LF, Halicka E, Rejman K, Kowrygo B, Rodrigues S, Pinhao S, Ferreira LS, Lopes C, Ramos E, Vaz Almeida MD, Vlad M, Simcic M, Podgrajsek K, Serra Majem L, Roman Vinas B, Ngo J, Ribas Barba L, Becker V, Fransen H, Van Rossum C, Ocke M and Margetts B, 2009b. European Nutrition and Health Report 2009. Forum of Nutrition, 62, 1-412.

FAO/WHO/UNU (Food and Agriculture Organization of the United Nations/World Health Organization/United Nations University), 2004. Human energy requirements. Report of a Joint FAO/WHO/UNU Expert Consultation: Rome, 17-24 October 2001. FAO food and nutrition technical report series, 103 pp.

Finley JW, Johnson PE and Johnson LK, 1994. Sex affects manganese absorption and retention by humans from a diet adequate in manganese. American Journal of Clinical Nutrition, 60, 949-955.

Finley JW, 1999. Manganese absorption and retention by young women is associated with serum ferritin concentration. American Journal of Clinical Nutrition, 70, 37-43.

Finley JW, Penland JG, Pettit RE and Davis CD, 2003. Dietary manganese intake and type of lipid do not affect clinical or neuropsychological measures in healthy young women. Journal of Nutrition, 133, 2849-2856.

Fitsanakis VA, Zhang N, Garcia S and Aschner M, 2010. Manganese (Mn) and iron (Fe): interdependency of transport and regulation. Neurotoxicity Research, 18, 124-131.

816 Freeland-Graves JH, Behmardi F, Bales CW, Dougherty V, Lin PH, Crosby JB and Trickett PC, 1988.
817 Metabolic balance of manganese in young men consuming diets containing five levels of dietary
818 manganese. Journal of Nutrition, 118, 764-773.

819 Freeland-Graves JH and Turnlund JR, 1996. Deliberations and evaluations of the approaches,
820 endpoints and paradigms for manganese and molybdenum dietary recommendations. Journal of
821 Nutrition, 126, 2435S-2440S.

822 Friedman BJ, Freeland-Graves JH, Bales CW, Behmardi F, Shorey-Kutschke RL, Willis RA, Crosby
823 JB, Trickett PC and Houston SD, 1987. Manganese balance and clinical observations in young men
824 fed a manganese-deficient diet. Journal of Nutrition, 117, 133-143.

825 Friel JK, Gibson RS, Balassa R and Watts JL, 1984. A comparison of the zinc, copper and manganese
826 status of very low birth weight pre-term and full-term infants during the first twelve months. Acta
827 Paediatrica Scandinavica, 73, 596-601.

828 Friel JK, Andrews WL, Jackson SE, Longerich HP, Mercer C, McDonald A, Dawson B and Sutradhar
829 B, 1999. Elemental composition of human milk from mothers of premature and full-term infants
830 during the first 3 months of lactation. Biological Trace Element Research, 67, 225-247.

831 Garcia-Aranda JA, Wapnir RA and Lifshitz F, 1983. In vivo intestinal absorption of manganese in the
832 rat. Journal of Nutrition, 113, 2601-2607.

833 Garrick MD, Dolan KG, Horbinski C, Ghio AJ, Higgins D, Porubcin M, Moore EG, Hainsworth LN,
834 Umbreit JN, Conrad ME, Feng L, Lis A, Roth JA, Singleton S and Garrick LM, 2003. DMT1: a
835 mammalian transporter for multiple metals. Biometals, 16, 41-54.

836 Gibson RS and DeWolfe MS, 1980. The dietary trace metal intake of some Canadian full-term and
837 low birthweight infants during the first twelve months of infancy. Journal of the Canadian Dietetic
838 Association, 41, 206-215.

839 Greger JL, Baligar P, Abernathy RP, Bennett OA and Peterson T, 1978. Calcium, magnesium,
840 phosphorus, copper, and manganese balance in adolescent females. American Journal of Clinical
841 Nutrition, 31, 117-121.

842 Greger JL, Davis CD, Suttie JW and Lyle BJ, 1990. Intake, serum concentrations, and urinary
843 excretion of manganese by adult males. American Journal of Clinical Nutrition, 51, 457-461.

844 Greger JL, 1999. Nutrition versus toxicology of manganese in humans: evaluation of potential
845 biomarkers. Neurotoxicology, 20, 205-212.

846 Gunshin H, Mackenzie B, Berger UV, Gunshin Y, Romero MF, Boron WF, Nussberger S, Gollan JL
847 and Hediger MA, 1997. Cloning and characterization of a mammalian proton-coupled metal-ion
848 transporter. Nature, 388, 482-488.

849 Hallfrisch J, Powell A, Carafelli C, Reiser S and Prather ES, 1987. Mineral balances of men and
850 women consuming high fiber diets with complex or simple carbohydrate. Journal of Nutrition, 117,
851 48-55.

852 Hambidge M, 2003. Biomarkers of trace mineral intake and status. Journal of Nutrition, 133, 948S-
853 955S.

854 He P, Liu DH and Zhang GQ, 1994. [Effects of high-level-manganese sewage irrigation on children's
855 neurobehavior]. Zhonghua Yu Fang Yi Xue Za Zhi [Chinese Journal of Preventive Medicine], 28,
856 216-218.

857 Health Council of the Netherlands, 2009. Towards an adequate intake of vitamins and minerals.
858 Publication no. 2009/06E, 94 pp.

859 Henderson L, Irving K, Gregory J, Bates C, Prentice A, Perks J, Swan G and Farron M, 2003. The
860 National Diet & Nutrition Survey: adults aged 19 to 64 years. Vitamin and mineral intake and
861 urinary analytes. A survey carried out in Great Britain on behalf of the Food Standards Agency and

862 the Departments of Health by the Social Survey Division of the Office for National Statistics and
863 Medical Research Council Human Nutrition Research. 160 pp.

864 Henn CB, Ettinger AS, Schwartz J, Tellez-Rojo MM, Lamadrid-Figueroa H, Hernandez-Avila M,
865 Schnaas L, Amarasiriwardena C, Bellinger DC, Hu H and Wright RO, 2010. Early postnatal blood
866 manganese levels and children's neurodevelopment. Epidemiology, 21, 433-439.

867 Himeno S, Yanagiya T, Enomoto S, Kondo Y and Imura N, 2002. Cellular cadmium uptake mediated
868 by the transport system for manganese. Tohoku Journal of Experimental Medicine, 196, 43-50.

869 Himeno S, Yanagiya T and Fujishiro H, 2009. The role of zinc transporters in cadmium and
870 manganese transport in mammalian cells. Biochimie, 91, 1218-1222.

871 Holbrook JT, Smith JC, Jr. and Reiser S, 1989. Dietary fructose or starch: effects on copper, zinc, iron,
872 manganese, calcium, and magnesium balances in humans. American Journal of Clinical Nutrition,
873 49, 1290-1294.

874 Hope S, Daniel K, Gleason KL, Comber S, Nelson M and Powell JJ, 2006. Influence of tea drinking
875 on manganese intake, manganese status and leucocyte expression of MnSOD and cytosolic
876 aminopeptidase P. European Journal of Clinical Nutrition, 60, 1-8.

877 Hunt JR, Gallagher SK, Johnson LK and Lykken GI, 1995. High- versus low-meat diets: effects on
878 zinc absorption, iron status, and calcium, copper, iron, magnesium, manganese, nitrogen,
879 phosphorus, and zinc balance in postmenopausal women. American Journal of Clinical Nutrition,
880 62, 621-632.

881 Hunt JR, Matthys LA and Johnson LK, 1998. Zinc absorption, mineral balance, and blood lipids in
882 women consuming controlled lactoovovegetarian and omnivorous diets for 8 wk. American Journal
883 of Clinical Nutrition, 67, 421-430.

884 Hurley LS and Keen CL, 1987. Manganese. In: Trace elements in human and animal nutrition, volume
885 1. Ed Mertz W. Academic Press, San Diego, USA, 185-223.

886 IoM (Institute of Medicine), 2001. Dietary Reference Intakes for vitamin A, vitamin K, arsenic, boron,
887 chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. 773
888 pp.

889 IUNA (Irish Universities Nutrition Alliance), 2011. National Adult Nutrition Survey. Summary Report
890 edited by Dr. Janette Walton. 40 pp.

891 Ivaturi R and Kies C, 1992. Mineral balances in humans as affected by fructose, high fructose corn
892 syrup and sucrose. Plant Foods for Human Nutrition, 42, 143-151.

893 Jenkitkasemwong S, Wang CY, Mackenzie B and Knutson MD, 2012. Physiologic implications of
894 metal-ion transport by ZIP14 and ZIP8. Biometals, 25, 643-655.

895 Johnson MA, Baier MJ and Greger JL, 1982. Effects of dietary tin on zinc, copper, iron, manganese,
896 and magnesium metabolism of adult males. American Journal of Clinical Nutrition, 35, 1332-1338.

897 Johnson PE, Lykken GI and Korynta ED, 1991. Absorption and biological half-life in humans of
898 intrinsic and extrinsic 54Mn tracers from foods of plant origin. Journal of Nutrition, 121, 711-717.

899 Johnson PE and Lykken GI, 1991. Manganese and calcium absorption and balance in young women
900 fed diets with varying amounts of manganese and calcium. Journal of Trace Elements in
901 Experimental Medicine, 4, 19-35.

902 Kawamura R, Ikuta H, Fukuzumi S, Yamada R, Tsubaki S, T K and Kurata S, 1941. Intoxication by
903 manganese in well water. Kitasato Archives of Experimental Medicine, 18, 145-169.

904 Kondakis XG, Makris N, Leotsinidis M, Prinou M and Papapetropoulos T, 1989. Possible health
905 effects of high manganese concentration in drinking water. Archives of Environmental Health, 44,
906 175-178.

907 Kopp RS, Kumbartski M, Harth V, Bruning T and Kafferlein HU, 2012. Partition of metals in the
908 maternal/fetal unit and lead-associated decreases of fetal iron and manganese: an observational
909 biomonitoring approach. Archives of Toxicology, 86, 1571-1581.

910 Krachler M, Li FS, Rossipal E and Irgolic KJ, 1998. Changes in the concentrations of trace elements
911 in human milk during lactation. Journal of Trace Elements in Medicine and Biology, 12, 159-176.

912 Laohaudomchok W, Lin X, Herrick RF, Fang SC, Cavallari JM, Christiani DC and Weisskopf MG,
913 2011. Toenail, blood, and urine as biomarkers of manganese exposure. Journal of Occupational and
914 Environmental Medicine, 53, 506-510.

915 Leach RM and Lilburn MS, 1978. Manganese metabolism and its function. World Review of Nutrition
916 and Dietetics, 32, 123-134.

917 Leotsinidis M, Alexopoulos A and Kostopoulou-Farri E, 2005. Toxic and essential trace elements in
918 human milk from Greek lactating women: Association with dietary habits and other factors.
919 Chemosphere, 61, 238-247.

920 Ljung KS, Kippler MJ, Goessler W, Grander GM, Nermell BM and Vahter ME, 2009. Maternal and
921 early life exposure to manganese in rural Bangladesh. Environmental Science and Technology, 43,
922 2595-2601.

923 Marti-Cid R, Perello G and Domingo JL, 2009. Dietary exposure to metals by individuals living near a
924 hazardous waste incinerator in Catalonia, Spain: temporal trend. Biological Trace Element
925 Research, 131, 245-254.

926 Maynard LS and Cotzias GC, 1955. The partition of manganese among organs and intracellular
927 organelles of the rat. Journal of Biological Chemistry, 214, 489-495.

928 McLoed BE and Robinson MF, 1978. Metabolic balance of manganese in young women. British
929 Journal of Nutrition, 27, 221-227.

930 Mena I, Horiuchi K, Burke K and Cotzias GC, 1969. Chronic manganese poisoning. Individual
931 susceptibility and absorption of iron. Neurology, 19, 1000-1006.

932 Mensink GB and Beitz R, 2004. Food and nutrient intake in East and West Germany, 8 years after the
933 reunification--The German Nutrition Survey 1998. European Journal of Clinical Nutrition, 58,
934 1000-1010.

935 Mensink GB, Bauch A, Vohmann C, Stahl A, Six J, Kohler S, Fischer J and Heseker H, 2007.
936 [EsKiMo - the nutrition module in the German Health Interview and Examination Survey for
937 Children and Adolescents (KiGGS)]. Bundesgesundheitsblatt Gesundheitsforschung
938 Gesundheitsschutz, 50, 902-908.

939 Mertz W, 1987. Use and misuse of balance studies. Journal of Nutrition, 117, 1811-1813.

940 Milne DB, Sims RL and Ralston NV, 1990. Manganese content of the cellular components of blood.
941 Clinical Chemistry, 36, 450-452.

942 Momcilovic B, Lykken GI, Ivicic N and Prejac J, 2009. Low serum ferritin slowed 54Mn
943 gastrointestinal transit time in women fed low manganese diet. Trace Elements and Electrolytes,
944 26, 131-136.

945 Mordukhovich I, Wright RO, Hu H, Amarasiriwardena C, Baccarelli A, Litonjua A, Sparrow D,
946 Vokonas P and Schwartz J, 2012. Associations of toenail arsenic, cadmium, mercury, manganese,
947 and lead with blood pressure in the normative aging study. Environmental Health Perspectives,
948 120, 98-104.

949 Mullee A, Brown T, Collings R, Harvey L, Hooper L and Fairweather-Tait S, 2012. Literature search
950 and review related to specific preparatory work in the establishment of Dietary Reference Values.
951 Preparation of an evidence report identifying health outcomes upon which Dietary Reference
952 Values could potentially be based for chromium, manganese and molybdenum

(CT/EFSA/NDA/2010/03). Scientific Report submitted to EFSA, 171 pp. Available online: http://www.efsa.europa.eu/en/efsajournal/doc/284e.pdf.

NFA (National Food Agency), 2012. Market Basket 2010 - chemical analysis, exposure estimation and health-related assessment of nutrients and toxic compounds in Swedish food baskets. Sweden National Food Agency Report nr 7 - 2012, 140 pp.

NHMRC (National Health and Medical Research Council), 2006. Nutrient Reference Values for Australia and New Zealand Including Recommended Dietary Intakes. 317 pp.

Nielsen FH, 1996. How should dietary guidance be given for mineral elements with beneficial actions or suspected of being essential? Journal of Nutrition, 126, 2377S-2385S.

Nielsen FH, 1999. Ultratrace minerals. In: Modern Nutrition in Health and Disease. 9th ed. Eds Shils M, Olson J, Shike M, Ross A. Williams & Wilkins, Baltimore, USA, 283-303.

Nielsen FH, 2004. The alteration of magnesium, calcium and phosphorus metabolism by dietary magnesium deprivation in postmenopausal women is not affected by dietary boron deprivation. Magnesium Research, 17, 197-210.

NNR (Nordic Nutrition Recommendations), 2012. Manganese [For Public Consultation]. Nordic Council of Ministers, 4 pp.

Parr RM, DeMaeyer EM, Iyengar VG, Byrne AR, Kirkbright GF, Schoch G, Niinisto L, Pineda O, Vis HL, Hofvander Y and et al., 1991. Minor and trace elements in human milk from Guatemala, Hungary, Nigeria, Philippines, Sweden, and Zaire. Results from a WHO/IAEA joint project. Biological Trace Element Research, 29, 51-75.

Patterson KY, Holbrook JT, Bodner JE, Kelsay JL, Smith JC, Jr. and Veillon C, 1984. Zinc, copper, and manganese intake and balance for adults consuming self-selected diets. American Journal of Clinical Nutrition, 40, 1397-1403.

Pleban PA and Pearson KH, 1979. Determination of manganese in whole blood and serum. Clinical Chemistry, 25, 1915-1918.

Qian J, Chen T, Lu W, Wu S and Zhu J, 2010. Breast milk macro- and micronutrient composition in lactating mothers from suburban and urban Shanghai. Journal of Paediatrics and Child Health, 46, 115-120.

Randhawa RK and Kawatra BL, 1993. Effect of dietary protein on the absorption and retention of Zn, Fe, Cu and Mn in pre-adolescent girls. Nahrung, 37, 399-407.

Rose M, Baxter M, Brereton N and Baskaran C, 2010. Dietary exposure to metals and other elements in the 2006 UK Total Diet Study and some trends over the last 30 years. Food Additives & Contaminants. Part A, Chemistry, analysis, control, exposure & risk assessment, 27, 1380-1404.

Rossander-Hulten L, Brune M, Sandstrom B, Lonnerdal B and Hallberg L, 1991. Competitive inhibition of iron absorption by manganese and zinc in humans. American Journal of Clinical Nutrition, 54, 152-156.

Roth JA, 2006. Homeostatic and toxic mechanisms regulating manganese uptake, retention, and elimination. Biological Research, 39, 45-57.

Rubio C, Gutierrez AJ, Revert C, Reguera JI, Burgos A and Hardisson A, 2009. Daily dietary intake of iron, copper, zinc and manganese in a Spanish population. International Journal of Food Sciences and Nutrition, 60, 590-600.

Rudge CV, Rollin HB, Nogueira CM, Thomassen Y, Rudge MC and Odland JO, 2009. The placenta as a barrier for toxic and essential elements in paired maternal and cord blood samples of South African delivering women. Journal of Environmental Monitoring, 11, 1322-1330.

Sandström B, Davidsson L, Cederblad A, Eriksson R and Lönnerdal B, 1986. Manganese absorption and metabolism in man. Acta Pharmacologica et Toxicologica, 59 Suppl 7, 60-62.

999 SCF (Scientific Committee for Food), 1993. Report on nutrient and energy intakes for the European
1000 Community, 31st Series. Food - Science and Technique, European Commission, 255 pp.

1001 SCF (Scientific Committee on Food), 2000. Opinion of the Scientific Committee on Food on the
1002 Tolerable Upper Intake Level of manganese expressed on 19 October 2000.
1003 SCF/CS/NUT/UPPLEV/21 Final, 11 pp.

1004 Schäfer U, Anke M, Seifert M and Fischer AB, 2004. Influences on the manganese intake, excretion
1005 and balance of adults, and on the manganese concentration of the consumed food determined by
1006 means of the duplicate portion technique. Trace Elements and Electrolytes, 21, 68-77.

1007 Sharma R and Pervez S, 2005. Toxic metals status in human blood and breast milk samples in an
1008 integrated steel plant environment in Central India. Environmental Geochemistry and Health, 27,
1009 39-45.

1010 Spencer H, Asmussen CR, Holtzman RB and Kramer L, 1979. Metabolic balances of cadmium,
1011 copper, manganese, and zinc in man. American Journal of Clinical Nutrition, 32, 1867-1875.

1012 Sumino K, Hayakawa K, Shibata T and Kitamura S, 1975. Heavy metals in normal Japanese tissues.
1013 Amounts of 15 heavy metals in 30 subjects. Archives of Environmental Health, 30, 487-494.

1014 Takser L, Mergler D, Hellier G, Sahuquillo J and Huel G, 2003. Manganese, monoamine metabolite
1015 levels at birth, and child psychomotor development. Neurotoxicology, 24, 667-674.

1016 Takser L, Lafond J, Bouchard M, St-Amour G and Mergler D, 2004. Manganese levels during
1017 pregnancy and at birth: relation to environmental factors and smoking in a Southwest Quebec
1018 population. Environmental Research, 95, 119-125.

1019 Thomson AB, Olatunbosun D and Valverg LS, 1971. Interrelation of intestinal transport system for
1020 manganese and iron. Journal of Laboratory and Clinical Medicine, 78, 642-655.

1021 Tipton IH and Cook MJ, 1963. Trace elements in human tissue. II. Adult subjects from the United
1022 States. Health Physics, 9, 103-145.

1023 Tripathi RM, Mahapatra S, Raghunath R, Sastry VN and Krishnamoorthy TM, 2000. Daily intake of
1024 manganese by the adult population of Mumbai. Science of the Total Environment, 250, 43-50.

1025 Turconi G, Minoia C, Ronchi A and Roggi C, 2009. Dietary exposure estimates of twenty-one trace
1026 elements from a Total Diet Study carried out in Pavia, Northern Italy. British Journal of Nutrition,
1027 101, 1200-1208.

1028 Utter MF, 1976. The biochemistry of manganese. Medical Clinics of North America, 60, 713-727.

1029 van Buuren S, Schönbeck Y and van Dommelen P, 2012. Collection, collation and analysis of data in
1030 relation to reference heights and reference weights for female and male children and adolescents
1031 (0-18 years) in the EU, as well as in relation to the age of onset of puberty and the age at which
1032 different stages of puberty are reached in adolescents in the EU (CT/EFSA/NDA/2010/01).
1033 Technical Report submitted to EFSA, 59 pp. Available online:
1034 http://www.efsa.europa.eu/en/supporting/pub/255e.htm.

1035 Vigeh M, Yokoyama K, Ramezanzadeh F, Dahaghin M, Fakhriazad E, Seyedaghamiri Z and Araki S,
1036 2008. Blood manganese concentrations and intrauterine growth restriction. Reproductive
1037 Toxicology, 25, 219-223.

1038 Vuori E, 1979. Intake of copper, iron, manganese and zinc by healthy, exclusively-breast-fed infants
1039 during the first 3 months of life. British Journal of Nutrition, 42, 407-411.

1040 Vuori E, Makinen SM, Kara R and Kuitunen P, 1980. The effects of the dietary intakes of copper,
1041 iron, manganese, and zinc on the trace element content of human milk. American Journal of
1042 Clinical Nutrition, 33, 227-231.

1043 WHO (World Health Organization), 1996. Trace elements in human nutrition and health. pp. 361.

1044 WHO Multicentre Growth Reference Study Group (World Health Organization), 2006. WHO (World
1045 Health Organization) Child Growth Standards: Length/height-for-age, weight-for-age, weight-for-
1046 length, weight-for-height and body mass index-for-age: Methods and development. 312 pp.

1047 WHO/FAO (World Health Organization / Food and Agriculture Organization of the United Nations),
1048 2004. Vitamin and mineral requirements in human nutrition: report of a joint FAO/WHO Expert
1049 Consultation, Bangkok, Thailand, 21-30 September 1998. 341 pp.

1050 Wünschmann S, Kühn I, Heidenreich H, Fränzle S, Wappelhorst O and Markert B, 2003. Transfer von
1051 Elementen in die Muttermilch. Forschungsbericht StSch 4258 im Auftrag des Bundesamtes für
1052 Strahlenschutz, Bundesministerium für Umwelt, Naturschutz und Reaktorsicherheit. 122 pp.

1053 Yamawaki N, Yamada M, Kan-no T, Kojima T, Kaneko T and Yonekubo A, 2005. Macronutrient,
1054 mineral and trace element composition of breast milk from Japanese women. Journal of Trace
1055 Elements in Medicine and Biology, 19, 171-181.

1056 Young VR, 1986. Nutritional balance studies: indicators of human requirements or of adaptive
1057 mechanisms? Journal of Nutrition, 116, 700-703.

1058 Zota AR, Ettinger AS, Bouchard M, Amarasiriwardena CJ, Schwartz J, Hu H and Wright RO, 2009.
1059 Maternal blood manganese levels and infant birth weight. Epidemiology, 20, 367-373.

1060

1061

1062 **APPENDICES**

1063 **A. MANGANESE CONCENTRATION IN HUMAN MILK**

Reference[14]	n women (number of samples)	Country	Maternal intake (mg/day)	Stage of lactation	Manganese concentration (µg/L)		
					Mean ± SD	Median	Range
Abdulrazzaq et al. (2008)	209 (205)	United Arab Emirates	Not reported	Infants aged up to 80 wk	0.93 ± 1.20	0.29	0.002-9.1
Al-Awadi and Srikumar (2000)	34 (34)	Kuwait	Not reported	0-6 mo	Kuwaitis: 6.0 ± 0.04 Non-Kuwaitis: 5.7 ± 0.02		
				6-12 mo	Kuwaitis: 4.2 ± 0.2 Non-Kuwaitis: 3.7 ± 0.3		
				12-18 mo	Kuwaitis: 3.8 ± 0.2 Non-Kuwaitis: 3.1 ± 0.1		
Anderson (1992)	7 (84)	USA	Not reported	Up to 5 mo	7.0		
Aquilio et al. (1996)	8	Italy	Not reported	2-6 d	3.9 ± 0.1		
				12-16 d	3.9 ± 0.3		
				21 d	4.1 ± 0.1		
Arnaud and Favier (1995)	82 (143)	France	Not reported	d 1	6.04 ± 3.29		
				d 2	11.81 ± 5.77		
				d 3	7.14 ± 4.12		
				d 4	5.49 ± 2.75		
				d 5	3.29 ± 1.10		
				d 6	3.02 ± 1.65		
				d 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	Wk 1		median (absolute deviation) 17.00 (10.38)	10-17 (median values)
				Wk 2		13.00 (7.41)	
				Wk 3		11.50 (7.41)	
				Wk 4		14.00 (8.90)	

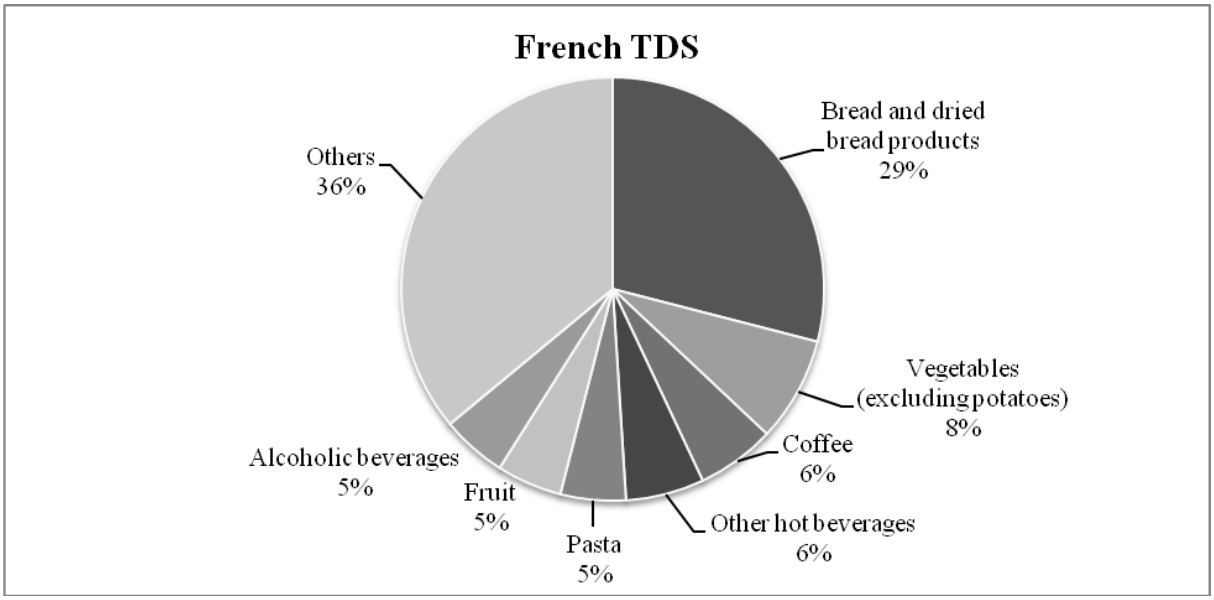
[14] Studies published since 1990

Reference[14]	n women (number of samples)	Country	Maternal intake (mg/day)	Stage of lactation	Manganese concentration (µg/L)		
					Mean ± SD	Median	Range
				Wk 5		14.00 (7.41)	
				Wk 6		14.00 (16.31)	
				Wk 7		11.00 (10.38)	
				Wk 8		10.00 (10.38)	
				Wk 12		13.00 (13.34)	
Krachler et al. (1998)	46 (55)	Austria	Not reported	1-3 d	9.4	7.2	3.6-22
				4-17 d	5.3	5.5	1.3-9.1
				42-60 d	4.2	3.9	1.6-6.5
				66-90 d	4.3	4.5	3.1-5.5
				97-293 d	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 (Nagelkere R^2 value: 0.15)	d 3	4.79 ± 3.23	3.58	1.01-15.70
				d 17	3.13 ± 2.00	2.56	0.17-9.89
Ljung et al. (2009)	408 (67)	Bangladesh	mean of 720 µg Mn/L in water samples	2 mo	9.2	6.6	2.4-59
Parr et al. (1991)	(84)	Guatemala	Not reported	3 mo		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 samples)	China:	median (interquartile range)	8-10 d		median (interquartile range)	
		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)	

Reference[14]	n women (number of samples)	Country	Maternal intake (mg/day)	Stage of lactation	Manganese concentration (µg/L)		
					Mean ± SD	Median	Range
Sharma and Pervez (2005)	35 (35) maternal age: 20-25 y 25-30 y 30-35 y 35-40 y 40-45 y	India	Not reported	Up to 1 wk	 below detection below detection below detection 0.8 ± 0.1 1.5 ± 0.8		
Tripathi et al. (2000)	(25)	India	2.21 (range: 0.67-4.99)	Not reported	1.0		0.69-1.8
Wünschmann et al. (2003)	(23)	Germany	3.5 ± 46 %	2-71.2 wk	4.6 ± 28 %		1.5-290
Yamawaki et al. (2005)	(1167)	Japan	Not reported	Summer Winter 1-5 d 6-10 d 11-20 d 21-89 d 90-180 d 181-365 d Overall	9 ± 16 12 ± 29 12 ± 8 18 ± 53 25 ± 66 8 ± 22 12 ± 11 9 ± 11 11 ± 23		

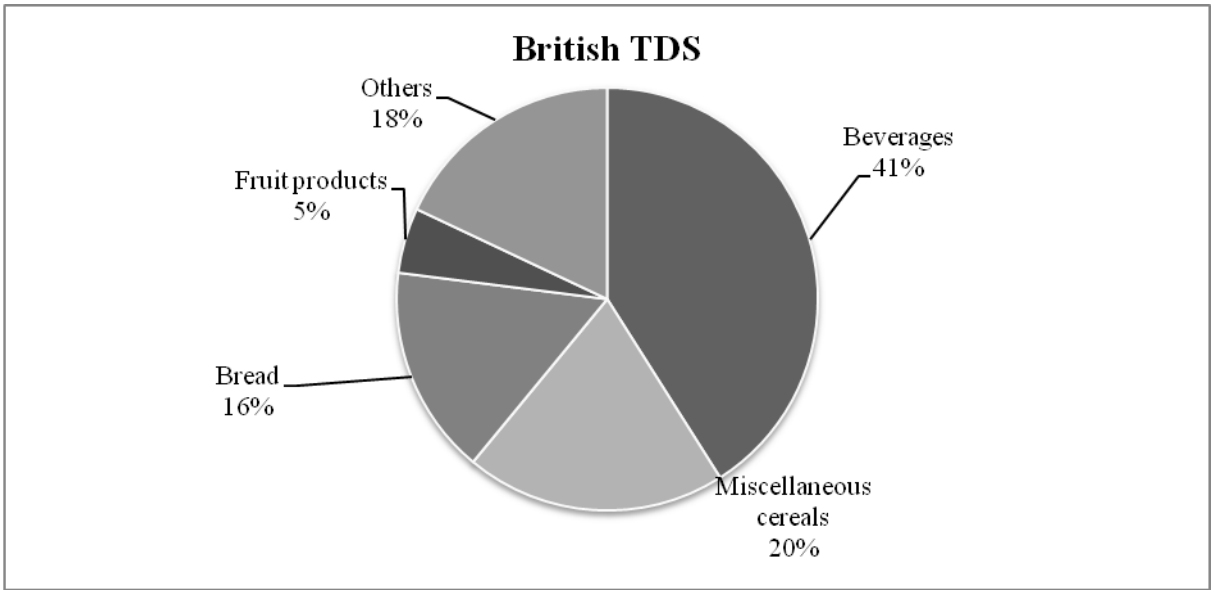
d: day; wk: week; mo: month; y: year

1064 **B. MAIN FOOD CONTRIBUTORS TO MANGANESE INTAKE IN THE FRENCH AND BRITISH TOTAL**
1065 **DIET STUDIES**



1066

1067 Based on Anses (2011)



1068

1069 Based on Rose et al. (2010)

C. MANGANESE INTAKE AMONG 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-d 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-d 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 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-d 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		

d, day.

1073

1074 **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 mo: 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 mo	Boys and girls	23	0.004		
				2 mo	Boys and girls	18	0.003		
				3 mo	Boys and girls	14	0.003		
France	Anses (2011)	2nd TDS. Analysed food samples. Food consumption data from INCA2.	Under-reporters excluded	3-17 y	Boys and girls	1 444	1.5	0.7	2.6

1075 bw, body weight; mo, month; y, year; TDS, Total Diet Study.
1076

1077

1078 **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 mo: 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 mo	Boys	12		0.0009	
					Girls	11		0.0009	
					Boys and girls	23	0.0009		
				2 mo	Boys	9		0.0006	
					Girls	9		0.0005	
					Boys and girls	18	0.0006		
				3 mo	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: NDNS study.	Toddlers	1.5-4.5 y	Boys and girls	n.a.	0.168		0.305
			Older children	4-18 y	Boys and girls	n.a.	0.106		0.201

1079 bw, body weight; mo, month; y, year; TDS, Total Diet Study

1080

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-d record		≥ 65	Men	147	4.3	1.7		
					Women	202	4.4	2.0		
France	(Afssa, 2009)	7-d 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-d 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-d 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-d 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

d, day;

1085

1086 **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 wk) was kept between 6 and 8 wk and the 2nd record (2nd survey wk) between 17 and 22 wks postpartum. A mixture representing the calculated average daily food consumption for both survey wks separately was prepared from the foodstuffs bought from supermarkets in the Helsinki area, and analysed.	1st survey wk	24-35	Women	15	4.45	1.13			
				2nd survey wk	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, sub-divided in 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 ~thirty 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-h duplicates of all meals and beverages, as well as fruit, sweets, 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-h 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 mean and seven women) collected the exact 24-h duplicate portions of all foods and beverages	Breast-feeding, 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)
				Non-breast-feeding, 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 wks 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 NW 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 wk each, in October 1984 and March 1985. On each day of these two wks, 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		
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 analyzed (360 samples). Food consumption data from regional nutritional survey (ENCAT) were used.	Estimated intake for a man (70 kg bw)		Men		2.23				

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	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 regional nutritional survey (ENCA) were used, based on 24-h 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	Collection of food baskets, 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 divided into 12 food groups and analysed as purchased (n=123 samples).		Adults and children			4				
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; d: day; wk: week; mo, month, y, year; TDS, Total Diet Study

1089

1090 **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)	Sex/ Group	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	Adults	0.067	0.124
				Elderly, free living.	≥ 65	Adults	0.056	0.112
				Elderly, institutional.	≥ 65	Adults	0.05	0.121

1091 bw: body weight

GLOSSARY AND 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
COMA	Committee on Medical Aspects of Food Policy
D-A-CH	Deutschland- Austria- Confoederatio Helvetica
DCT	Divalent Cation Transporter
DMT	Divalent Metal Transporter
DoH	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	U.S. Institute of Medicine of the National Academy of Sciences
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

1093