1 **DRAFT SCIENTIFIC OPINION**

2 Scientific Opinion on Dietary Reference Values for selenium[1]

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

4 European Food Safety Authority (EFSA), Parma, Italy

5 **ABSTRACT**

6 Following a request from the European Commission, the Panel on Dietetic Products, Nutrition and Allergies
7 (NDA) derived Dietary Reference Values (DRVs) for selenium. The levelling off of plasma selenoprotein P
8 (SEPP1) concentration was considered to be indicative of an adequate supply of selenium to all tissues and to
9 reflect saturation of the functional selenium body pool, ensuring that selenium requirement is met. This criterion
10 was used for establishing DRVs for selenium in adults. Evidence from human studies on the relationship between
11 selenium intakes and plasma SEPP1 concentrations was reviewed. Given the uncertainties in available data on
12 this relationship, they were considered insufficient to derive an Average Requirement and an Adequate Intake
13 (AI) of 70 µg/day for adults was set. A review of observational studies and randomised controlled trials which
14 investigated the relationship between selenium and health outcomes did not provide evidence for additional
15 benefits associated with selenium intakes beyond those required for the levelling off of SEPP1. No specific
16 indicators of selenium requirements were available for infants, children and adolescents. For infants aged 7–
17 11 months, an AI of 15 µg/day was derived by extrapolating upwards from the estimated selenium intake with
18 breast milk of younger exclusively breast-fed infants and taking into account differences in reference body
19 weights. For children and adolescents, the AIs for selenium were extrapolated from the AI for adults by isometric
20 scaling and range from 15 µg/day for 1 to 3 year-old children to 65 µg/day for adolescents aged 15–17 years.
21 Considering that adaptive changes in the metabolism of selenium occur during pregnancy, the AI set for adult
22 women applies to pregnancy. For lactating women, an additional selenium intake of 15 µg/day was estimated to
23 cover the amount of selenium secreted in breast milk, and an AI of 85 µg/day was set.

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26 **KEY WORDS**

27 selenium, selenoprotein P, Adequate Intake, Dietary Reference Value

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SUMMARY

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

In the diet, selenium is mainly present in organic compounds, as L-selenomethionine and L-selenocysteine, with lower amounts in inorganic compounds, as selenate and selenite. Because quantification and speciation of selenium in foods is complex and because there is large variation in the selenium content of foods, food composition tables are often inaccurate resulting in imprecise estimates of selenium intake.

A total of 25 selenoproteins with a variety of functions, including antioxidant effects, T-cell immunity, thyroid hormone metabolism, selenium homeostasis and transport, and skeletal and cardiac muscle metabolism, have been identified in humans. Selenoprotein P (SEPP1) plays a central role in selenium supply to tissues and participates in the regulation of selenium metabolism in the organism.

Selenium in its various forms appears to be well absorbed from the diet. Upon absorption, selenocysteine, selenate, and selenite are available for the synthesis of selenoproteins. Selenomethionine is nonspecifically integrated into the methionine pool and can substitute for methionine in proteins. Selenomethionine may also be converted to selenocysteine and enter the functional selenium body pool. The body selenium content is regulated by the production of methylated selenium compounds in the liver, which are excreted predominantly in the urine.

Selenium deficiency affects the expression and function of selenoproteins and has been involved in the degeneration of organs and tissues leading to the manifestation of Keshan and Kashin-Beck diseases.

Plasma selenium includes selenium in selenoproteins (the functional body pool of selenium), and other plasma proteins in which selenomethionine nonspecifically substitutes for methionine. Thus, plasma selenium is not a direct marker of the functional selenium body pool. Measures of glutathione peroxidases (GPx) activity can be used as a biomarker of selenium function. However, the activity of GPx reaches a steady state with levels of selenium intake that are lower than those required for the levelling off of SEPP1. SEPP1 is considered the most informative biomarker of selenium function on the basis of its role in selenium transport and metabolism and its response to different forms of selenium intake. Intervention studies using different levels of selenium intakes showed that plasma SEPP1 concentration levels off in response to increasing doses of selenium. The levelling off of plasma SEPP1 was considered to be indicative of an adequate supply of selenium to all tissues and to reflect saturation of the functional selenium body pool, ensuring that selenium requirement is met. This criterion was used for establishing DRVs for selenium in adults.

Evidence from human studies on the relationship between selenium intakes and plasma SEPP1 concentrations was reviewed. The Panel noted uncertainties with respect to estimates of background selenium intake in most studies. Habitual selenium intakes of 50–60 µg/day were not sufficient for SEPP1 concentration to reach a plateau in Finnish individuals, while selenium intakes of 100 µg/day and above were consistently associated with plasma SEPP1 concentration at a plateau in population groups from Finland, the UK and the US. In a study in healthy individuals from New Zealand, selenium intakes of around 60–70 µg/day were required for SEPP1 concentration to level off. Although this was the only study which quantified background selenium intake from the analysed selenium content of consumed foods, the Panel noted the large variability in the results of this study. In another study among Chinese subjects, a selenium intake of 0.85 µg/kg body weight per day led to the levelling off of plasma SEPP1 concentration. The Panel noted, however, that there were uncertainties related to the intake estimates and to the extrapolation of results from Chinese

individuals to the European population. The Panel also noted uncertainties in extrapolating values derived from studies which administered selenium as L-selenomethionine to dietary selenium comprising also other forms of selenium.

Given the uncertainties in available data on the relationship between total selenium intake and SEPP1 concentration, they were considered insufficient to derive an Average Requirement for selenium in adults. Instead, an Adequate Intake (AI) of 70 µg/day for adult men and women was set. A review of observational studies and randomised controlled trials which investigated the relationship between selenium and health outcomes did not provide evidence for additional benefits associated with selenium intakes beyond those required for the levelling off of SEPP1.

No specific indicators of selenium requirements were available for infants, children and adolescents.

For infants aged 7–11 months, an AI of 15 µg/day was derived by extrapolating upwards from the estimated selenium intake with breast milk of younger exclusively breast-fed infants and taking into account differences in reference body weights. For children and adolescents, the AIs for selenium were extrapolated from the AI for adults by isometric scaling. The AIs range from 15 µg/day for 1 to 3 year-old children, to 65 µg/day for adolescents aged 15–17 years.

There is evidence suggesting adaptive changes in the metabolism of selenium during pregnancy and it was considered that these changes cover the additional selenium needs during this period. The Panel proposes that the AI set for adult women also applies to pregnancy. Based on an average amount of selenium secreted in breast milk of 12 µg/day and an absorption efficiency of 70 % from usual diets, an additional selenium intake of 15 µg/day was considered to replace these losses. Thus, an AI of 85 µg/day is proposed for lactating women.

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BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

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

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

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

In this context the 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 the 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,[5] the Commission requests EFSA to review the existing advice of the Scientific Committee for Food on population reference intakes for energy, nutrients and other substances with a nutritional or physiological effect in the context of a balanced diet which, when part of an overall healthy lifestyle, contribute to good health through optimal nutrition.

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

- Carbohydrates, including sugars;

[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.

[5] Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. OJ L 31, 1.2.2002, p. 1-24.

- Fats, including saturated fatty acids, polyunsaturated fatty acids and monounsaturated fatty acids, *trans* fatty acids;
- Protein;
- Dietary fibre.

Following on from the first part of the task, the 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, the 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) published an opinion on the nutrient and energy intakes for the European Community and derived for selenium an Average Requirement (AR) and a Population Reference Intake (PRI) for adults. PRIs were also set for pregnant and lactating women, infants and children. A Lowest Threshold Intake (LTI) and a maximum safe intake were proposed as well.

2. Definition/category

2.1. Chemistry

Selenium is a non-metal with an atomic mass of 78.96 Da. Along with oxygen and sulphur, it belongs to the group of "chalcogens", i.e. group 16 (VI A) of the periodic table. It resembles sulphur, its group superior homologue in the periodic table, both in its inorganic and organic compounds (Garrow et al., 2000).

In nature, selenium rarely occurs in its elemental state, but when it does it is stable in soils. Selenium forms inorganic and organic compounds, with most common oxidation states – 2, + 4 or + 6. The inorganic species include selenides (e.g. sodium selenide, Na_2Se), selenites (SeO_3^{-2}, selenium [+ 4]) and selenates (SeO_4^{-2}, selenium [+ 6]). Selenites and selenates are the most common inorganic compounds, they are water-soluble and can be found in water.

Selenium forms stable bonds to carbon in organic compounds. They include selenides (R–Se–R) such as dimethylselenide, selenium amino acids (selenomethionine, selenocysteine), selenium-containing proteins and selenoproteins.

Dietary L-selenomethionine and L-selenocysteine (referred to as selenomethionine and selenocysteine in this Opinion) are naturally occurring amino acids which have structures similar to L-methionine and L-cysteine, except that selenium replaces sulphur.

Selenomethionine may unspecifically replace methionine residues in proteins, as the methionine-tRNA cannot distinguish between the two compounds (Whanger, 2002). Resulting proteins are referred to as selenium-containing proteins.

Dietary selenocysteine is considerably more reactive than selenomethionine. Selenocysteine constitutes a specific amino acid residue in a number of proteins named selenoproteins (section 2.2.1). There is no evidence that selenocysteine substitutes for cysteine in proteins.

Several analytical methods exist for the determination of total selenium in foods or biological samples (ATSDR, 2003). A number of methods to separate and quantify different selenium compounds have also been developed (Chatterjee et al., 2003; Infante et al., 2005; Dumont et al., 2006; Mazej et al., 2006).

2.2. Functions of selenium

2.2.1. Biochemical functions

Selenomethionine is not known to have a physiological function different from that of methionine, as a substitute amino acid residue in proteins.

The main form of selenium in mammalian proteins is selenocysteine. It is essential for the synthesis of selenoproteins and is found in the active centre of a number of selenoprotein enzymes (Kryukov et al., 2003). Selenocysteine is encoded by the UGA codon in mRNAs by the presence of specific secondary structures termed selenocysteine insertion sequences (SECIS) (Squires and Berry, 2008; Lu and Holmgren, 2009).

Currently, 25 selenoprotein genes have been identified in the human genome (Kryukov et al., 2003). Selenoproteins have a variety of functions, including antioxidant effects, T-cell immunity, thyroid hormone metabolism, selenium homeostasis and transport, and skeletal and cardiac muscle metabolism. Table 1 lists selenoproteins whose functions have been identified, which include iodothyronine deiodinases (DIOs), glutathione peroxidases (GPxs), thioredoxin reductases (Txnrds) and selenoprotein P (SEPP1).

Human selenoproteins whose roles are as yet either unknown or not fully elucidated include selenoprotein I, selenoprotein K, selenoprotein M, selenoprotein O, selenoprotein T, selenoprotein V, and selenoprotein 15 kDa (Reeves and Hoffmann, 2009; Bodnar et al., 2012; Mehdi et al., 2013).

A “hierarchy” of selenoproteins, as to the preferential incorporation of selenium into certain selenoproteins and the prioritisation of selenium supply to specific organs, has been studied in rodents. Under selenium restriction, a priority supply of the element to the brain, the reproductive and the endocrine organs, in particular the thyroid gland, was observed (Burk et al., 1973; Behne et al., 1988; Bermano et al., 1995). In studies in rats and mice, selenium deficiency was observed to cause less pronounced decreases in the concentrations of SEPP1, type I iodothyronine 5-deiodinase (DIO1) and in the activity of GPx4, than in the activities of GPx1 and thioredoxin reductases (Hill et al., 1992; Lei et al., 1995; Sunde et al., 2009). SEPP1, DIO1 and GPx4 mRNA levels were also shown to decrease less than GPx1 and Txnrds mRNA levels, suggesting that a pretranslational regulation, affecting mRNA levels, might be a mechanism underlying this hierarchy (Hill et al., 1992; Sunde et al., 2009).

283 **Table 1:** Human selenoproteins and their functions

Selenoproteins (Abbreviations)	Location	Functions
Classical or Cellular Glutathione Peroxidase (cGPx, GPx1)	Widely distributed. Intracellular.	Reduces hydrogen peroxide and organic peroxides to water and alcohols, respectively. Plays a role in the protection of the cells from oxidative damage.
Gastrointestinal Glutathione Peroxidase (giGPx, GPx2)	Mainly gastrointestinal tract. Detectable in the liver.	Protects intestinal epithelium from oxidative damage induced by ingested prooxidants or gut microbiota. Involved in metabolism of ingested peroxides of fats by reducing free hydroperoxides of fatty acids and hydrogen peroxide.
Extracellular or Plasma Glutathione Peroxidase (eGPx, GPx3)	Plasma and extracellular fluids. Primarily produced in the kidney and secreted in plasma; also expressed in liver, heart, lung, thyroid, gastrointestinal tract and breast. High concentrations in the heart and thyroid gland.	Local source of extracellular antioxidant. Protects cell membranes by reducing hydrogen and organic peroxides in the presence of glutathione, as well as phospholipid hydroperoxides.
Phospholipid Hydroperoxide Glutathione Peroxidase (phGPx, GPx4)	Widely distributed. Sperm (structural role). High expression in the testes.	Enzyme and structural protein. Protects membranes from oxidative damage by reducing phospholipid hydroperoxides. Involved in metabolism of lipids such as arachidonic and linoleic acids, cholesterol and its esters. Structural protein constitutive of the mitochondria that make up the midpiece sheath of the sperm tail.
Glutathione Peroxidase 6 (GPx6)	Embryo. Olfactory epithelium.	Homologue of GPx3. Unknown role.
Iodothyronine deiodinase type 1 (D1, DIO1, 5'DI)	Kidney, liver, thyroid, brown adipose tissue	Involved in thyroid hormone metabolism. D2 regulates thyroid hormone metabolism in response to changes in iodine supply, cold exposure, and changes in thyroid gland function. D1 or D2 carry out the conversion of T4 to T3. D3 is involved in the irreversible inactivation of T4 and T3 D1 is involved in the irreversible inactivation of T3 to inactive T2.
Iodothyronine deiodinase type 2 (D2, DIO2, 5'DII)	Thyroid, central nervous system, pituitary, brown adipose tissue, skeletal muscle.	
Iodothyronine deiodinase type 3 (D3, DIO3, 5'DIII)	Placenta, central nervous system, fetus.	

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Selenoproteins (Abbreviations)	Location	Functions
Cytoplasmic/nuclear Thioredoxin Reductase (TR1, TrxR1, Txnrd1)	Intracellular, widely distributed.	Catalyse the reduction of oxidised thioredoxin (Trx), which is in turn used by several cellular enzymes. TR1 is involved in embryogenesis. TR2 affords protection against the hydrogen peroxide produced by the mitochondrial respiratory chain. Responsible for reducing ribonucleotides to deoxyribonucleotides and for maintaining intracellular redox potential.
Mitochondrial Thioredoxin Reductase (TR2, TrxR2, TxnR2, Txnrd2)	Mitochondrial, widely distributed.	
Testes-specific thioredoxin-glutathione reductase (TR3, TrxR3, Txnrd3, TxnR3, TGR)	Testes.	
Selenophosphate synthetase (SPS2)	Widely distributed.	Involved in synthesis of all selenoproteins. Catalyses the reaction of selenide with ATP, which forms selenophosphate, a selenium donor in the biosynthesis of selenocysteine.
Selenoprotein H (SelH)	Widely distributed. DNA-binding protein.	Regulates expression levels of genes involved in *de novo* glutathione synthesis and phase II detoxification.
Selenoprotein N (SelN, SEPN1, SepN)	Widely distributed. Transmembrane glycoprotein associated to endoplasmic reticulum.	Muscle development, cell proliferation, redox signalling, calcium homeostasis.
Selenoprotein P (SEPP1, SelP, SeP)	Widely distributed. Extracellular glycoprotein. Mainly synthesised in the liver.	Storage and transport of selenium from the liver via the plasma to other tissues, particularly the brain, the kidney and the testes. Has antioxidant properties and is involved in immune function. Forms heavy metal ion complexes.
Selenoprotein R (SelR, MsrB1)	Widely distributed.	Protects against oxidative damage. Involved in methionine metabolism and protein repair. Reduction of sulfoxymethyl group.
Selenoprotein S (SelS, SEPS1, SELENOS, Tanis, VIMP)	Widely distributed. Transmembrane protein associated to endoplasmic reticulum.	Elimination of misfolded proteins from the endoplasmic reticulum, protecting the cell from oxidative stress and inflammatory events which accompany the misfolded protein response.
Selenoprotein W (SelW, SEPW1)	Widely distributed. Abundant in brain, colon, heart, skeletal muscles and prostate.	Skeletal and cardiac muscle growth and function. Antioxidant function. Calcium-binding.

286 Modified from Reeves and Hoffmann (2009); Fairweather-Tait et al. (2010); Bodnar et al. (2012); Rayman (2012); Mehdi et al. (2013).

2.2.2. Health consequences of deficiency and excess

2.2.2.1. Deficiency

Selenium deficiency affects the expression and function of selenoproteins. In children with phenylketonuria given a low protein diet, low selenium intake reduced glutathione peroxidase activity and plasma thyroid hormones concentrations, and they responded to selenium supplementation (Lombeck et al., 1984; Lombeck et al., 1996; Jochum et al., 1997; van Bakel et al., 2000). A median selenium intake of 6.9 µg/day was estimated in one of the studies, which was in children aged 3 to 18 months (median weight 8.8 kg) (Lombeck et al., 1984). Clinical manifestations of selenium deficiency are poorly defined. Symptoms observed in patients receiving selenium-free total parenteral nutrition (TPN) include skeletal myopathy and muscle weakness (Gramm et al., 1995). Several cases of cardiomyopathy were reported, although selenium deficiency appeared to be only one of the aetiological factors in these subjects. Pseudoalbinism and red blood cell macrocytosis were also observed in children receiving selenium-free TPN.

There are concerns that combined low intakes of iodine and selenium contributes to the risk of myxoedematous cretinism, described in the endemic goitre area of central Africa (Dumont et al., 1994).

Selenium deficiency is also involved in the degeneration of organs and tissues leading to the manifestation of Keshan and Kashin-Beck diseases (Fairweather-Tait et al., 2011).

Keshan disease is an endemic cardiomyopathy occurring mainly in children and young women. It is apparent in population groups in China with particularly low selenium intakes (around 15 µg/day) (Ge and Yang, 1993). Keshan disease is not yet fully understood, but there is some evidence for a dual aetiology, including both selenium deficiency and infection with an enterovirus, such as the Coxsackie virus B3 or a mild strain of influenza virus (H3N2) (Beck et al., 2003; Loscalzo, 2014). Mechanisms related to the antioxidant role of selenoproteins have been suggested to be involved in the contribution of selenium deficiency to the development of the cardiomyopathy of Keshan disease (Loscalzo, 2014). An amyocarditic strain of Coxsackie virus B3 converted to a virulent form when it was inoculated into selenium-deficient mice (Beck et al., 1994). GPx1 knockout mice infected with the benign strain of Coxsackie virus were shown to develop the disease, even when fed with adequate amounts of selenium, indicating a role of this selenoprotein in the development of the disease (Beck et al., 1998).

Kashin-Beck disease is a chronic degenerative osteochondropathy occurring in pre-adolescence or adolescence in selenium-deficient areas. It is endemic in some areas in China, but also in Mongolia, Siberia and North Korea. The aetiology of the disease is largely unknown. Possible risk factors seem to include mycotoxins in food, humic and fulvic acids in drinking water, and selenium and iodine deficiency (Sudre and Mathieu, 2001; Yao et al., 2011).

2.2.2.2. Excess

An excess of body selenium can give rise to selenosis occurring in population groups (e.g. in China) exposed to levels of dietary selenium above 1 000 µg/day (Yang et al., 1983; Yang et al., 1989a; Yang et al., 1989b). Characteristic features of selenosis include headache, loss of hair, deformation and loss of nails, skin rash, malodorous (garlic) breath and skin, excessive tooth decay and discoloration, as well as numbness, paralysis, and hemiplegia. The molecular mechanisms of selenium toxicity remain unclear. Levels of dietary exposure at which selenium becomes toxic and selenosis develops are difficult to establish because toxicity is affected by the selenium compounds in the food supply, and

probably the combination of other components of the diet and interactions with genotype (Fairweather-Tait et al., 2011).

The SCF (2000) adopted the value of 300 µg/day as a Tolerable Upper Intake Level (UL) for adults including pregnant and lactating women, on the basis of a No-Observed-Adverse-Effect-Level (NOAEL) of 850 µg/day for clinical selenosis and applying an uncertainty factor of 3, supported by three studies reporting no adverse effects for selenium intakes between about 200 and 500 µg/day.

Since there were no data to support a derivation of a UL for children, the SCF (2000) extrapolated the UL from adults to children on the basis of reference body weights (SCF, 1993). The proposed UL values range from 60 µg/day (1 to 3 years) to 250 µg selenium/day (15 to 17 years).

2.3. Physiology and metabolism of selenium

2.3.1. Intestinal absorption

When supplied as selenomethionine and presumably as selenocysteine more than 90 % of selenium is absorbed (Swanson et al., 1991; IOM, 2000). Selenium in inorganic compounds such as selenate or selenite also appears to be well absorbed, but less is retained than with organic compounds (Thomson and Robinson, 1986; Fairweather-Tait et al., 2010). Selenite has been observed to be better absorbed than selenate but retention of the two species appears to be similar (Finley et al., 1999; Van Dael et al., 2002). The mechanisms of absorption of the different selenium compounds require further elucidation (Fairweather-Tait et al., 2010). Absorption efficiency does not seem to be affected by selenium status or to play a role in the homeostatic regulation of selenium (Sunde, 2012).

Dietary selenium from plant and animal sources occurs mainly as organic compounds, with smaller amounts present as inorganic compounds (section 3.1). Balance studies measuring faecal excretion of selenium after dietary intake of selenium from controlled diets based on conventional foods found an apparent absorption of around 70 % in healthy adolescents girls (n = 16; 11–14 years; mean selenium intake 105–131 µg/day for two weeks) (Holben et al., 2002) and men (n = 12; 20–45 years; mean selenium intake 47 µg/day for 21 days) (Hawkes et al., 2003) once subjects had equilibrated to the experimental diet. Two other studies reported average apparent absorption figures of 83 % and 95 % in healthy young subjects (n = 12; 20–33 years) receiving controlled amounts of selenium (93–137 µg/day) from a rich food source (shrimps or meat and meat products from pig, respectively) given in addition to a basal diet (Bugel et al., 2001; Bugel et al., 2004). Apparent absorption of selenium from bread or meat using three selenium dose levels (55, 135 and 215 µg/day) was assessed by van der Torre et al. (1991). Mean absorption efficiency from bread and meat was 57 and 38 %, 73 and 75 %, 74 and 80 % in the low, medium and high dose groups, respectively.

A number of studies estimated selenium absorption by using foods intrinsically labelled with selenium isotopes provided with a test meal. Most studies were conducted in small groups of young men with 100 to 300 µg selenium/test dose. Mean absorption was 70–72 % from chicken (Christensen et al., 1983), 74 % from broccoli (Finley et al., 1999), 81 %, 78 % and 56 % from wheat, garlic and cod (Fox et al., 2005) and 85–86 % from raw and cooked fish (Fox et al., 2004). The Panel notes that these studies used a single labelled food as the main selenium source and considers that it is not appropriate to extrapolate these results to selenium absorption from whole diets, as the selenium forms specific to the test foods may not be representative of dietary selenium.

The Panel notes that data on selenium absorption from whole diets are limited. Based on available data, the Panel considers an absorption efficiency of selenium of 70 % from usual diets.

2.3.2. Transport in blood

In plasma, the most abundant selenoproteins are SEPP1 and extracellular glutathione peroxidase GPx3, accounting for approximately 30–60 % and 10–30 % of selenium, respectively (Wastney et al., 2011). The rest of plasma selenium consists of selenomethionine in albumin and other proteins (Deagen et al., 1993; Ducros et al., 2000; Burk et al., 2006) and a minor fraction (< 3 %) in small molecular compounds such as selenosugars (Burk et al., 2006). The relative distribution of selenium among these different compounds is affected by the amount and chemical nature of selenium in the diet (Burk et al., 2006). Selenium is also present in platelet and red blood cells in glutathione peroxidase GPx1.

2.3.3. Distribution to tissues

Studies in rodents indicate that SEPP1 plays a key role in the delivery of selenium to tissues, in particular brain and testes through the specific receptor ApoER2 (Hill et al., 2003; Schomburg et al., 2003; Olson et al., 2007). Megalin receptors mediate SEPP1 uptake from glomerular filtrate in kidneys (Olson et al., 2008). Although SEPP1 is the major circulating form of selenium in plasma, it is likely that other selenoproteins are also important tissue-specific transporters. For instance, the form in which selenium leaves the enterocyte and is presented to the liver for incorporation into SEPP1 is unknown. The mechanisms involved in delivery of selenium to the tissues have not been fully elucidated (Fairweather-Tait et al., 2011).

Studies in rodents have demonstrated a "hierarchy" amongst the selenoproteins, with preferential incorporation of selenium into certain selenoproteins and the prioritisation of selenium supply to specific organs, in particular the brain, the reproductive and the endocrine organs (section 2.2.1).

The thyroid gland has the highest selenium concentration (Kohrle, 1999), followed by the kidneys, testes and liver (Oster et al., 1988; Oldereid et al., 1998). Skeletal muscles account for the major part of selenium body content (30–50 %), while less selenium is contained in the bones (15 %), blood (10 %), liver (8 %), kidneys (3 %) and brain (3 %) (Oster et al., 1988; Zachara et al., 2001b). The selenium concentrations in human tissues vary significantly depending on geographic location, with lower selenium concentrations found in subjects from regions where soil is low in selenium (Zachara et al., 2001b). Consequently, total body content varies; values between about 5 mg and 20 mg have been reported for total body contents of Polish, German and American adults (Zachara et al., 2001b).

Oster et al. (1988) reported a mean selenium concentration of 274 ± 48 ng/g wet weight in 16 testis samples of adults, similar to the concentration found in the liver. On a dry weight basis, Oldereid et al. (1998) found that the selenium concentration in the testes of 41 Norwegian men was somewhat higher than in the liver and about twice that of the other reproductive organs (epididymis, prostate and seminal vesicle). Selenium is delivered to the testes in the form of SEPP1 through ApoER2-mediated uptake, and the majority of the selenium is incorporated into GPx4 (Olson et al., 2007), which plays multiple roles in sperm maturation (Ursini et al., 1999).

During pregnancy, selenium progressively accumulates in the organs of the growing fetus (Bayliss et al., 1985; Zachara et al., 2001a). Fetal hepatic selenium concentration appears relatively constant during gestation, while the concentration is falling in the months following birth, concurrent with stable selenium concentrations in other organs (Westermarck, 1977; Bayliss et al., 1985). This indicates that the liver may act as a store of selenium during gestation and selenium may be redistributed after birth to other organs.

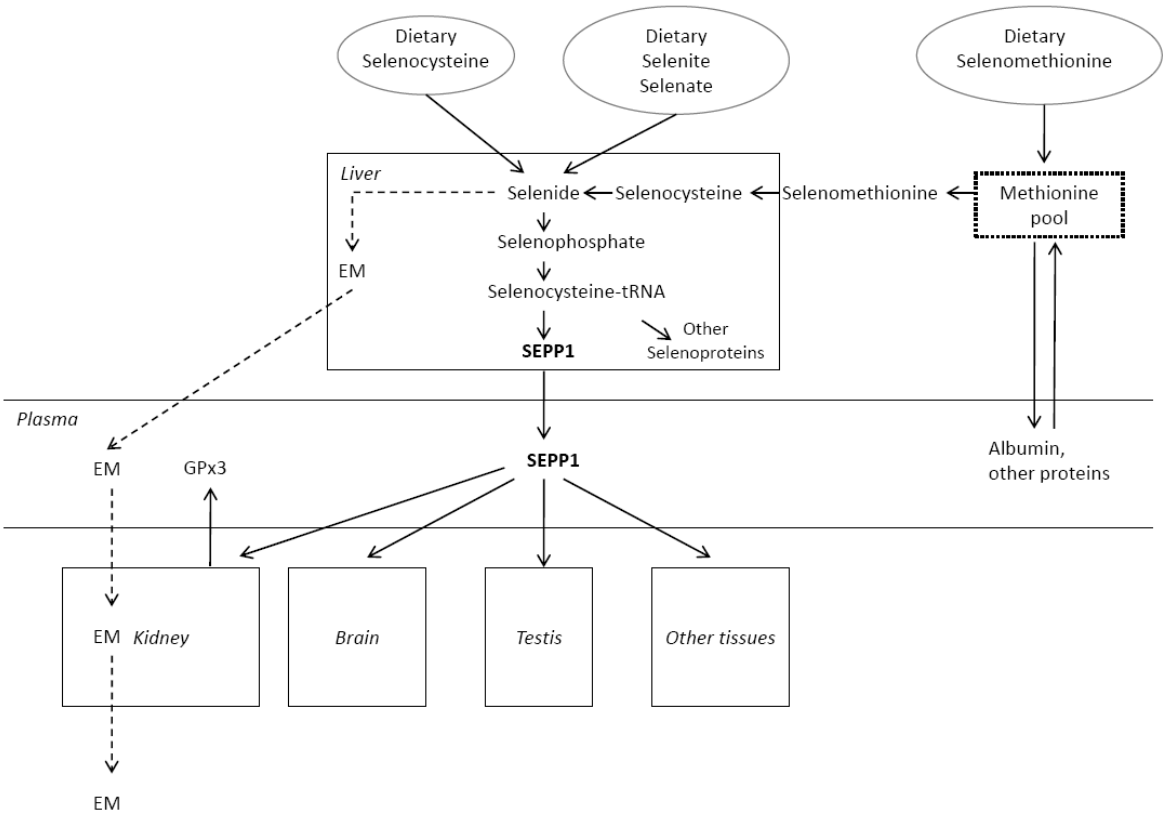
Data in mice indicate transfer of selenium to the fetus through uptake of SEPP1 from maternal blood via ApoER2-mediated endocytosis, as well as an additional maternal-fetal transfer mechanism which remains to be elucidated (Burk et al., 2013). Transfer of selenomethionine-containing proteins or selenomethionine also supplies the fetus with selenium (Anan et al., 2009; Burk et al., 2013).

2.3.4. Storage

Selenomethionine is nonspecifically incorporated into body proteins, particularly in organs with high rates of protein synthesis, such as the skeletal muscles, red blood cells, pancreas, liver, kidney, stomach and the gastrointestinal mucosa, which enables selenium to be stored (Schrauzer, 2000). Selenium from selenomethionine may be mobilised for metabolic processes through conversion of selenomethionine to selenocysteine in the liver or kidney (section 2.3.5).

SEPP1 has a high selenium content (10 selenocysteine residues) and is the main carrier of selenium in plasma, and is thus thought to play a role in selenium retention and storage (section 2.3.5).

2.3.5. Metabolism



EM, excretory metabolites ; GPx3; glutathione peroxidase 3 ; SEPP1, selenoprotein P.

Figure 1: Selenium metabolism

Absorbed selenocysteine, selenate, and selenite are available for the synthesis of selenoproteins. Cellular selenoprotein synthesis involves the degradation of free selenocysteine to selenide, which is then converted to selenophosphate and selenocysteine-tRNA$^{[ser]sec}$ before integration of selenocysteine into the expanding polypeptide chain. Utilisation of selenate or selenite for selenoprotein synthesis first requires reduction to selenide via interaction with glutathione (Rayman et al., 2008).

Selenomethionine is nonspecifically integrated into the methionine pool where it acts as a substitute amino acid residue in proteins. Dietary selenomethionine is also a source of selenium as it may enter the functional selenium body pool through conversion to selenocysteine by the transsulphuration pathway in the liver or kidney.

Wastney et al. (2011) compared selenomethionine and selenite metabolism using isotope tracers and compartmental modelling in humans. After ingestion of the tracer dose, selenium from both compounds entered a common pool, and metabolism was then similar for several days before diverging due to higher urinary excretion of selenium compounds derived from selenite compared to selenomethionine from one of the plasma pools. The final model consisted of a large number of pools, reflecting the complexity of selenium metabolism, as selenium is incorporated in a number of selenoproteins as well as other proteins that contain nonspecifically incorporated selenomethionine, which may be expected to differ in turnover rates.

Deletion of hepatic SEPP1 production in a mouse model induced an increase in liver selenium at the expense of other tissues, and a decrease in whole-body selenium content associated with increasing excretion of selenium metabolites (Hill et al., 2012). Thus, the regulation of hepatic SEPP1 production appears to play an important role in selenium homeostasis (Figure 1). Although the molecular mechanisms of this regulation is not known, it has been hypothesised to occur at the biochemical level of selenide, which can either be metabolised to selenophosphate or be methylated to produce excretory metabolites (Hill et al., 2012) (section 2.3.6). The lipoprotein receptor ApoER2 binds SEPP1 and facilitates its uptake into the testes and the brain. SEPP1 is filtered by the kidney into the glomerular filtrate and binds to megalin in the brush border of proximal convoluted tubules. These cells endocytose the SEPP1 bound to megalin and presumably use its selenium to synthesise plasma glutathione peroxidase (GPx3) (Burk and Hill, 2009).

Thus, SEPP1 appears to play a central role in selenium supply to tissues and to participate in the regulation of selenium metabolism in the organism. Whole body selenium appears to be regulated in the liver through the distribution from the functional selenium body pool between the pathways of selenoprotein synthesis, including SEPP1, and selenium excretory metabolites.

2.3.6. Elimination

2.3.6.1. Urine and breath

The body selenium content is regulated by the production of methylated selenium compounds in the liver (section 2.3.5), which are excreted predominantly in the urine. The rate of excretion of selenium is greatest within 24 hours of ingestion (Swanson et al., 1991; Wastney et al., 2011).

Characterisation of selenium excretory metabolites in human urine is difficult due to methodological and analytical issues in separating and identifying urinary selenium compounds (Gammelgaard and Bendahl, 2004). Urinary metabolites include a methylated selenosugar, Se-methyl-*N*-acetylgalactosamine, which is the major selenium compound in urine at usual dietary intakes of selenium (Kobayashi et al., 2002; Francesconi and Pannier, 2004; Gammelgaard and Bendahl, 2004; Suzuki, 2005). Other minor urinary metabolites, such as Se-methyl-*N*-acetylglucosamine and Se-methylselenoneine, have also been identified (Gammelgaard and Bendahl, 2004; Klein M et al., 2011) and methods to quantify volatile urine selenium species have recently been developed (Hurst et al., 2013). At high intakes, excess selenium is eliminated through urine as trimethylselenonium ion (Foster et al., 1986b, 1986a; Suzuki, 2005) and in breath as dimethylselenide (Kremer et al., 2005).

Balance studies with selenium intakes between about 10 and 80 µg/day indicate that urinary excretion accounts for around 40–60 % of selenium intakes (Robinson et al., 1973; Levander and Morris, 1984; Luo et al., 1985). The fraction of selenium that is excreted in the urine depends, among others, on the chemical nature of the ingested selenium. In a supplementation trial involving "selenium-replete" adults from the US who received 200–600 µg/day selenium in different forms, Burk et al. (2006) observed average urinary excretion of 60 ± 26 % when selenium was provided as selenomethionine, 41 ± 15 % when it was provided as sodium selenite, and 52 ± 23 % when provided as selenium-rich

yeast. The difference reached significance between the groups receiving selenomethionine and sodium selenite.

It is unknown whether the synthesis of excretory selenium metabolites is a passive process, guided by the amount of selenium that cannot be accommodated by the selenoprotein synthesis pathway entering the excretory pathway, or whether it involves active regulation (Burk and Hill, 2009).

2.3.6.2. Faeces

Selenium in the faeces consists of unabsorbed selenium and some endogenous excretion from the turnover of intestinal mucosal cells, which contain selenium in the form of selenoproteins. Around 30 % of ingested selenium was excreted via the faeces when selenium was provided through controlled diets based on conventional foods (Holben et al., 2002; Hawkes et al., 2003). A recent experiment in mice receiving various amounts of selenium as selenite suggests that an active process may be involved in the faecal excretion of selenium, as indicated by a significantly higher fractional faecal excretion (30 %) in mice fed a "moderately high selenium diet" (intake 7.4 ± 1.0 µg selenium/day) compared to mice fed a "selenium adequate diet" (20 %) (intake 0.87 ± 0.09 µg selenium/day) (Pedrosa et al., 2012). Results are, however, limited and require further elucidation in humans.

2.3.6.3. Breast milk

Breast milk concentration reflects maternal selenium intakes and increases in response to organic and, to a lesser extent, inorganic selenium intake from supplements (Kumpulainen et al., 1985; Trafikowska et al., 1998; Dorea, 2002). Selenium appears in breast milk as a component of specific selenoproteins, mainly as GPx (15–30 % of total milk selenium) and seleno-amino acids in milk proteins, while inorganic species are undetectable (Dorea, 2002). Maternal plasma/serum selenium concentration is higher than in breast milk. Dorea (2002) observed a high variability in the ratio of maternal plasma/serum selenium to milk selenium concentration across studies, but statistically significant positive correlations were reported in most studies.

There are variations in breast milk selenium concentrations between countries or regions within a country. Parr et al. (1991) reported a range in mean breast milk selenium concentrations of 13 to 32 µg/L in Guatemala, Hungary, Nigeria, Philippines, Sweden and Zaire. Breast milk from mothers living in an area of low soil selenium compared to a seleniferous region of China had mean concentrations of 15 µg/kg and 120 µg/kg, respectively (Yang et al., 1989a).

There is a decline in selenium concentration in breast milk over the course of lactation, with a high selenium concentration in colostrum followed by a decrease in breast milk concentration as lactation progresses (Dorea, 2002).

The Panel considered an average selenium concentration of 16 µg/L in its recent opinion on nutrient requirements and dietary intakes of infants and young children in the European Union (EFSA NDA Panel, 2013), based on results from four studies.

Mean/median selenium concentrations in mature breast milk from 16 studies in women from EU countries were between 7 and 21 µg/L, with most values between 10 and 18 µg/L (Robberecht et al., 1985; Schramel et al., 1988a; Bratakos and Ioannou, 1991; Brätter et al., 1991; Kantola and Vartiainen, 1991; Debski et al., 1992; Jochum et al., 1995; Kantola et al., 1997; Krachler et al., 1998; Li et al., 1999; Krachler et al., 2000; Zachara and Pilecki, 2000; Martino et al., 2001; Navarro-Blasco and Alvarez-Galindo, 2004; Valent et al., 2011; Miklavcic et al., 2013) (see Appendix A).

Based on available data (Appendix A), the Panel considers an approximate midpoint of selenium concentration in mature breast milk in the EU of 15 µg/L. Assuming an average milk volume of

0.8 L/day (Butte et al., 2002; FAO/WHO/UNU, 2004; EFSA NDA Panel, 2009), the Panel estimates that the amount of selenium secreted in breast milk during the first six months of lactation is 12 µg/day.

2.3.7. Interaction with other nutrients

Glutathione peroxidases, SEPP1 and other selenoproteins belong to the human antioxidant network and selenium is likely to interact with other nutrients that affect the antioxidant-prooxidant balance of the cell (Sunde, 2012). The interaction between vitamin E and selenium has been a subject of research, although data are still limited (Hurst et al., 2013). Selenium and iodine play critical roles in thyroid hormone metabolism and combined effects of selenium and iodine deficiencies on thyroid function have been observed in animals and humans (Arthur et al., 1999). An influence of ascorbic acid on the absorption and metabolism of selenium, more particularly selenite, has also been suggested, but data are scarce (Martin et al., 1989).

2.4. Biomarkers

Dietary assessment methods are imprecise measures of selenium intake, mainly because of large variability in the selenium content of foods (section 3). Various markers of intake or status are used, including concentrations of selenium in blood cells (red blood cells, platelets), hair, nails, or body fluids (whole blood, plasma or urine), and concentration of selenoproteins or activity of selenoenzymes (Fairweather-Tait et al., 2011). Plasma, red blood cell and whole blood selenium concentration, plasma SEPP1 concentration, and GPx activity (assessed in plasma, platelets or whole blood) have been considered useful markers of selenium intake/status (Ashton et al., 2009; Rayman, 2012; Hurst et al., 2013).

2.4.1. Plasma/serum and whole blood selenium concentration

Plasma/serum selenium is comprised of selenium from selenoproteins and selenomethionine-containing proteins, mainly albumin (Burk et al., 2001; Hurst et al., 2010). Serum and plasma selenium concentrations are considered equivalent.

Although plasma selenium concentrations are affected by factors such as sex, age, and smoking status, these effects tend to be small and dietary selenium intake appears to be the major determinant of the plasma selenium concentration (Robberecht and Deelstra, 1994). Besides, plasma selenium concentration decreases with inflammation (Nichol et al., 1998; Maehira et al., 2002; Huang et al., 2012).

Plasma selenium responds to supplementation with selenomethionine or selenium-enriched yeast across a wide range of intakes (20–700 µg/day) and in subjects with low (< 60 µg/L) to high (> 100 µg/L) baseline plasma selenium (Ashton et al., 2009). Besides the dose, plasma response to dietary selenium also depends on the chemical nature of selenium, so intake of two different selenium compounds (at the same dose) may result in different plasma selenium concentrations (Fairweather-Tait et al., 2010). Plasma selenium is a sensitive marker of recent dietary selenomethionine intake or selenium-enriched yeast supplements, but not of intake of inorganic selenium species (Hurst et al., 2013). It is therefore considered a useful marker for monitoring compliance of selenomethionine intake in supplementation trials (Burk et al., 2006).

There is no homeostatic regulation of plasma selenium concentration and it does not appear to reach a plateau (Fairweather-Tait et al., 2010). In subjects whose SEPP1 and GPx3 pools have reached steady state concentrations, plasma selenium continues to increase with organic selenium supplementation, predominantly reflecting the intake of selenium from selenomethionine, which nonspecifically substitutes for methionine in plasma proteins (Burk et al., 2001; Burk et al., 2006; Xia et al., 2010;

Combs et al., 2011). However, plasma concentration appears to reach a steady state at any constant level of intake after approximately 10 to 12 weeks, although it may take longer in subjects with a baseline plasma concentration > 130 µg/L (Fairweather-Tait et al., 2010; Hurst et al., 2013).

Relationships between dietary selenium intake and plasma selenium have been described (Yang et al., 1989b; Burk et al., 2006; Combs et al., 2012) and equations to estimate dietary selenium intake from plasma/serum or whole blood selenium concentrations (Yang et al., 1989b; Yang and Xia, 1995; Longnecker et al., 1996) or selenomethionine intake from plasma selenium data (Burk et al., 2006) have been published. For example, log-log regression equations were derived between whole blood and plasma/serum selenium concentrations and dietary selenium intake of individuals from free-living population groups in China (Yang et al., 1989b; Yang and Xia, 1995). Such equations have generally not been validated. The Panel notes that the plasma response to selenium intakes depends on the chemical nature of ingested selenium and exhibits large individual variation in response to a given intake. In addition, the proposed equations are affected by the baseline selenium status of the study participants. The Panel therefore considers that these equations are semi-quantitative and concludes that they can only provide an approximate estimate of selenium intake of population groups from plasma or whole blood selenium concentrations.

Plasma selenium concentrations from 70 to 100 µg/L (0.9 to 1.3 µmol/L) have been proposed by different authors to reflect "selenium adequacy" (Combs, 2001). By plotting the percentage increments in GPx activity versus plasma selenium concentration in various supplementation studies, Alfthan et al. (1991) estimated that maximal platelet GPx activity is achieved with a plasma selenium concentration of about 100–115 µg/L (1.25–1.45 µmol/L). Thomson et al. (1993) observed saturation of GPx activity in whole blood, platelet and plasma with whole blood concentration of 100 µg/L (i.e. plasma selenium concentration of 95 µg/L). In a review of the effect of selenium supplementation on GPx activity in healthy subjects (Neve, 1995), no detectable increase in plasma GPx activity was observed in response to selenium supplementation in subjects with a plasma concentration of 70 µg/L at baseline (Levander et al., 1983; van der Torre et al., 1991). Based on data from US "selenium-replete" individuals, Hill et al. (1996) estimated that maximal concentrations of SEPP1 and GPx3 would account for 80 µg selenium/L plasma, based on the selenium content of these selenoproteins. Data from supplementation studies indicate that maximal SEPP1 concentrations are associated with plasma selenium concentrations of 90–140 µg/L (Hurst et al., 2013).

Studies in European adult populations, reviewed by Carmona-Fonseca (2010), report average plasma selenium concentrations ranging from 48–124 µg/L, with most mean values 75–110 µg/L. In European populations aged below 19 years, average plasma selenium concentrations ranged from 47–145 µg/L, with most mean values 60–90 µg/L. Significant differences were observed by sex and age and by country, region, and measurement technique.

The Panel notes that the use of plasma selenium as a biomarker of selenium intake requires careful interpretation as plasma response to dietary selenium depends on the chemical nature of selenium in the diet. The Panel also notes that plasma selenium represents a pool of selenium that is non-saturable and includes selenium in selenoproteins (the functional body pool of selenium), and other plasma proteins in which selenomethionine nonspecifically substitutes for methionine. The Panel notes that plasma selenium is not a direct marker of the functional selenium body pool. The Panel further notes, however, that there is evidence from human intervention studies that a plasma selenium concentration below 70 µg/L is associated with levels of GPx activity and SEPP1 concentration that have not reached a plateau, which indicates inadequate selenium status.

2.4.2. Glutathione peroxidase activity

Glutathione peroxidases (GPxs) are part of the human antioxidant network and contribute to protecting the organism from oxidative damage. Measures of GPx activity in plasma (GPx3) and other

blood compartments (GPx1 activity in platelets and red blood cells; whole blood GPx activity) have been commonly used as biomarkers of selenium status or function.

Plasma GPx3 appears to reach maximum activity at intakes of 40–60 µg/day (Yang et al., 1987; Duffield et al., 1999; Xia et al., 2005; Xia et al., 2010). In individuals with selenium intakes above 100 µg/day or plasma selenium concentrations > 100 µg/L, plasma GPx3 or red blood cells/platelet GPx1 activities do not reflect selenium intake (Burk et al., 2006; Hurst et al., 2010; Combs et al., 2012).

There are several limitations to the use of the activity of GPxs as markers of selenium status. Importantly, maximal GPx activity has consistently been observed to be reached with selenium intake below that required for the achievement of maximal SEPP1 concentrations (Xia et al., 2005; Hurst et al., 2010; Xia et al., 2010). Thus, GPx activity may only be a useful indicator of selenium status in subjects with habitually low selenium intakes. The source of plasma GPx3 is almost entirely kidney tubule cells (Avissar et al., 1994) and kidney cells have a specific receptor-mediated supply of selenium (Olson et al., 2008) (section 2.3.5). Therefore, plasma GPx3 activity probably reflects selenium status in the kidney rather than in the whole body. In addition, the relationship between selenium intakes and GPx activity (plasma GPx3 and red blood cell GPx1, in particular) is difficult to interpret since these biomarkers are affected by dietary and other factors, such as the chemical nature of selenium ingested, baseline selenium status, or the presence of certain diseases or polymorphisms (reviewed by Hurst et al. (2013)). In addition, differences in the units used to express GPx activity limit comparisons between studies.

The Panel notes that GPxs activity in plasma, platelet and whole blood can be used as biomarkers of selenium function. However, maximal GPx activity has consistently been observed to be reached with selenium intake below that required for the achievement of maximal SEPP1 concentrations and is thus considered less informative than SEPP1 to define selenium requirement.

2.4.3. Plasma selenoprotein P concentration

SEPP1 is central for selenium transport and homeostasis (section 2.2.1). The liver, which synthesises most of plasma SEPP1, regulates whole body selenium transport and homeostasis and plasma SEPP1 appears to reflect the selenium status of the whole organism (Burk et al., 2006) (Figure 1).

Plasma SEPP1 has been reported to respond to selenium supplementation over a large range of intakes (20–200 µg/day), irrespective of the chemical nature of dietary selenium (Persson-Moschos et al., 1998; Duffield et al., 1999; Xia et al., 2005; Hurst et al., 2010; Xia et al., 2010; Hurst et al., 2013) (section 5.2). Depending on the initial size of the selenium body pool and the doses administered, SEPP1 reached steady state concentrations after a supplementation period of 4–10 weeks (Persson-Moschos et al., 1998; Duffield et al., 1999; Hurst et al., 2010), but longer supplementation times were required in populations from a low-selenium area in China (Xia et al., 2005; Xia et al., 2010). Plasma SEPP1 appears to represent a saturable pool of selenium. No increment in plasma SEPP1 concentration was observed in subjects with average habitual intakes of around 100 µg/day (Persson-Moschos et al., 1998) or a baseline plasma selenium concentration of 122 µg/L (Burk et al., 2006) when supplemented with doses of 200–600 µg/day in various compounds, which indicates that the baseline SEPP1 concentration was already at its maximum. In supplementation studies, maximal SEPP1 concentration was associated with plasma selenium concentrations of 90–140 µg/L (reviewed by Hurst et al. (2013)). The Panel notes that several factors may influence the plasma selenium concentration associated with a plateau of SEPP1, such as baseline dietary intake of selenomethionine which is nonspecifically incorporated into plasma proteins.

SEPP1 may be influenced by inflammation (Hollenbach et al., 2008); proinflammatory cytokines have been observed to inhibit the expression of SEPP1 *in vitro* (Dreher et al., 1997).

Data on usual SEPP1 concentrations in population groups are scarce. Plasma concentrations of SEPP1 of about 5.5 mg/L were observed in a group of US American subjects (Burk et al., 2006) compared to 2.0 mg/L in Chinese subjects from a low-selenium area (Xia et al., 2010), measured by the same enzyme-linked immunosorbent assay. Different isoforms of SEPP1 have been identified (Ballihaut et al., 2012) and results of SEPP1 measurements from studies using assays based on different antibodies cannot be directly compared, because of the different analytical performance of these assays.

The Panel notes that SEPP1 is a transport protein which ensures selenium supply to tissues and plays a central role in selenium metabolism. Plasma SEPP1 concentration responds to a wide range of selenium intakes and various forms of selenium. The Panel considers that SEPP1 is the most informative biomarker of selenium function on the basis of its role in selenium transport and metabolism and its response to different forms of ingested selenium. The Panel considers that when the plasma SEPP1 concentration levels off, this indicates that there is an adequate supply of selenium to all tissues and reflects saturation of the functional selenium body pool, ensuring that all physiological functions involving selenium are covered. The Panel considers that the levelling off of plasma SEPP1 concentration is associated with the fulfilment of selenium requirement and this can be used as a criterion for establishing DRVs for selenium.

2.4.4. Urinary selenium excretion

Urinary excretion plays a central role in selenium homeostasis (section 2.3.6). Supplementation studies with different selenium compounds have shown that urinary selenium reflects selenium intake in a dose-dependent manner and is influenced by the chemical nature of dietary selenium (Burk et al., 2006; Combs et al., 2011). Significant changes in urinary selenium excretion in response to controlled diets naturally rich (297 µg/day) or poor (14 µg/day) in selenium have also been observed (Hawkes et al., 2003). In this study, urinary excretion increased rapidly in the high selenium group (within three days), but decreased more slowly with selenium restriction (no evident change until 18 days). This is consistent with observations from another balance study showing that urinary excretion of selenium required almost two weeks to stabilise under depletion conditions (Levander et al., 1981).

In observational settings, high non-linear correlations between recent dietary selenium intake (as assessed by duplicate diet method) and 24-hour urinary selenium excretion have been reported (Yang et al., 1989b; Longnecker et al., 1996). In the study by Longnecker et al. (1996), the assessment of selenium intake and 24-hour urinary excretion referred to the same day, reflecting the association between urinary selenium and short-term intake. In addition, the ratio of within- to between-person variation in urinary selenium was 0.30, which was higher than for the other biological samples studied (serum, 0.14; whole blood 0.05; toenails, 0.10). By reviewing data on urinary selenium from various populations, Sanz Alaejos and Diaz Romero (1993) reported a strong correlation between dietary selenium and daily urinary selenium excretion over a wide range of dietary selenium intakes ($r = 0.962$, $p < 0.001$; log-log relationship). Linear equations between 24-hour urinary selenium and selenium intakes have been published by these authors (log-log relationships) (Yang et al., 1989b; Sanz Alaejos and Diaz Romero, 1993; Longnecker et al., 1996). However, in addition to the amount of selenium ingested, various factors influence 24-hour urinary selenium excretion, including the chemical nature of dietary selenium (Burk et al., 2006), the composition of the diet, baseline selenium status and kidney function (Oster and Prellwitz, 1990). Thus, the applicability of these equations in different populations is subject to the influence of these factors.

When dietary selenium intakes are relatively stable, urinary excretion may reflect body status, as shown by the close relationship between urine and plasma selenium observed under controlled conditions (Robinson et al., 1978; Robinson et al., 1985; Yang et al., 1989b).

Some authors have used 24-hour urinary excretion as an indicator of changes in selenium intake in populations (Varo et al., 1988) or to predict selenium intakes by considering that about 50 % of

dietary selenium is excreted in urine (section 2.3.6.1) (Alfthan et al., 1991). In a systematic review on selenium biomarkers, Ashton et al. (2009) retrieved four supplementation studies assessing urinary selenium (as µmoles per day or as µmoles per gram creatinine). Selenium supplementation significantly increased selenium urinary excretion. However, data were limited and the heterogeneity between studies prevented a meta-analysis from being undertaken. The two types of units used impaired the combination of the studies in the analysis.

The Panel notes that strong non-linear relationships between recent dietary intake (analysed through duplicate portions) and urinary excretion have been reported. Since the rate of selenium excretion in urine is greatest within 24 hours after ingestion and given the large intra-individual variability, the Panel notes that urinary selenium may be considered as a useful marker of recent selenium intake. It may also be considered a useful surrogate measure for changes in selenium intake in population groups. However, urinary selenium is variable and influenced by a number of factors (e.g. recent selenium intake, dietary form, renal function) which limit its interpretation as a marker of status. There are no established cut-off values for characterising selenium status of individuals or populations on the basis of urinary selenium excretion. The Panel notes that the excretory forms of selenium in urine and their relationship to selenium intakes also require further elucidation (section 2.3.6.1).

2.4.5. (Toe)Nail and hair selenium concentrations

Selenium concentration in (toe)nails and hair have been related to chronic/long-term selenium intake and to selenium status.

In observational studies, hair and (toe)nail selenium concentrations were shown to be related to selenium intakes over a relatively wide range of intakes (Yang et al., 1987; Yang et al., 1989b; Longnecker et al., 1996) and the correlations between the selenium concentration of hair and nail samples and whole blood selenium were high (Yang et al., 1989b). A number of investigations have shown a good relationship between selenium supplementation and selenium concentration in human nails, with higher selenium concentrations in toenails of supplement users compared with non-users, and increased toenail selenium with increasing supplement dose (Hunter et al., 1990; Longnecker et al., 1993; Ovaskainen et al., 1993; Baskett et al., 2001; Behne et al., 2010). The selenium concentration in nails has been widely used in epidemiological studies investigating the association between selenium status and chronic disease risk (Rajpathak et al., 2005; Geybels et al., 2013).

A number of factors, also applying to other selenium biomarkers, influence the association between selenium intake and toenail/hair concentration, namely, weaknesses in intake assessment methods (e.g. errors in assessing food intake, inaccurate food composition data), the chemical nature of selenium in food, non-dietary contamination (e.g. through shampoos), as well as variations in sample collection and treatment affecting the selenium concentration in samples (Slotnick and Nriagu, 2006; Hurst et al., 2013; SACN, 2013).

The Panel notes that toenail and hair selenium concentrations may be used as biomarkers of long-term selenium intake provided that sample collection and treatment followed standardised procedures. The extent to which these biomarkers reflect, however, functional needs for selenium remains to be elucidated.

2.4.6. Other biomarkers

The ratio of plasma triiodothyroxine to thyroxine (T3:T4), plasma thyroxine, and plasma total homocysteine concentration have also been used as biomarkers of selenium status (Ashton et al., 2009). However, data are too limited to allow any conclusions to be made on the potential use of these markers (Ashton et al., 2009).

The Panel notes the limited information available on these biomarkers and that they are likely to lack specificity as markers of selenium status.

2.5. Effects of genotypes

A total of 25 selenoprotein genes have been identified in the human genome (Rayman, 2012). Health effects which have been associated with polymorphisms in selenoprotein genes in observational studies, in healthy populations and patient groups, have been documented in recent reviews (Fairweather-Tait et al., 2011; Hesketh and Meplan, 2011; Rayman, 2012; Hurst et al., 2013).

Two single nucleotide polymorphisms (SNPs) of the SEPP1 gene have been identified. For both SNPs, one homozygote and the heterozygote genotypes were observed to be common in Caucasian, Chinese, and South Asian ethnic groups in a UK population (Meplan et al., 2007). A supplementation study suggested that these SNPs may influence selenium markers and response to supplementation (Meplan et al., 2007). However, the possible impact of these polymorphisms on selenium requirement and health consequences requires further elucidation.

The effect of genetic factors on interindividual variations in selenium metabolism and functions is a subject of current research. The Panel notes that present knowledge as to how such polymorphisms in selenoprotein genes influence selenium status and requirement is limited and cannot be used for setting DRVs.

3. Dietary sources and intake data

3.1. Dietary sources

Currently, there are no methods available that can reliably extract the totality of selenium from foods without potentially affecting the chemical structure of selenium compounds (Fairweather-Tait et al., 2010).

The selenium content of grains and vegetables generally depends on the selenium content of the soil (Mehdi et al., 2013). The uptake of selenium by plants also depends on soil pH, redox potential and water content. Plants may be classified as "selenium-accumulators" or "non-accumulators", depending on their ability to assimilate and accumulate selenium (Terry et al., 2000; Broadley et al., 2006). The Brazil nut tree, as well as Brassica species (rapeseed, broccoli, cabbage) and Allium species (garlic, onion, leek and wild leek), are "selenium-accumulators", while cereal crops such as wheat, oat, rye and barley are "non-accumulators" (Rayman, 2008).

Wheat, other grains and soya contain predominantly selenomethionine with smaller amounts of selenocysteine and selenate. The major seleno-amino acids found in allium and brassica species are Se-methyl-selenocysteine and γ-glutamyl-Se-methyl-selenocysteine (considered as "detoxification agents", notably formed in "selenium-accumulators") with smaller amounts of selenomethionine, particularly when grown in selenium-enriched conditions (Rayman et al., 2008; Fairweather-Tait et al., 2010). Brazil nuts are potentially the richest source of selenium, but the content is very variable (Rayman et al., 2008). The major selenium species in Brazil nuts appears to be selenomethionine (Rayman et al., 2008; Fairweather-Tait et al., 2010; Mehdi et al., 2013).

Data on the forms of selenium in animal foods are limited and the selenium content of foods from animal sources varies according to the diet of the animals (Mehdi et al., 2013). When inorganic selenium is given to animals, selenocysteine is the main seleno-compound formed. When animals consume selenium-containing foods of plant origin, protein containing selenomethionine will also be formed from the incorporation of plant-derived selenomethionine in place of methionine (Rayman et al., 2008). Selenotrisulfide, glutathione selenopersulfide and selenides have also been reported to

occur in tissues (Rayman, 2008). Lamb and chicken meat have been reported to contain selenocysteine and selenomethionine (Fairweather-Tait et al., 2010). Selenate and selenite have been detected in fish and recently, selenoneine (2-selenyl-Nα,Nα,Nα-trimethyl-L-histidine) has been identified as the major selenium compound in swordfish, tuna, mackerel and sardine (Yamashita and Yamashita, 2010; Yamashita et al., 2011). It is also present in lower concentrations in other fish species, pigs and chicken (Yamashita and Yamashita, 2010; Yamashita et al., 2011).

Although water may contain selenium, predominantly as selenate, its content is typically low and does not significantly contribute to selenium intakes (WHO, 2011).

Various selenium-enriched food items (often termed "selenised") may be produced by means of selenium enrichment of fertilisers (selenised garlic, onion, broccoli, wheat), feed (selenised milk, selenised eggs) or growth medium (selenised yeast) (Demirci et al., 1999; Heard et al., 2004; Fisinin et al., 2008; Fairweather-Tait et al., 2011).

Currently, sodium selenate, sodium hydrogen selenite, sodium selenite, L-selenomethionine and selenium-enriched yeast may be added to food[6] and food supplements.[7] The selenium content of infant and follow-on formulae is regulated.[8]

3.2. Dietary intake

There is a large variability in the selenium content of foods, which is, as yet, poorly characterised and may result in important inaccuracies in food composition tables, especially if the analyses have not been recently completed (Fairweather-Tait et al., 2011; SACN, 2013). Importantly, the selenium content of foods depends on the selenium content of soil and soil geochemistry (section 3.1). Besides, the different selenium compounds present in foods add further complexity with respect to intake data (Fairweather-Tait et al., 2011). Estimates of dietary intakes may be of limited reliability for determining actual selenium intakes. Low correlation coefficients (r 0.1–0.4) have generally been estimated between selenium intakes assessed through food frequency questionnaire (FFQs) or dietary records and plasma/serum, whole blood or toenail selenium concentrations (Duffield and Thomson, 1999; Karita et al., 2003; Satia et al., 2006; Vinceti et al., 2012), while Longnecker et al. (1996) and Yang et al. (1989b) found high correlations between selenium intake as estimated from duplicate food portions and single measurements from whole blood, serum/plasma and toenail samples.

EFSA's Evidence Management Unit (DATA) estimated dietary intakes of selenium from food consumption data from the EFSA Comprehensive Food Consumption Database (EFSA, 2011) combined with data on the selenium content of foods from the EFSA nutrient composition database (Roe et al., 2013). Data were available from seven countries, namely Finland, Germany, Ireland, Italy, Latvia, Netherlands and the United Kingdom (UK). Food composition information of Finland, Germany, Italy, Netherlands and the UK were used to calculate selenium intakes in these countries, assuming that the best intake estimate would be obtained when both the consumption data and the composition data are from the same country. For nutrient intake estimates of Ireland and Latvia, food composition data from the UK and Germany, respectively, were used, because no specific composition data from these countries were available. The amount of borrowed selenium values in the five composition databases used varied as follows: Germany 100 %, Italy 91 %, UK 68 %, Finland 58 % and the Netherlands 50 %, respectively. The Panel notes the large amounts of borrowed values and that there are uncertainties on how accurately the information contained in the nutrient

[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.

composition database reflects the variability in selenium concentrations in foods. Therefore, the results should be considered indicative and be interpreted with caution.

The data covered all age groups from infants to adults aged 75 years and older (Appendix B). Estimates were based on food consumption only (i.e. without dietary supplements). Average selenium intakes ranged from 17.2–36.3 µg/day in toddlers (1 to < 3 years) (four surveys), between 20.6–45.9 µg/day in other children (3 to < 10 years) (six surveys), between 33.9–60.3 µg/day in adolescents (10 to < 18 years) (five surveys) and between 31.0–65.6 µg/day in adults (≥ 18 years) (five surveys). Average daily intakes were slightly higher in males (Appendix C) compared to females (Appendix D) mainly due to larger quantities of food consumed per day.

Main food groups contributing to selenium intakes were milk and dairy products, meat and meat products, grains and grain-based products and fish and fish products (Appendix E and F). Differences in main contributors to selenium intakes between sexes were minor.

When available, EFSA selenium intake estimates were compared with values from the same national surveys published in the literature. EFSA average selenium intake estimates were similar to the published results from the UK National Diet and Nutrition survey (NDNS) survey (Bates et al., 2011) and the Dutch national food consumption survey (van Rossum et al., 2011) (± 5 % difference), while EFSA values were up to 25 % higher than the published results from the Swedish Riksmaten survey (Amcoff et al., 2012) and up to 20 % lower than the published values from the INCA 2 survey in France (AFSSA, 2009) and the FINDIET 2012 Survey (Helldán et al., 2013) and NWSSP Study in adolescents (Hoppu et al., 2010) in Finland. Several sources of uncertainties may contribute to these differences, including discrepancies in mapping food consumption data according to food classifications and in nutrient content estimates available from the food composition tables. The differences in the case of Finland, France and Sweden could be due to national estimates that are partially based on a different composition database compared to the one used in the EFSA nutrient assessments as well as different intake modelling methods. In particular, the lower estimates for Finland may be due to lower borrowed values than the selenium contents of Finnish foods which were used in the intake assessments at the national level due to the national selenium enrichment program implemented in Finland, which has significantly increased the selenium content of Finnish cow's milk, meat and cereal products (Allen et al., 2006). As the intake calculations rely heavily on estimates of both food composition and food consumption, it is not possible to conclude, which of these intake estimates would be closer to the actual selenium intakes.

4. Overview of Dietary Reference Values and recommendations

4.1. Adults

In the 2012 update of the Nordic Nutrition Recommendations (NNR), the Nordic countries stated that plasma SEPP1 is a better marker of selenium status than the previously considered activity of glutathione peroxidases (GPx) in plasma or serum (Nordic Council of Ministers, 2014). Based on "optimisation of the concentration of plasma SEPP1" with 50 µg/day in a study in China (Xia et al., 2010) and correcting for body size, a recommended intake of 50 µg/day for women and 60 µg/day for men was derived. The NNR also proposes a "lower intake level" for adults of 20 µg/day based on symptoms of selenium deficiency as observed in Keshan disease associated with intakes below 20 µg/day.

The German speaking countries (D-A-CH, 2013) set an Adequate Intake (AI) range of 30–70 µg/day based on observed dietary intakes considering the absence of signs of selenium deficiency. Plasma selenium concentrations were found to be normal (> 50 µg/L) at these levels of intakes.

IOM (2000) set an AR of 45 µg/day for the age group 19–50 years based on the criterion of maximising plasma GPx activity (Yang et al., 1987; Duffield et al., 1999) and taking into account body weights of North American men. Given the reported greater susceptibility of women to develop Keshan disease (Ge et al., 1983) and the fact that the data used to set the Estimated Average Requirement (EAR) came largely from men, selenium requirements for both males and females were based on the higher reference weights for males. The recommended dietary allowance (RDA, equivalent to a PRI) was set at the EAR plus twice the coefficient of variation (CV) assumed to be 10 %, because information on the standard deviation (SD) of the requirement for selenium was not available, and by rounding to the nearest 5 µg.

WHO/FAO (2004) used evidence from a dose-response study showing that total selenium intakes of above 41 µg/day were sufficient to saturate plasma GPx activity in male subjects with a body weight of 60 kg within 5–8 months (Yang et al., 1987). It was estimated that satisfactory concentrations of plasma selenium (> 80 µmol/L) and approximately two thirds of plasma saturation activity of GPx would be attained after intakes of 27 µg/day by males weighing 65 kg. This intake level, which was denoted the average normative requirement for selenium, was used as the basis to calculate recommended nutrient intakes after interpolating estimates of ARs by allowing for differences in body weights and basal metabolic rate of age groups up to 65 years and adding twice the assumed SD of 12.5 % to allow for individual variability in the estimates of the recommended nutrient intake. The recommended nutrient intake was set at 26 µg/day for women and 34 µg/day for men aged 18-65 years.

Afssa (2001) advised an intake between 50 and 80 µg/day for adults, considering that a dose of 1 µg/kg body weight per day was an adequate dose.

The SCF (1993) stated that studies which investigated the saturation of GPx activity suggest that an AR would be about 40 µg/day (Yang et al., 1987), which would give a PRI of 55 µg/day. An LTI was proposed at 20 µg/day based on studies showing absence of Keshan disease in China at intakes of 19 µg/day or higher, and taking into account the higher body weight of European individuals.

The UK DH (1991) established a Reference Nutrient Intake (RNI) at an intake of 1 µg/kg body weight per day as the level associated with functional saturation of GPx activity.

An overview of DRVs for selenium for adults is given in Table 1.

Table 2: Overview of Dietary Reference Values for selenium for adults

	NNR 2012	D-A-CH (2013) [a]	WHO/FAO (2004)	Afssa (2001) [a]	IOM (2000)	SCF (1993)	DH (1991)
Age (years)	≥ 18	≥ 19	19–65	20–65	≥ 19	≥ 18	≥ 19
PRI [b]							
Men (µg/day)	60	30–70	34	60	55	55	75
Women (µg/day)	50	30–70	26	50	55	55	60
Age (years)			≥ 65	66–74			
PRI							
Men (µg/day)			33	70			
Women (µg/day)			25	60			
Age (years)				≥ 75			
AI [a] (µg/day)				80			

(a): Adequate Intake (AI)
(b): Population Reference Intake (PRI)

4.2. Children

In the 2012 update of the NNR, the recommended intakes for children were based on extrapolation from the adult values (Nordic Council of Ministers, 2014).

The German-speaking countries (D-A-CH, 2013) estimated AI ranges for children by interpolating from the AI ranges in infants and adults, taking into account nutrient density.

The WHO/FAO (2004) based their recommended nutrient intakes for children on the average normative requirement for male subjects and interpolated estimates of ARs by allowing for differences in body weights and basal metabolic rate and adding a 25 % increase (twice the assumed SD of 12.5 %) to allow for individual variability in the estimates of recommended nutrient intakes.

For infants aged 0 to 6 months, IOM (2000) derived an AI by assuming an average intake of human milk of 0.78 L/day and an average concentration of selenium in human milk of unsupplemented women of 18 µg/L (Shearer and Hadjimarkos, 1975; Smith et al., 1982; Levander et al., 1987; Mannan and Picciano, 1987). The AI was calculated as 14 µg/day and rounded up to 15 µg/day. For infants aged 7 to 12 months, the AI was extrapolated from the AI for infants aged 0 to 6 months and rounded, giving an AI of 20 µg/day. This was comparable to estimating the selenium intake from human milk and complementary foods in the second half of the first year of life. For children and adolescents aged 1 to 18 years the IOM found no data on which to base an EAR. Thus, EARs for children were estimated by extrapolating downwards from adult values using an adjustment for metabolic body size and growth. As most selenium is metabolised by a mechanism similar to that of methionine (Esaki et al., 1982), the formula used for determining selenium requirements for children were metabolic formulas rather than those based upon body weights alone. Given the reported slightly increased susceptibility of females to developing Keshan disease (Ge et al., 1983), selenium requirements for the various age groups were based on the higher reference body weights for males. Studies in China indicated that Keshan disease does not occur in populations with a selenium intake of adults of 17 µg/day or greater (Yang et al., 1987). Thus, the IOM considered that the EARs (17–45 µg/day depending on age and sex group) should be sufficient to prevent Keshan disease in all children. The RDAs were calculated by assuming a CV of 10 % and rounded to the nearest 5 µg.

Afssa (2001) recommended a selenium intake between 50 and 80 µg/day for adolescents, accepting that a dose of 1 µg/kg body weight per day was an adequate dose. For infants and children intakes between 15 and 45 µg/day were advised.

For children, the SCF (1993) and the DH (1991) stated that blood selenium concentrations at one year of age are about 80 % of those of adults, increasing to adult values by three years, and then remaining fairly constant (Ward et al., 1984). PRIs were calculated from adult values on the basis of body weight. The requirement for growth was estimated to be small (0.2 µg/kg gain in body weight) and to be covered by the proposed PRIs.

An overview of DRVs for selenium for children is given in Table 3.

954 **Table 3:** Overview of Dietary Reference Values for selenium for children

	NNR 2012	D-A-CH (2013) [a]	WHO/FAO (2004)	Afssa (2001) [a]	IOM (2000)	SCF (1993)	DH (1991)
Age (months)	6–11	4–<12	7–12	7–12	7–12	6–11	7–12
PRI [b] (µg/day)	15	7–30	10	20	20 [a]	8	10
Age (years)	1–<2	1–<4	1–3	1–3	1–3	1–3	1–3
PRI (µg/day)	20	10–40	17	20	20	10	15
Age (years)	2–5	4–<7	4–6	4–6	4–8	4–6	4–6
PRI (µg/day)	25	15–45	22	30	30	15	20
Age (years)	6–9	7–<10	7–9	7–9		7–10	7–10
PRI (µg/day)	30	20–50	21	30		25	30
Age (years)	10–13	10–<13	10–18	10–12	9–13	11–14	11–14
PRI							
Boys (µg/day)	40	25–60	32	45	40	35	45
Girls (µg/day)	40	25–60	26	45	40	35	45
Age (years)	14–17	13–<15		13–19	14–18	14–18	15–18
PRI							
Boys (µg/day)	60	25–60		50	55	45	70
Girls (µg/day)	50	25–60		50	55	45	60
Age (years)		15–<19					
PRI (µg/day)		30–70					

955 (a): Adequate Intake (AI)
956 (b): Population Reference Intake (PRI)

957 ### 4.3. Pregnancy

958 In the 2012 update of the NNR, the recommended intake for pregnant women was increased by
959 10 µg/day to 60 µg/day in line with the approach by IOM and the increased recommended intake for
960 adults (Nordic Council of Ministers, 2014).

961 The recommended nutrient intakes by WHO/FAO (2004) were based on the assumption that the total
962 products of conception amount to 4.6–6 kg of lean tissue with a protein content of approximately
963 18.5–20 %. Assuming that the selenium content of this protein resembles that of skeletal muscle, it
964 was estimated that growth of these tissues could account for between 1.0 and 4.5 µg/day of selenium
965 depending on whether the analyses reflect consumption of diets from a low-selenium (but non-
966 pathogenic) environment such as that found in New Zealand (Millar and Sheppard, 1972; Williams,
967 1983), or from a region with relatively high selenium intakes, such as the United States (Levander et
968 al., 1987; Xia et al., 2010). Assuming that the efficiency of absorption and utilisation of dietary
969 selenium is 80 % and assuming a CV of 12.5 %, an increased selenium intake of 2 µg/day for the
970 second trimester and of 4 µg/day for the third trimester was recommended.

971 IOM (2000) considered that the requirement should allow accumulation of enough selenium by the
972 fetus to saturate its selenoproteins. Based on an estimated selenium content of 250 µg/kg body weight
973 (Schroeder et al., 1970), IOM assumed that a fetus weighing 4 kg would contain 1 000 µg of
974 selenium. It was estimated that this need could be met by an additional selenium intake of 4 µg/day
975 over the 270 days of pregnancy, resulting in an EAR of 49 µg/day. No adjustment was made for
976 absorption or the age of the mother. The RDA was set by assuming a CV of 10 %, and the calculated
977 RDA was rounded to the nearest 5 µg.

978 The German-speaking countries (D-A-CH, 2013), Afssa (2001), the SCF (1993) and DH (1991) did
979 not propose any additional selenium intake for pregnant women, and advised the same intake as for
980 non-pregnant and non-lactating women. The SCF (1993) stated that adaptive changes in the
981 metabolism of selenium occur during pregnancy (Swanson et al., 1983).

982 An overview of DRVs for selenium for pregnant women is given in Table 4.

983 **Table 4:** Overview of Dietary Reference Values for selenium for pregnant women

	NNR 2012	D-A-CH (2013)	WHO/FAO (2004)	Afssa (2001)	IOM (2000)	SCF (1993)	DH (1991)
Age (years)					14–50		
PRI [(a)] (µg/day)	60	30–70 [(b)]	28/30 [(c)]	60 [(b, d)]	60	55	60

984 (a): Population Reference Intake (PRI)
985 (b): Adequate Intake (AI)
986 (c): 2nd trimester/3rd trimester
987 (d): 3rd trimester

988 ### 4.4. Lactation

989 The Nordic countries (Nordic Council of Ministers, 2014) stated that the selenium concentration of
990 human milk is reduced over time when selenium intake is less than 45–60 µg/day, but remains
991 unchanged at intakes of 80–100 µg/day. For the 2012 update of the NNR, the recommended intake
992 was increased to 60 µg/day in line with the increase for pregnant women.

993 WHO/FAO (2004) based their recommended nutrient intake for lactation on the recommended
994 nutrient intakes for infants aged 0–6 months and 7–12 months, respectively. To meet an infant's
995 recommended nutrient intake of 6 µg/day during the first half year of life, it was assumed that the
996 mother needs to provide 9 µg/day via her milk. This value assumed that the selenium in maternal milk
997 is absorbed and used with an efficiency of 80 % and that the SD is 12.5 %. Likewise, the
998 corresponding increase to meet the recommended nutrient intake of 10 µg/day for infants aged 7 to 12
999 months was estimated to be 16 µg/day. Added to the recommended nutrient intake of 26 µg/day for
1000 non-pregnant women, the total recommended nutrient intake for lactating women was set at 35 µg/day
1001 for the first six months *post partum* and 42 µg/day for months 7 to 12 after giving birth.

1002 IOM (2000) estimated that the average daily amount of selenium secreted in human milk is 14 µg in
1003 women fully breastfeeding during the first six months *post partum* (see also section 4.2). An
1004 adjustment for bioavailability or age of the mother was not considered necessary, and this estimated
1005 secreted amount was added to the EAR for non-pregnant and non-lactating woman, giving an EAR of
1006 59 µg/day. The RDA was calculated by assuming a CV of 10 %, and the calculated RDA was rounded
1007 to the nearest 5 µg.

1008 The German-speaking countries (D-A-CH, 2013) and Afssa (2001) did not recommend any additional
1009 selenium intake for lactating women and advised the same intake as for non-pregnant and non-
1010 lactating women.

1011 The SCF (1993) and the DH (1991) used the factorial approach to estimate the additional selenium
1012 requirement during lactation. Based on a selenium concentration in human milk of 12 µg/L and 60 %
1013 absorption of selenium from the diet an incremental intake of 15 µg/day was derived.

1014 An overview of DRVs for selenium for lactating women is given in Table 4.

1015 **Table 5:** Overview of Dietary Reference Values for selenium for lactating women

	NNR 2012	D-A-CH (2013)	WHO/FAO (2004)	Afssa (2001)	IOM (2000)	SCF (1993)	DH (1991)
Age (years)					14–50		
PRI [(a)] (µg/day)	60	30–70 [(b)]	35⁄42 [(c)]	60 [(b)]	70	70	75

1016 (a): Population Reference Intake (PRI)
1017 (b): Adequate Intake (AI)
1018 (c): 0–6 months *post partum*/7–12 months *post partum*

1019 ## 5. Criteria (endpoints) on which to base Dietary Reference Values

1020 Authoritative bodies have traditionally used plasma GPx activity as an indicator of dietary
1021 requirement to derive DRVs for selenium for adults (DH, 1991; SCF, 1993; IOM, 2000; WHO/FAO,
1022 2004). More recently, "optimisation of the plasma SEPP1 concentration" has been considered as the
1023 criterion to derive DRVs for selenium (Nordic Council of Ministers, 2014) (section 4).

1024 ### 5.1. Indicators of selenium requirement in adults

1025 The Panel considers that SEPP1 is the most informative biomarker of selenium function on the basis
1026 of its role in selenium transport and metabolism and its response to different forms of selenium intake.
1027 The Panel considers that the levelling off of plasma SEPP1 concentration is indicative of an adequate
1028 supply of selenium to all tissues and reflects saturation of the selenium functional body pool, ensuring
1029 that all physiological functions involving selenium are covered. The Panel considers that the levelling
1030 off of plasma SEPP1 concentration is associated with the fulfilment of selenium requirement and this
1031 can be used as a criterion for establishing DRVs for selenium (section 2.4).

1032 Several studies have investigated the dose-response relationship between selenium intake and plasma
1033 SEPP1 concentrations.

1034 Duffield et al. (1999) investigated the effect of various amounts of supplemental selenium on plasma
1035 SEPP1 in 52 adults (17 men and 35 women) aged 19–59 years (mean weight adjusted for sex,
1036 73.7 kg) in New Zealand. Individuals with baseline whole blood selenium concentrations
1037 < 1.26 µmol/L (< 70 µg/L) were recruited. Placebo or 10, 20, 30, or 40 µg selenium as L-
1038 selenomethionine were administered daily for 20 weeks (n = 10 or 11 per arm). Based on the analysis
1039 of duplicate diets and 3-day diet records, mean (± SD) background daily selenium intakes were
1040 28 ± 15 and 29 ± 13 µg, respectively. Plasma SEPP1 concentration was assessed by a
1041 radioimmunoassay using ^{75}Se-labelled human SEPP1, every two weeks for two months, then every
1042 four weeks for a further 12 weeks. Differences between the control group and the group receiving
1043 40 µg selenium/day were significant at each time period, with an apparent plateau of plasma SEPP1
1044 concentration reached after four weeks. The SEPP1 concentration of the group receiving 30 µg was
1045 significantly different from that of the control group at week 4 and again at week 12, while the group
1046 receiving 20 µg was different from the control group only at week 4. The Panel notes the considerable
1047 variability in SEPP1 concentrations across time points for some groups; despite this variability, the
1048 Panel notes that there was an apparent plateau of SEPP1 concentration in this population with
1049 supplemental selenium intakes of 30–40 µg/day corresponding to a total selenium intake of around
1050 60–70 µg/day for 12 weeks.

1051 Xia et al. (2005; 2010) conducted two double-blind, randomised, placebo-controlled supplementation
1052 trials in a region of China (Mianning County, Sichuan Province) where Keshan disease is endemic.
1053 The baseline average plasma selenium concentrations were 22 ± 7 µg/L and 37 ± 8 µg/L in the
1054 respective study populations (Xia et al., 2005; Xia et al., 2010).

The first study involved 119 adult men (n = 64; mean weight ± SD: 53.3 ± 8.5 kg) and women (n = 55; 58.4 ± 5.5 kg), aged ≥ 18 years (Xia et al., 2005). Average selenium intake was 9 µg/day in women and 11 µg/day in men, estimated from whole blood and hair selenium concentrations (Yang 1995). This was in agreement with a nutrition survey previously carried out in the area which had determined an average selenium intake of 10 µg/day in adults, based on FFQ and a table of the selenium contents of local foods. Participants were randomly assigned to placebo, or to one tablet per day containing on average either 13, 24, 37, 48 or 61 µg of selenium as L-selenomethionine or 15, 31, 52, 47 or 66 µg of selenium as sodium selenite, for a period of 20 weeks (n = 10–20 per group). Plasma was sampled at baseline and at four-week-intervals for the assessment of plasma concentrations of SEPP1 by using an enzyme-linked immunosorbent assay. A sigmoidal dose-response was observed between selenium intake and plasma SEPP1 concentration. The smaller doses of selenium were associated with a steep rise in SEPP1 concentration, while with daily doses of 37 µg selenium as selenomethionine and above the concentration of SEPP1 rose more gradually. The response curve suggested that full expression of SEPP1 was not achieved at the highest doses of either form (61 µg/day of selenium as L-selenomethionine or 66 µg/day of selenium as sodium selenite) within the timeframe of the study. Supplementation with selenomethionine increased SEPP1 concentration more than selenite. The Panel notes that selenium intakes of 70–80 µg/day for 20 weeks were not sufficient for SEPP1 to reach a plateau in this population.

The second study involved a longer period of selenium supplementation of 40 weeks (Xia et al., 2010). The study population consisted of 95 healthy Chinese men (n = 43) and women (n = 52) aged 37 ± 7 years, with an average (± SD) body weight of 58 ± 8 kg. Mean estimates (± SD) of selenium intakes of 13.3 ± 3.1 µg/day for men and 12.6 ± 2.8 µg/day for women were predicted using participants' whole-blood selenium concentrations (Yang, 1995). Mean dietary selenium intake of 16.5 ± 3.0 µg/day for men (n = 17) and 13.4 ± 2.8 µg/day for women (n = 23) were estimated in a sub-sample of subjects using FFQ and local food tables. The average value of the two estimated intakes was used as the mean dietary selenium intake of the study subjects. Participants were randomly assigned to receive daily doses of 0, 21, 35, 55, 79, 102, or 125 µg of selenium as L-selenomethionine (n = 12–14 per group). SEPP1 in plasma was measured by using an enzyme-linked immunosorbent assay. At week 40, SEPP1 concentration had reached a plateau in groups receiving selenium doses of 35 µg or higher and did not significantly differ between these groups (mean ± SD: 4.9 ± 1.1, 5.1 ± 0.7, 5.1 ± 0.7, 5.4 ± 1.1 and 5.6 ± 1.1 mg/L in the groups receiving 35, 55, 79, 102 and 125 µg selenium/day, respectively). In addition, they were in the range of SEPP1 concentrations measured in US subjects using the same assay (5.3 ± 0.9 mg/L). Considering a mean dietary selenium intake of 14 µg/day in addition to the 35 µg/day provided by the supplement, the Panel notes that a total intake of 49 µg/day (i.e. 0.85 µg/kg body weight per day) for 40 weeks was associated with the levelling off of SEPP1 in this population.

Hurst et al. (2010) carried out a randomised, double-blind, placebo-controlled dietary intervention in 119 healthy men and women, aged 50–64 years living in the UK (BMI range: 20.0–34.5 kg x m^{-2}). Individuals with plasma selenium concentration < 110 µg/L were recruited. An average baseline selenium intake of 55 µg/day was estimated from plasma selenium concentrations based on the equations associating plasma selenium with 24-hour urine selenium levels and, subsequently, 24-hour urine selenium with selenium intake from Yang et al. (1989b), which concurred with recent data from the UK Total Diet Study and estimates from a recent observational study using food diaries in a British cohort. Study participants were assigned to: (a) placebo, (b) selenium-enriched yeast supplements (50, 100, or 200 µg of selenium/day), (c) three meals per week containing selenium-enriched onions (providing an additional selenium intake of 50 µg/day), or (d) meals containing unenriched onions (providing an additional selenium intake of 0.4 µg/day, placebo), for a total period of 12 weeks (n = 18 to 23 per group). Changes in plasma SEPP1 concentrations were measured by using an enzyme-linked immunosorbent assay in blood samples collected at baseline and at weeks 6 and 10 of the intervention. Plasma SEPP1 concentrations increased in all four intervention groups from week 0–6, with no further significant increase for the three selenium-yeast supplement groups

after week 6, indicating that a steady state had been reached. At week 6, plasma SEPP1 concentration was significantly higher in the group receiving selenium-enriched onions compared to the group receiving unenriched onion (but lower than the groups receiving selenium-yeast) and continued to increase significantly until week 10, reaching a mean concentration of SEPP1 comparable with that of the group who had received the yeast supplement. Considering a mean dietary selenium intake of 55 µg/day in addition to the 50 µg/day provided by the supplement, the Panel notes that a total intake of 105 µg/day for 6 weeks was associated with the levelling off of SEPP1 in this population.

Two studies were conducted in populations in the US with a higher baseline selenium status, as indicated by mean baseline plasma selenium concentrations > 120 µg/L.

Burk et al. (2006) studied the effects of relatively high-dose selenium supplementation on plasma selenium biomarkers and urinary selenium excretion in 81 subjects aged ≥ 18 years. Mean plasma selenium concentration at baseline was 122 ± 13 µg/L. Considering that the mean (± SD) urinary excretion of selenium in the placebo group was 55 ± 22 µg/day and that selenium is also lost through faeces and other routes, the authors estimated that the daily intake of these subjects was above 55 µg. Subjects were randomised to ten intervention groups receiving a placebo or selenium supplements providing approximately 200, 380 or 600 µg/day in the form of sodium selenite, high-selenium yeast, and L-selenomethionine. Plasma SEPP1 concentrations were determined before supplementation and every four weeks for a period of 16 weeks by using a sandwich ELISA with two monoclonal antibodies and did not change during the study.

Combs et al. (2012) performed a one-year supplementation trial with selenium doses of 50, 100 or 200 µg/day as selenomethionine. The study sample included 261 US men and women (age 49.6 ± 16.3 years) with a baseline plasma selenium concentration of 142 ± 23.5 µg/L and an average selenium intake of 109 ± 44 µg/day, estimated through FFQ. Responses of serum SEPP1 were determined by using an enzyme-linked immunoassay. No effect of supplemental selenomethionine on mean SEPP1 concentration was found in this population.

The Panel notes that additional selenium had no effect on SEPP1 concentration in these two populations (Burk et al., 2006; Combs et al., 2012), which indicates that the individuals were "selenium-replete" at the start of the intervention.

One study compared the effect of selenium supplementation on SEPP1 concentration in two trials involving the same subjects, before (trial I, 1981) and after (trial II, 1987) the introduction in 1985 of a nationwide programme of fertiliser enrichment with selenium which led to an increase in average selenium intake in Finland from 40 to 100 µg/day (Persson-Moschos et al., 1998).

At the time of trial I, 50 healthy men (36–60 years) were recruited, with baseline plasma selenium concentration < 77 µg/L and estimated selenium intakes of 50–60 µg/day, derived from chemical analysis of composite diets (containing local foods) that were based on 24-hour dietary recalls (Levander et al., 1983). In trial II, baseline mean plasma selenium concentration was 110 µg/L and mean basal intake of selenium was estimated to be 110–130 µg/day, estimated from 24-hour urinary selenium excretion (Alfthan et al., 1991). Volunteers (body weight not reported) received daily placebo or supplements providing 200 µg of selenium as selenium-enriched yeast, sodium selenate or selenium-enriched wheat for 11 weeks (trial I) or selenium-enriched yeast, sodium selenate or sodium selenite (trial II) for 16 weeks (n = 10 to 20 per group). SEPP1 concentration was determined by a radioimmunoassay. In trial I, the mean plasma SEPP1 concentration in all supplemented groups increased significantly, approaching a plateau at two weeks and reaching a plateau at four weeks. In trial II, the mean SEPP1 concentrations of the supplemented groups were not significantly different from each other or from the placebo group at the start or at any time point of the supplementation period.

The Panel notes that a background dietary selenium intake of 50–60 µg/day was not sufficient for SEPP1 to reach a plateau in this population, as plasma SEPP1 concentration increased and levelled off after selenium supplementation in trial I. In contrast, supplementation had no effect when background intake increased to 110–130 µg/day, indicating that subjects had become "selenium-replete" by the time of the second intervention.

The Panel notes that there are uncertainties with respect to the estimates of background selenium intake in these studies, due to the difficulty in obtaining accurate intake estimates from dietary surveys (section 3.2) and uncertainties related to extrapolating intakes from surrogate markers (whole blood or hair concentrations, 24-hour urinary excretion) (section 2.4). Only in the study by Duffield et al. (1999) was the background selenium intake derived from analysed selenium content of consumed foods.

Overall, the Panel notes that intervention studies using different levels of selenium intakes showed that plasma SEPP1 concentration levels off in response to increasing doses of selenium. There is consistent evidence that the length of the supplementation period, the dose and the chemical nature of selenium compounds administered, and the baseline selenium status all affect the time it takes for SEPP1 concentration to level off. The Panel notes that habitual selenium intakes of 50–60 µg/day were not sufficient for SEPP1 concentration to reach a plateau in Finnish individuals (Persson-Moschos et al., 1998), while selenium intakes of 100 µg/day and above have consistently been associated with plasma SEPP1 concentration at a plateau in population groups from Finland, the UK and the US (Persson-Moschos et al., 1998; Hurst et al., 2010; Combs et al., 2012). In the study by Duffield et al. (1999) in healthy individuals from New Zealand, selenium intakes of around 60–70 µg/day were required for SEPP1 concentration to level off. In the study by Xia et al. (2010) in Chinese subjects, a selenium intake of 49 µg/day (0.85 µg/kg body weight per day) led to the levelling off of plasma SEPP1 concentration. Data came from studies involving subjects aged 18 to 64 years.

5.2. Indicators of selenium requirement in infants, children and adolescents

Hill et al. (1996) assessed the effect of selenium supplementation on plasma SEPP1 concentration in boys (8–12 years; 100 µg selenium/day) and men (> 17 years; 200 µg selenium/day) during a 14-day uncontrolled intervention study in two low-selenium areas in China. The Panel notes the lack of information on background selenium intakes, the short duration of the intervention and the use of relatively high supplemental selenium doses and concludes that this study cannot be used to assess selenium requirements in male children.

In rats, it has been shown that the selenium concentration of testes increases during pubertal maturation, coincident with the beginning of spermatogenesis (Behne et al., 1986; Behne et al., 1996). During that time, the amount of selenium taken up by the rat testes was observed to be 50 % of the amount deposited in muscle and liver, whereas before and after pubertal maturation it was about 10 % (Behne et al., 1986). The Panel considers that the maintenance requirement for sperm production of male adolescents is likely the same as in adult men. However, the Panel notes that there is a lack of data on how development of sexual organs during puberty affects selenium metabolism and requirement in adolescent boys, especially with regard to selenium concentrations in testes before, during and after sexual maturation. The Panel concludes that it is not possible to assess the selenium requirement for development of sexual organs in male adolescents.

No specific indicators of selenium requirements are available for infants, children and adolescents.

5.3. Indicators of selenium requirement in pregnancy and lactation

In a recent study, Rayman et al. (2014) investigated the effect of selenium supplementation on the risk of pre-eclampsia in pregnant women with "inadequate selenium status" as defined by low whole

blood selenium concentration. In a double-blind, placebo-controlled pilot trial, 230 pregnant women from the UK were randomised to selenium (60 µg/day, as selenium-enriched yeast) or placebo, from 12–14 weeks of gestation until delivery. Whole-blood selenium concentration was measured at baseline and 35 weeks, and plasma SEPP1 concentration at 35 weeks. Between 12–35 weeks of gestation, whole-blood selenium concentration increased significantly in the selenium-supplemented group (from 103 (range 75–263) to 148 (range 83–295) µg/L, $p < 0.0001$) but decreased significantly in the placebo group (from 104 (range 66–173) to 92 (range 54–170) µg/L, $p < 0.0001$). At 35 weeks, significantly higher concentrations of plasma SEPP1 were observed in the selenium-supplemented group (median 5.3 (range 2.4–7.4) mg/L) than in the placebo group (median 3.0 (range 0.9–5.8) mg/L, $p < 0.0001$). The Panel notes the background dietary selenium intakes were not assessed. In addition, in the absence of information on baseline plasma SEPP1 concentrations, it is unknown whether higher plasma SEPP1 concentration in the supplemented compared to the control group indicates that selenium supplementation allowed to maintain or rather "improve" selenium status of the subjects. The Panel considers that no conclusions can be drawn from this study as to selenium requirement during pregnancy.

Several investigators reported that maternal selenium biomarkers, such as whole blood/plasma selenium concentration and whole blood/plasma GPx activity, decrease over the course of pregnancy (Rudolph and Wong, 1978; Behne and Wolters, 1979; Swanson et al., 1983; Zachara et al., 1993; Mihailovic et al., 2000; Thomson et al., 2001). The fall in whole blood/plasma selenium concentration reflects to some extent the increase in plasma volume and may also be caused by the maternal-fetal transfer of selenium. The Panel considers that these observations are difficult to interpret in terms of selenium requirement in pregnancy.

Swanson et al. (1983) conducted a study in ten pregnant (six in early and four in late pregnancy) and six non-pregnant women in the US. Mean plasma selenium concentrations of the three groups were 110–130 µg/L. A controlled diet providing about 150 µg selenium/day was fed for 20 days, and selenium balance was measured during the last 12 days. Urinary and faecal excretion of 40 µg of a stable isotope of selenium (^{76}Se) from intrinsically labelled egg was also assessed. The habitual selenium intake of the subjects before the study was not assessed. Apparent absorption of selenium, as measured by balance and tracer methods, was around 80 % for all groups. Urinary and faecal selenium excretion was, respectively, 111 ± 2 and 25 ± 1 µg/day in the non-pregnant group compared to 100 ± 6 and 33 ± 3 µg/day in the "early pregnancy" group and 96 ± 2 and 28 ± 1 µg/day in the "late pregnancy" group. Mean apparent selenium retention was 11 ± 2, 21 ± 4 and 34 ± 2 µg/day for the non-pregnant women, and women in early and late pregnancy, respectively. Net selenium retention of the women in early and late pregnancy was 10 and 23 µg/day, respectively. Both methods indicated a trend to a lower urinary excretion of selenium in pregnant compared to non-pregnant women and a more pronounced conservation in late than in early pregnancy, but inter-individual variability was high and results not statistically significant. The Panel notes that the habitual selenium intake of the subjects was not assessed which makes the interpretation of the balance data difficult regarding the actual additional requirement due to pregnancy. Considering that approximately 5 kg of lean tissue are deposited during pregnancy and assuming that lean tissue contains 0.2 to 0.3 mg/kg of selenium, Swanson et al. (1983) estimated an average selenium retention over 280 days of pregnancy of about 3.5 to 5 µg/day.

The influence of pregnancy on selenium urinary excretion was studied in groups of pregnant and non-pregnant women in New Zealand, selected for their "low selenium status" (mean baseline plasma selenium concentrations of around 60 µg/L) (Thomson et al., 2001). In a group of non-supplemented pregnant women, daily urinary excretion of selenium remained constant throughout pregnancy, at a low level of around 15 µg/day. Increased daily urinary excretion was observed in groups of pregnant and non-pregnant women receiving selenium supplementation (50 µg/day of selenium as L-selenomethionine), which may reflect homeostatic response to supplementation.

Overall, the Panel notes that available data provide some evidence that adaptive changes occur during pregnancy, as indicated by a trend to lower urinary excretion of selenium in pregnant compared to non-pregnant women and a more pronounced conservation in late than in early pregnancy observed in the study by Swanson et al. (1983).

Considering an average selenium concentration in mature breast milk of 15 µg/L, and assuming an average milk volume of 0.8 L/day (Butte et al., 2002; FAO/WHO/UNU, 2004; EFSA NDA Panel, 2009), the Panel estimates that the amount of selenium secreted in breast milk during the first six months of lactation is 12 µg/day (section 2.3.6.3).

5.4. Selenium intake/status and health consequences

Associations between dietary selenium intake and health outcomes have been investigated in observational studies, in particular in relation to cancer risk (Vinceti et al., 2014). Most studies used FFQs, which rely on food composition tables and provide imprecise estimates of selenium intakes. Low correlations coefficients have been estimated between selenium intakes assessed through FFQs and selenium biomarkers (section 3.2). Because of the high uncertainties in selenium intake estimates, the Panel considers that no conclusions can be drawn from these studies for the setting of DRVs for selenium.

Intervention trials with selenium as a single nutrient are scarce and were mostly undertaken with respect to secondary prevention. Two large trials in the US, the Nutritional Prevention of Cancer (NPC) study and the Selenium and Vitamin E Cancer Prevention Trial (SELECT), investigated the effect of selenium supplementation on cancer risk and addressed other health outcomes as secondary endpoints. Both studies involved "selenium-replete" American individuals. In the NPC trial, 1 312 subjects with a history of skin cancer were randomised to receive supplements containing 200 µg/day of selenium, administered as selenised yeast or placebo, and were followed up for an average of 7.7 years for recurrence of non-melanoma skin cancer (Clark et al., 1996; Clark et al., 1998; Stranges et al., 2007). Secondary endpoints included incidence and mortality of cancer at any site, as well as lung, prostate, and colorectal cancers. SELECT was a randomised, double-blind, placebo-controlled, 2 × 2 factorial design trial and enrolled more than 35 000 healthy men who received supplemental selenium as selenomethionine (200 µg/day), vitamin E, selenium plus vitamin E or placebo, for a median of 5.5 years to investigate the effect on prostate cancer prevention (Lippman et al., 2009; Klein EA et al., 2011; Nicastro and Dunn, 2013). Pre-specified secondary endpoints included other cancers, including colorectal and lung cancer, total cancer incidence, serious cardiovascular events, diabetes, and all-cause mortality. Other smaller RCTs have assessed the effect of selenium supplementation on a variety of outcomes, including blood lipids, fertility and reproduction, immunity and thyroid function. The Panel considers that, although RCTs typically used "high" selenium doses (100–800 µg/day) and background selenium intakes were usually not assessed, they may provide evidence for effects at selenium intake levels beyond those associated with the levelling off of SEPP1.

The relationship between biomarkers of selenium status and various health outcomes has been investigated in a number of observational studies. The vast majority of studies made use of serum/plasma or toenail selenium concentrations as biomarkers to assess associations between selenium levels and disease incidence or mortality. To date, the association between SEPP1 concentration and health outcomes has only been investigated in two nested case-control studies (Persson-Moschos et al., 2000; Epplein et al., 2014). This section summarises evidence from meta-analyses or individual prospective observational studies on the relationship between plasma/serum selenium or SEPP1 concentrations and health outcomes. For the interpretation of findings, the Panel notes that in a review of supplementation studies, the levelling off of plasma SEPP1 concentration was found to be associated with plasma selenium concentrations between 90 and 140 µg/L (Hurst et al., 2013) (section 2.4.3). As toenail concentrations can not be reliably related to selenium intakes and there is no information regarding toenail concentrations associated to the levelling off of SEPP1, the

Panel considers that no conclusions can be drawn from studies using toenail concentration as a biomarker, for the setting of DRVs for selenium.

5.4.1. Mortality

A non-linear association was described between serum selenium concentration and all-cause mortality in 13 887 adult participants (1 968 deaths) followed up for up to 12 years in the US Third National Health and Nutrition Examination Survey (NHANES III) (Bleys et al., 2008). Vital status was ascertained through the National Death Index. Hazard ratios adjusted for age, sex, ethnicity, education, family income, menopausal status, smoking status, serum cotinine concentration, alcohol consumption, physical activity, body mass index (BMI), vitamin and/or mineral supplement use, C-reactive protein concentration, hypercholesterolaemia, hypertension, glomerular filtration rate and diabetes mellitus were estimated. The multivariate adjusted HRs for all-cause mortality comparing the second tertile (serum selenium concentration between 117.32 and 130.38 μg/L) and the third tertile (serum selenium concentration ≥ 130.39 μg/L) with the first tertile (serum selenium concentration < 117.32 μg/L) were 0.84 (95 % CI 0.73–0.96) and 0.83 (95 % CI 0.72–0.96), respectively. In spline regression models, the reference value was set at a serum selenium concentration of 105.4 μg/L (10^{th} percentile). A non-linear association was described between serum selenium concentrations and overall mortality, with an increase in the risk for lower serum selenium concentrations (< 105 μg/L) and a decreasing risk (HRs and 95 % CI below 1) as serum selenium concentrations increased up to 130 μg/L. The HRs remained constant at their lowest values with serum selenium concentrations increasing up to 150 μg/L and mortality rates gradually increased at serum selenium concentrations above 150 μg/L, although the increase was not statistically significant. Exclusion of participants with cardiovascular disease or cancer at baseline or exclusion of participants who died in the first two or five years of follow-up did not alter the HRs of serum selenium concentrations with all-cause mortality.

In the 9-year longitudinal Epidemiology of Vascular Ageing (EVA) study of 1 389 French individuals aged 59–71 years, the association between baseline plasma selenium concentration and mortality (101 deaths) was evaluated, adjusting for age, sex, education, smoking status, alcohol consumption, use of medication, cognitive function, diabetes, hypertension, dyslipidaemia, history of cardiovascular disease and presence of obesity (Akbaraly et al., 2005). In the multivariate model, baseline plasma selenium concentrations were expressed as quartiles and the reference category was set at quartile 4 (plasma selenium concentrations ≥ 1.22 μmol/L or ≥ 96 μg/L). Individuals with plasma selenium below 0.95 μmol/L (quartile 1, ≤ 75 μg/L) had a significantly higher risk of mortality (HR 3.34, 95 % CI 1.71–6.53), as well as individuals with plasma selenium concentrations between 0.96–1.09 μmol/L (quartile 2, 76–86 μg/L) (HR 2.49, 95% CI 1.25–4.94). When individuals with plasma selenium concentrations between 1.10–1.21 μmol/L (quartile 3, 87–95 μg/L) were compared to the reference category, the HR was 1.67 (95 % CI 0.78–3.56).

In the Baltimore Women's Health and Aging Study (WHAS), women (n = 632) aged 70–79 years were followed for a period of five years and the association between baseline serum selenium concentration and overall mortality (89 deaths) was assessed (Ray et al., 2006). Multivariate Cox proportional hazards models were used to examine the relationship between serum selenium concentrations (per SD increment in log scale) and mortality, adjusting for age, education, current smoking, alcohol use, BMI, fair-to-poor appetite, diabetes mellitus, cardiovascular and renal diseases. Based on these models, higher serum selenium concentration at baseline was associated with a lower risk of death from any cause (HR 0.71, 95 % CI 0.56–0.90). When selenium concentrations were expressed in quartiles, women with serum selenium < 1.38 μmol/L (<110 μg/L) had lower survival than women with higher baseline serum selenium concentrations (p = 0.0009, by log-rank test).

Wei et al. (2004) examined the relationship between baseline serum selenium concentration and the subsequent risk of death, using data from 1 103 Chinese subjects (average age 57 years), who were

randomly selected from the larger Linxian study cohort and were followed up for 15 years (516 deaths). Using the first quartile of serum selenium concentrations as the reference category (≤ 0.77 μmol/L, ≤ 61 μg/L) and after adjusting for smoking, alcohol consumption, BMI and serum cholesterol concentration, the HRs for quartiles 2 (> 0.77 and ≤ 0.91 μmol/L; or > 61 and ≤ 72 μg/L), 3 (> 0.91 and ≤ 1.06 μmol/L; or > 72 and ≤ 83 μg/L) and 4 (> 1.06 μmol/L or > 83 μg/L) were 1.01 (95 % CI 0.79–1.30), 0.96 (95 % CI 0.75–1.23) and 0.93 (95 % CI 0.72–1.19), respectively. The Panel notes that in this cohort no significant association was observed between baseline serum selenium concentration (mean 73 μg/L) and risk of death from any cause.

The Panel considers that three of four observational studies provide evidence for an inverse association between serum selenium concentration and mortality, with a reduction in risk of death from any cause at baseline serum selenium concentrations above around 100 μg/L, i.e. above 105–117 μg/L in the US NHANES III, above 87 μg/L in the EVA study, and above 110 μg/L in the WHAS study, which fall within the range of plasma selenium concentrations associated with the levelling off of SEPP1 concentration. The Panel concludes that these data cannot be used to derive DRVs, but that the information provided is compatible with the DRVs derived based on the levelling off of plasma SEPP1.

5.4.2. Cardiovascular-related outcomes

A number of selenoproteins have antioxidant and anti-inflammatory properties, and cardiometabolic effects have been linked to polymorphisms in several selenoproteins (Rayman, 2012). It has been hypothesised that selenium could affect the risk of cardiovascular diseases.

In a recent review of the evidence, SACN (2013) found inconsistent results from observational studies assessing the relationship between selenium status and cardiovascular disease. In a meta-analysis, Flores-Mateo et al. (2006) combined results from 13 cohort and 9 case-control studies that measured plasma/serum selenium concentrations. The risk of coronary heart disease in the highest vs. lowest categories of plasma/serum selenium concentration were compared. The authors found an inverse association between plasma/serum selenium concentrations and coronary heart disease in case-control studies (RR 0.47, 95 % CI 0.29–0.75, 9 studies). When results from 13, mostly small, prospective cohort studies were combined, a modest significant inverse association was also found (RR 0.84, 95 % CI 0.71–0.99). Subsequently, no significant association between serum selenium concentrations and cardiovascular mortality was found in the large US NHANES III cohort (Bleys et al., 2008; Eaton et al., 2010). The Panel considers that the evidence from observational studies on an association between plasma/serum selenium and cardiovascular disease is inconclusive.

Few randomised trials have addressed the effect of selenium supplementation on cardiovascular-related outcomes. The SELECT and NPC trials found no evidence of a protective effect of selenium at an intake of 200 μg/day in addition to selenium intake via the diet on cardiovascular mortality, non-fatal cardiovascular events and strokes (Flores-Mateo et al., 2006; Rees et al., 2013). Smaller trials evaluated the effect of selenium supplementation (typical doses 100–800 μg/day for some weeks–5 years) on blood lipid and blood pressure measurements, with inconsistent results (Rees et al., 2013). The Panel notes that there is no evidence from intervention trials that selenium doses of 100 μg/day or higher ingested in addition to dietary selenium, leading to total intake levels well above those associated with the levelling off of SEPP1, can prevent cardiovascular disease or influence cardiovascular disease-related risk factors in humans.

The Panel concludes that these data cannot be used to derive DRVs.

5.4.3. Cancer

The association between baseline plasma SEPP1 concentration and cancer risk (incidence and mortality) has been investigated in two nested case-control studies in Swedish men (302 cases and 604 controls) (Persson-Moschos et al., 2000) and men and women in the US (372 cases and 716 controls) (Epplein et al., 2014). The Panel notes that these studies suggest an inverse association between plasma SEPP1 concentration and overall cancer risk and, in particular, risk of cancer of the digestive and respiratory tract. The Panel notes that evidence is limited and that the associations between SEPP1 concentrations and health outcomes are difficult to interpret to date, due to the lack of standardisation of SEPP1 measurements, which preclude comparisons between studies (section 2.4.3). The Panel considers that no conclusions can be drawn from these studies for the setting of DRVs for selenium.

A recent Cochrane review of prospective observational studies and RCTs evaluated the evidence for a relationship between selenium exposure and cancer risk in humans and for the efficacy of selenium supplementation for cancer prevention (Vinceti et al., 2014). A total of 40 prospective studies, which used serum/plasma selenium concentrations as biomarker, and eight RCTs (selenium dose 200–500 µg/day) were included. Random-effects meta-analyses were applied, using OR and RR as measures of the association between cancer risk and selenium exposure and comparing the highest and lowest exposure categories.

Based on RCTs, there was no evidence that selenium supplementation reduced the risk (incidence or mortality) of any cancer (RR 0.90, 95 % CI 0.70–1.17, n = 18 698) or cancer-related mortality (RR 0.81, 95 % CI 0.49–1.32, n = 18 698), when evidence from SELECT and NPC trials were combined. A significant effect of selenium supplementation on liver cancer risk was found (RR 0.50, 95 % CI 0.35–0.77, n = 4 765, I^2=0 %) when combining results from three studies conducted among high-risk groups (first-degree relatives of liver cancer patients of hepatitis B-surface antigen carriers) from China. All three trials were considered to have unclear risk of bias. No significant effect of supplementation was found for other cancer sites (prostate, bladder, colorectal, non-melanoma skin and lung).

Based on prospective studies, authors found reduced risk for total cancer incidence and mortality, bladder cancer risk and prostate cancer risk with higher serum/plasma selenium concentration. The summary risk estimates comparing the highest to the lowest categories of selenium exposure for both men and women were 0.69 (95 % CI 0.53–0.91, nine studies, p for heterogeneity = 0.05; I^2 = 49 %) for total cancer incidence; 0.60 (95 % CI 0.39–0.93, seven studies, p for heterogeneity = 0.02; I^2 = 62 %) for total cancer mortality; 0.67 (95 % CI 0.46–0.97, five studies, p for heterogeneity = 0.21; I^2 = 30 %) for bladder cancer risk (incidence and mortality); 0.79 (95 % CI 0.69–0.90, 17 studies, p for heterogeneity = 0.19; I^2 = 23 %) for prostate cancer risk. No significant association was found for cancers of other sites (female breast, lung, stomach, colon/colorectal). The Panel notes that the review combined results from studies using various numbers of exposure categories covering different absolute selenium concentrations and did not characterise the levels of serum/plasma selenium concentrations associated with a reduced cancer risk.

Hurst et al. (2012) undertook a dose-response analysis of biomarkers of selenium exposure and risk of prostate cancer in a systematic review and meta-analysis of randomised controlled trials, case-control studies, nested case-control and prospective cohort studies. Nine studies (two case-control and seven nested case-control) with a total of 3 579 cases of prostate cancer and 4 510 controls were included in the dose-response meta-analysis. Six of these studies were considered in the meta-analysis by Vinceti et al. (2014).

A gradual decrease in prostate cancer risk was found over the range of plasma/serum selenium from 60 to 170 µg/L. Considering plasma/serum selenium concentrations at about 60 µg/L as the reference category, at plasma/serum selenium concentrations of 135 µg/L the RR of total prostate cancer was

0.85 (95% CI 0.74–0.97) and at 170 µg/L (i.e. the upper range investigated) the RR was 0.75 (95% CI 0.65–0.86) (no risk estimates given for concentrations between 60 and 135 µg/L).

The Panel notes that the recent Cochrane review by Vinceti et al. (2014) found an inverse association between selenium exposure and risk of total cancer or risk of bladder and prostate cancer, and that the levels of serum/plasma selenium concentrations associated with a reduced cancer risk were not characterised. In a dose-response analysis of a selected subgroup of studies, Hurst et al. (2012) reported a reduced risk of prostate cancer with plasma/serum selenium concentrations between about 135 and 170 µg/L.

The Panel further notes that there is no evidence from intervention trials that selenium doses of 200 µg/day or higher ingested in addition to dietary selenium, leading to total intake levels well above those associated with the levelling off of SEPP1, can prevent cancer in humans.

The Panel concludes that these data cannot be used to derive DRVs, but that the information provided is compatible with the DRVs derived based on the levelling off of plasma SEPP1.

5.4.4. Other health related outcomes

Data from prospective and case-control studies as well as intervention trials investigating a relationship between selenium intake or status and glucose metabolism and risk of type 2 diabetes are variable and conflicting (reviewed by (Fairweather-Tait et al., 2011; Rayman, 2012; Rees et al., 2013)).

The relationship between selenium intakes and biomarkers of status and health outcomes related to fertility (e.g. sperm counts, motility or morphology), reproduction (e.g. pre-eclampsia, pre-term birth, miscarriage), immune function (e.g. incidence and severity of infectious episodes), thyroid hormone production and cognition has been studied in some observational studies and a small number of RCTs using selenium supplementation (reviewed by (Fairweather-Tait et al., 2011; Rayman, 2012; Hurst et al., 2013; SACN, 2013). The Panel notes that the available evidence is limited and inconclusive.

The Panel concludes that these data cannot be used to derive DRVs.

5.5. Conclusion on selenium intake and health consequences

The Panel considers that the evidence provided by observational studies should be interpreted with caution due to uncertainties related to the limitations inherent in the use of plasma/serum selenium, which is affected by dietary selenium species and inflammation (section 2.4), as well as the presence of possible confounding factors (e.g. other dietary, lifestyle factors) which may have an impact on the outcomes investigated. Available evidence suggests an inverse relationship between plasma/serum selenium concentration and risk of certain types of cancer and total mortality. The Panel notes that the latter association has been described for plasma/serum selenium concentrations above around 100 µg/L, which fall within the range of plasma selenium concentrations associated with the levelling off of SEPP1 concentration. A reduced risk of prostate cancer with plasma/serum selenium between about 135 and 170 µg/L has been described based on a subgroup of selected studies.

Few intervention trials have investigated the effect of selenium supplementation alone on health outcomes. Most trials were conducted in "selenium-replete" individuals, in which health benefits of supplemental selenium are less likely. These trials provided no evidence for a protective effect of selenium supplementation (≥ 100 µg/day), leading to total intake levels well above those associated with the leveling off of SEPP1, on any health outcome.

Overall, the Panel notes that further research is required to better characterise the relationship between selenium intake/status, in particular as assessed by SEPP1 concentration, and health consequences, including the influence of factors such as baseline selenium status, genotypes (polymorphisms in selenoprotein genes) or effect of different selenium compounds.

The Panel concludes that the information provided is compatible with the DRVs derived based on the levelling off of plasma SEPP1 concentration.

6. Data on which to base Dietary Reference Values

The Panel considers that the levelling off of plasma SEPP1 concentration is associated with the fulfilment of selenium requirement and is the most suitable criterion for establishing DRVs for selenium (sections 2.4 and 5.1).

6.1. Adults

The Panel notes that habitual selenium intakes of 50–60 µg/day were not sufficient for SEPP1 concentration to reach a plateau in Finnish individuals (Persson-Moschos et al., 1998), while selenium intakes of 100 µg/day and above have consistently been associated with plasma SEPP1 concentration at a plateau in population groups from Finland, the UK and the US (Persson-Moschos et al., 1998; Hurst et al., 2010; Combs et al., 2012).

Two intervention studies investigated the relationship between different supplemental doses of selenium in the range 10–125 µg/day and plasma SEPP1 concentrations. In the study by Duffield et al. (1999) in healthy individuals from New Zealand, selenium intakes of around 60–70 µg/day were required for SEPP1 concentration to level off. The Panel notes the large variability in the results of this study. In the study by Xia et al. (2010) in Chinese subjects, a selenium intake of 0.85 µg/kg body weight per day led to the levelling off of plasma SEPP1 concentration. Adjusting for body weight in the EU, this would correspond to a selenium intake of 60 µg/day for men with a reference body weight of 68.1 kg and 50 µg/day for women with a reference body weight of 58.5 kg. The Panel notes, however, that there are uncertainties related to the intake estimates in this study and to the extrapolation of results from Chinese individuals to the European population due to different characteristics of the populations in relation to their selenium status and background diet. The Panel also notes that supplemental selenium was administered as L-selenomethionine in both studies and that there are some uncertainties in extrapolating the values derived from these studies to dietary selenium comprising also other forms of selenium, due to differences in absorption and metabolism between the different forms of selenium.

Given the uncertainties in the dataset, the Panel considers that available data are not sufficient to derive an AR for selenium in adults, but considers that an AI can be set at 70 µg/day for adult men and women.

6.2. Infants and children

Assuming an average breast milk selenium concentration of 15 µg/L and an average breast milk intake of infants aged 0–6 months of 0.8 L/day (Butte et al., 2002; FAO/WHO/UNU, 2004; EFSA NDA Panel, 2009), the estimated selenium intake of infants between zero and six months is 12 µg/day. The AI for infants over six months of age can be derived by extrapolation from this figure. As there is no evidence that the requirement for selenium is associated to the metabolic rate, isometric scaling was applied, based on reference body weights of the respective age groups and rounding. The AI for infants aged 7–11 months is set at 15 µg/day.

For children and adolescents, the Panel considers that there are no data that can be used to set an AI, thus the AI for selenium is extrapolated from the AI for adults taking into account differences in reference body weight (isometric scaling):

$AI_{child} = AI_{adult}$ (body weight of child/body weight of adult).

There are no data indicating that specific categories of age should be considered for selenium requirement for children and adolescents. As a consequence, the age categories as proposed by the EFSA NDA Panel (2010) are applied for children and adolescents.

Table 6: Reference body weights and Adequate Intakes (AIs) of selenium for children

Age	Reference body weight (kg)	AI (µg/day) [f]
1–3 years	11.9 [a]	15
4–6 years	19.0 [b]	20
7–10 years	28.7 [c]	30
11–14 years	45.7 [d]	50
15–17 years	60.3 [e]	65

(a): Median body weight-for-age of boys or girls aged 24 months (WHO Multicentre Growth Reference Study Group, 2006).
(b): Median body weight of boys or girls aged 5 years (van Buuren et al., 2012).
(c): Median body weight of boys or girls aged 8.5 years (van Buuren et al., 2012).
(d): Median body weight of boys or girls aged 12.5 years (van Buuren et al., 2012).
(e): Median body weight of boys or girls aged 16 years (van Buuren et al., 2012).
(f): AIs derived from the AI for adults after adjustment on the basis of differences in reference weight, then rounded to the closest 5.

6.3. Pregnancy

The Panel notes that there is a lack of data on selenium requirement in pregnancy. In agreement with the previous assessement by SCF (1993), the Panel considers that adaptive changes in the metabolism of selenium occur during pregnancy to cover the additional selenium needs; thus, the AI set for adult women is also proposed for pregnancy.

6.4. Lactation

Even though it is conceivable that adaptive changes in selenium metabolism might also occur during lactation, there is no data on this. Taking a conservative approach, the Panel proposes to increase the AI for lactating women in order to compensate for the losses of selenium through breast milk.

An average amount of selenium secreted in breast milk of 12 µg/day was estimated (section 2.3.6.2). There is no specific information on selenium absorption efficiency in lactating women. Considering an absorption efficiency of 70 % from usual diets based on data in non-lactating subjects (section 2.3.1), an additional selenium intake of 15 µg/day was considered sufficient to replace these losses. Thus, an AI of 85 µg/day is proposed for lactating women.

CONCLUSIONS

The Panel concluded that there is insufficient evidence to derive an Average Requirement (AR) and a Population Reference Intake (PRI) for selenium. Data on the relationship between selenium intakes and the levelling off of plasma SEPP1 concentration were used to set an AI (Table 7). It was considered unnecessary to give sex-specific values. The Panel proposes that the adult AI also applies to pregnant women. For lactating women, an increase in AI was estimated based on the estimated loss

of selenium secreted in breast milk. In infants over six months of age, an AI is derived from the estimated selenium intake of breastfed infants between zero and six months and extrapolating from this value using isometric scaling and reference body weights of the respective age groups. In children, AIs are proposed based on extrapolation from the adult AI using isometric scaling and body weights of the respective age groups.

Table 7: Summary of Dietary Reference Values for selenium

	Adequate Intake (µg/day)
Age	
7-11 months	15
1-3 years	15
4-6 years	20
7-10 years	30
11-14 years	50
15-17 years	65
≥ 18 years	70
Pregnancy	70
Lactation	85

RECOMMENDATIONS FOR RESEARCH

The Panel recommends to further investigate the relationship between selenium intakes and SEPP1 in Western populations, to enable the determination of an Average Requirement and Population Reference Intake of selenium in adults.

The Panel also recommends to generate evidence that can be used to assess the selenium requirements of infants and children and during pregnancy.

The Panel recommends to better characterise the relationship of SEPP1 with relevant health outcomes such as mortality and cancer. Further research is required to better characterise the relationships between selenium intake/status and health consequences, including the influence of factors such as baseline selenium status, genotypes (polymorphisms in selenoprotein genes) or effect of different selenium compounds.

The Panel recommends that food composition tables are updated to improve selenium intake assessments.

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APPENDICES

A. SELENIUM CONCENTRATION IN HUMAN MILK

Reference	Number of women [a] (number of samples)	Country	Stage of lactation	Selenium concentration (µg/L)		
				Mean ± SD	Median	Range
Clemente et al. (1982)	21 (130)	Italy	15–75 days	13.3 ± 0.9	9.5	≤ 1.0–49.6
Robberecht et al. (1985)	32 (24)	Belgium	0–3 days	14.8 ± 4.9	15.0	6.6–27.2
	32 (13)		5–7 days	12.3 ± 4.4	11.0	5.5–18.7
	32 (11)		8–10 days	12.7 ± 3.5	12.6	6.7–17.7
	32 (15)		Day 30	9.4 ± 2.0	8.9	6.7–12.7
	32 (9)		Day 60	9.9 ± 3.4	9.0	5.6–15.4
Schramel et al. (1988b)	9 (9)	Germany	Day 1	43.0 ± 18	n.a.	n.a.
	25 (25)		Mature milk	21.0 ± 6	n.a.	n.a.
Brätter et al. (1991)	45 (45)	Germany (Berlin)	10–20 days	15.1	n.a.	9–25
	55 (55)	Germany (Lübeck)	12–63 days	15.2	n.a.	11–29
	40 (40)	Germany (Würzburg)	12–62 days	16.4	n.a.	8–40
Bratakos and Ioannou (1991)	11 (20)	Greece	Colostrum	41 ± 16	n.a.	20–79
	11 (12)		Transitional milk	23 ± 6	n.a.	16–36
	11 (36)		Mature milk	17 ± 3	n.a.	11–23
Debski et al. (1992)	10 (10)	Poland (Siedlce)	1–2 months	8.6	n.a.	n.a.
	10 (10)	Poland (P. Trybunalski)	1–2 months	16.1	n.a.	n.a.
	10 (10)	Poland (Warsaw)	1–2 months	14.7	n.a.	n.a.
Kantola and Vartiainen (1991)	85 (85)	Finland (Helsinki)	4–5 weeks	15.7	n.a.	11.2–22.4

Reference	Number of women [(a)] (number of samples)	Country	Stage of lactation	Selenium concentration (µg/L)		
				Mean ± SD	Median	Range
	87 (87)	Finland (Kuopio)	4–5 weeks	15.8	n.a.	8.9–24.3
Jochum et al. (1995)	30	Germany	4 months	9.9 ± 0.5	n.a.	n.a.
Kantola et al. (1997)	9 (9)	Finland (Kuopio)	Colostrum	22.1	n.a.	16–43
	32 (32)	Finland (Kuopio)	4–5 weeks	19.2	n.a.	14–25
	10 (10)	Estonia (Tallin)	Colostrum	11.2	n.a.	9–14
	2 (2)	Estonia (Tallin)	4–5 weeks	18.2	n.a.	8–29
	18 (18)	Estonia (Rakvere)	Colostrum	13.1	n.a.	5–19
	6 (6)	Estonia (Rakvere)	4–5 weeks	9.5	n.a.	7–11
Krachler et al. (1998)	(13)	Austria	1–3 days	33.4	32.7	13.1–52.7
	(18)	Austria	4–17 days	16.1	16.0	9.2–25.0
	(8)	Austria	40–60 days	11.8	12.5	8.3–13.8
	(8)	Austria	66–90 days	12.4	12.4	9.6–16.2
	(8)	Austria	97–293 days	10.2	8.9	6.6–18.6
Li et al. (1999)	(36)	Austria	1–7 days	23.9 ± 12.0	20.2	9.2–53.4
	(3)	Austria	9–12 days	18.2 ± 4.0	16.5	15.3–22.7
	(24)	Austria	15–60 days	12.2 ± 2.4	13.1	8.3–15.9
	(9)	Austria	66–79 days	10.9 ± 1.3	10.6	6.1–14.4
	(3)	Austria	97–150 days	7.0 ± 0.7	6.6	6.6–7.8
	(3)	Austria	224–293 days	13.5 ± 4.5	11.8	10.–18.6
Krachler et al. (2000)	(27)	Austria	“Transitional and mature milk”	17	n.a.	< 4.7–87
Zachara and Pilecki (2000)	905 (905)	Poland	12–75 days	10.24 ± 2.82	n.a.	3–23.4

Reference	Number of women [(a)] (number of samples)	Country	Stage of lactation	Selenium concentration (µg/L)		
				Mean ± SD	Median	Range
Micetic-Turk et al. (2000)	18 (18)	Slovenia	2–3 days	29.0 ± 10.0	n.a.	17–48
Rossipal et al. (2000)	(27)	Austria	1–3 days	n.a.	32.7	n.a.
(Kantola and Vartiainen, 2001)	175 (175)	Finland (1987)	4–6 weeks	16.4 ± 3.2	n.a.	n.a.
	81 (81)	Finland (1993–5)	4–6 weeks	18.9 ± 3.0	n.a.	n.a.
Wasowicz et al. (2001)	43 (43)	Poland	0–4 days	22.8 ± 10.1		
	46 (46)	Poland	5–9 days	11.3 ± 3.8		
	41 (41)	Poland	10–30 days	9.2 ± 3.6		
Martino et al. (2001)	n.a.	Spain	Week 3	14.1 ± 2.1	n.a.	n.a.
Navarro-Blasco and Alvarez-Galindo (2004)	(31)	Spain	"Mature milk"	16.3 ± 4.7	n.a.	9.4–29.0
Valent et al. (2011)	100 (100)	Italy	3–5 months	12.12 ± 3.02	11.33	6.5–20.02
Miklavcic et al. (2013)	39 (39)	Greece	3–8 months	n.a.	21 [(b)]	< LOD–168 [(b)]
	123 (123)	Croatia	1 month	n.a.	18 [(b)]	8.4–49 [(b)]
	287 (287)	Slovenia	1 month	n.a.	17 [(b)]	1.7–69 [(b)]
	602 (602)	Italy	1 month	n.a.	18 [(b)]	4.6–87 [(b)]

(a): Mothers of term infants
(b): µg/kg
n.a., not available; LOD, limit of detection

2212 **B. DIETARY SURVEYS IN THE UPDATED EFSA COMPREHENSIVE EUROPEAN FOOD CONSUMPTION DATABASE INCLUDED IN THE NUTRIENT INTAKE**
2213 **CALCULATION AND NUMBER OF SUBJECTS IN THE DIFFERENT AGE CLASSES.**

Country	Dietary survey (Year)	Year	Method	Days	Number of subjects [b]					
					Children 1–< 3 years	Children 3–< 10 years	Adolescents 10–< 18 years	Adults 18–< 65 years	Adults 65–< 75 years	Adults ≥ 75 years
Finland/1	DIPP	2000–2010	Dietary record	3	500	750				
Finland/2	NWSSP	2007–2008	48-hour dietary recall [a]	2x2 [a]			306			
Finland/3	FINDIET2012	2012	48-hour dietary recall [a]	2 [a]				1 295	413	
France	INCA2	2006–2007	Dietary record	7		482	973	2 276	264	84
Germany/1	EsKiMo	2006	Dietary record	3		835	393			
Germany/2	VELS	2001–2002	Dietary record	6	347	299				
Ireland	NANS	2008–2010	Dietary record	4				1 274	149	77
Italy	INRAN-SCAI 2005-06	2005–2006	Dietary record	3	36 [b]	193	247	2 313	290	228
Latvia	FC_PREGNANTWOMEN 2011	2011	24-hour dietary recall	2			12 [b]	991 [c]		
Netherlands	VCPBasis_AVL	2007–2009	24-hour dietary recall	2		447	1142	2 057	173	
Sweden	Riskmaten	2010–2011	Dietary records (Web)	4				1 430	295	72
United Kingdom	NDNS - Rolling Programme (1-3 years)	2008–2011	Dietary record	4	185	651	666	1 266	166	139

2214 (a): A 48-hour dietary recall comprises two consecutive days.
2215 (b): 5^{th} or 95^{th} percentile intakes calculated over a number of subjects lower than 60 require cautious interpretations as the results may not be statistically robust (EFSA, 2011) and therefore for
2216 these dietary surveys/age classes the 5^{th}, 95^{th} percentile estimates will not be presented in the intake results.
2217 (c): One subject with only one 24-hour dietary recall day was excluded from the dataset, i.e. the final n = 990.
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2219 **C. SELENIUM INTAKES AMONG MALES IN DIFFERENT SURVEYS ACCORDING TO AGE CLASSES AND COUNTRY (µG/DAY)**

Age class	Country	Survey	N	Average	P5	P50	P95
Boys 1–< 3 years	Finland	DIPP_2001_2009	245	36.3	13.1	36.2	61.6
	Germany	VELS	174	18.9	9.1	18.2	32.2
	Italy	INRAN_SCAI_2005_06	20	25.3	(a)	24.4	(a)
	United Kingdom	NDNS-RollingProgrammeYears1-3	107	25.3	15.1	23.9	41.1
Boys 3–< 10 years	Finland	DIPP_2001_2009	381	45.9	24.8	44.3	68.5
	France	INCA2	239	33.2	19.4	31.3	51.4
	Germany	EsKiMo	426	41.4	22.9	38.0	71.5
	Germany	VELS	146	22.5	13.9	22.0	33.9
	Italy	INRAN_SCAI_2005_06	94	37.6	16.2	33.9	66.3
	Netherlands	VCPBasis_AVL2007_2009	231	35.5	18.2	32.5	59.4
	United Kingdom	NDNS-RollingProgrammeYears1-3	326	33.8	18.4	32.0	53.4
Boys 10–< 18 years	Finland	NWSSP07_08	136	60.3	32.4	59.7	95.5
	France	INCA2	449	41.6	22.2	39.6	66.5
	Germany	EsKiMo	197	42.2	21.7	39.5	67.4
	Italy	INRAN_SCAI_2005_06	108	45.9	21.9	40.2	88.4
	Netherlands	VCPBasis_AVL2007_2009	566	45.5	23.8	42.7	77.5
	United Kingdom	NDNS-RollingProgrammeYears1-3	340	44.6	23.2	42.2	74.3
Men 18–< 65 years	Finland	FINDIET2012	585	65.6	28.9	60.9	113.0
	France	INCA2	936	48.8	24.2	46.2	78.8
	Ireland	NANS_2012	634	59.0	32.0	56.6	92.2
	Italy	INRAN_SCAI_2005_06	1068	42.7	19.9	37.4	82.3
	Netherlands	VCPBasis_AVL2007_2009	1023	56.9	29.3	52.7	97.1
	Sweden	Riksmaten 2010	623	63.3	29.7	60.0	111.5
	United Kingdom	NDNS-RollingProgrammeYears1-3	560	51.3	24.9	49.8	86.8
Men 65–< 75 years	Finland	FINDIET2012	210	54.1	25.4	52.9	95.5
	France	INCA2	111	49.8	28.1	48.2	80.0
	Ireland	NANS_2012	72	58.2	30.2	53.3	104.4

Age class	Country	Survey	N	Average	P5	P50	P95
	Italy	INRAN_SCAI_2005_06	133	41.6	18.3	36.3	93.4
	Netherlands	VCPBasis_AVL2007_2009	91	53.3	23.2	50.4	94.0
	Sweden	Riksmaten 2010	127	59.6	30.9	55.6	93.9
	United Kingdom	NDNS-RollingProgrammeYears1-3	75	52.2	22.2	49.8	84.9
Men ≥ 75 years	France	INCA2	40	44.1	(a)	41.4	(a)
	Ireland	NANS_2012	34	47.6	(a)	43.2	(a)
	Italy	INRAN_SCAI_2005_06	69	38.8	21.8	36.1	64.6
	Sweden	Riksmaten 2010	42	61.7	(a)	57.0	(a)
	United Kingdom	NDNS-RollingProgrammeYears1-3	56	44.3	(a)	43.1	(a)

(a): 5^{th} or 95^{th} percentile intakes calculated over a number of subjects lower than 60 require cautious interpretation as the results may not be statistically robust (EFSA, 2011) and therefore for these dietary surveys/age classes the 5^{th} and 95^{th} percentile estimates will not be presented in the intake results.

D. SELENIUM INTAKES AMONG FEMALES IN DIFFERENT SURVEYS ACCORDING TO AGE CLASSES AND COUNTRY (µG/DAY)

Age class	Country	Survey	N	Average	P5	P50	P95
Girls 1–< 3 years	Finland	DIPP_2001_2009	255	35.8	12.2	35.1	56.9
	Germany	VELS	174	17.2	9.2	17.0	28.3
	Italy	INRAN_SCAI_2005_06	16	24.9	(a)	25.8	(a)
	United Kingdom	NDNS-RollingProgrammeYears1-3	78	24.2	13.3	22.7	38.0
Girls 3–< 10 years	Finland	DIPP_2001_2009	369	41.1	24.7	40.1	62.3
	France	INCA2	243	29.7	17.6	28.4	46.5
	Germany	EsKiMo	409	34.9	19.6	32.6	57.1
	Germany	VELS	147	20.6	12.2	20.3	31.3
	Italy	INRAN_SCAI_2005_06	99	34.5	17.9	32.1	65.2
	Netherlands	VCPBasis_AVL2007_2009	216	32.8	18.3	31.6	51.3
	United Kingdom	NDNS-RollingProgrammeYears1-3	325	30.5	16.2	29.5	49.2
Girls 10–< 18 years	Finland	NWSSP07_08	170	46.9	25.6	46.3	76.4
	France	INCA2	524	33.9	18.2	32.4	55.9
	Germany	EsKiMo	196	39.0	19.4	37.3	63.8
	Italy	INRAN_SCAI_2005_06	139	39.6	16.7	33.2	87.8
	Latvia [(b)]	FC_PREGNANTWOMEN_2011	12	50.9	(a)	42.9	(a)
	Netherlands	VCPBasis_AVL2007_2009	576	36.8	20.2	35.0	59.6
	United Kingdom	NDNS-RollingProgrammeYears1-3	326	35.2	18.4	33.9	56.6
Women 18–< 65 years	Finland	FINDIET2012	710	49.6	23.9	47.0	81.1
	France	INCA2	1340	37.9	19.1	36.3	62.7
	Ireland	NANS_2012	640	44.0	22.7	42.3	70.4
	Italy	INRAN_SCAI_2005_06	1245	35.8	14.8	31.5	70.9
	Latvia	FC_PREGNANTWOMEN_2011	990	50.3	24.5	47.7	82.9
	Netherlands	VCPBasis_AVL2007_2009	1034	43.9	23.0	41.7	72.9
	Sweden	Riksmaten 2010	807	50.5	23.9	48.0	85.4
	United Kingdom	NDNS-RollingProgrammeYears1-3	706	41.6	19.0	39.6	71.2
Women 65–< 75 years	Finland	FINDIET2012	203	42.7	19.7	39.7	68.7

Age class	Country	Survey	N	Average	P5	P50	P95
	France	INCA2	153	38.8	18.6	37.4	62.8
	Ireland	NANS_2012	77	47.2	24.3	41.8	83.5
	Italy	INRAN_SCAI_2005_06	157	35.0	13.6	32.0	67.8
	Netherlands	VCPBasis_AVL2007_2009	82	40.7	18.3	37.4	70.9
	Sweden	Riksmaten 2010	168	50.7	27.2	46.8	88.6
	United Kingdom	NDNS-RollingProgrammeYears1-3	91	42.6	22.6	42.2	68.2
Women ≥ 75 years	France	INCA2	44	35.2	(a)	35.1	(a)
	Ireland	NANS_2012	43	40.2	(a)	38.6	(a)
	Italy	INRAN_SCAI_2005_06	159	31.0	14.3	30.0	49.6
	Sweden	Riksmaten 2010	30	49.5	(a)	41.3	(a)
	United Kingdom	NDNS-RollingProgrammeYears1-3	83	39.6	24.3	39.4	63.5

(a): 5^{th} or 95^{th} percentile intakes calculated over a number of subjects lower than 60 require cautious interpretation as the results may not be statistically robust (EFSA, 2011) and therefore for these dietary surveys/age classes the 5^{th} and 95^{th} percentile estimates will not be presented in the intake results.
(b): Pregnant women only.

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2230 **E. MINIMUM AND MAXIMUM % CONTRIBUTION OF DIFFERENT FOOD GROUPS TO SELENIUM INTAKES AMONG MALES**

Food groups	Boys 1–< 3 years	Boys 3–< 10 years	Boys 10–< 18 years	Men 18–< 65 years	Men 65–< 75 years	Men ≥ 75 years
Additives, flavours, baking and processing aids	<0.1	0	0	0	0	0
Alcoholic beverages	<0.1	<0.1	<0.1 - 0.7	0.3 - 2.7	0.2 - 1.8	0.2 - 1.5
Animal and vegetable fats and oils	0.1 - 1.4	0.1 - 1.8	0.1 - 1.9	0.1 - 2.1	0.2 - 2.2	0.2 - 2.2
Coffee, cocoa, tea and infusions	<0.1 - 0.4	<0.1 - 0.9	0.1 - 0.8	0.3 - 1.7	0.3 - 1.6	0.3 - 1.4
Composite dishes	0.3 - 12.5	0.1 - 11.6	0.1 - 13.1	1.6 - 19.2	2.3 - 15	2.8 - 15.6
Eggs and egg products	1.5 - 5.5	0.4 - 8.2	0.2 - 8	0.1 - 5.4	0.1 - 6	0.3 - 5
Fish, seafood, amphibians, reptiles and invertebrates	2.3 - 14.7	3.9 - 23.2	3.8 - 25.5	7.1 - 24.7	8.8 - 27.4	15.5 - 32.4
Food products for young population	1.8 - 16.7	0 - 0.6	<0.1 - 0.1	0	0	0
Fruit and fruit products	0.9 - 3.2	0.7 - 2	0.6 - 1.3	0.5 - 1.5	0.8 - 1.9	0.7 - 2.2
Fruit and vegetable juices and nectars	0.1 - 2.3	0.6 - 1.8	0.6 - 1.3	0.3 - 0.8	0.2 - 0.6	0.2 - 0.6
Grains and grain-based products	12.6 - 24.5	14.6 - 33.9	14.2 - 32.4	13.6 - 25.8	11.1 - 22.5	10.3 - 24.7
Legumes, nuts, oilseeds and spices	0.1 - 4.3	0.4 - 4.1	0.5 - 3.2	0.5 - 3.1	0.6 - 2.8	0.4 - 2.2
Meat and meat products	11.9 - 19.1	15.4 - 31.5	18.5 - 37.5	19.5 - 38.8	17.4 - 35.8	17.9 - 31.7
Milk and dairy products	26.2 - 47.7	13.8 - 45.2	10.7 - 38.4	9.5 - 27.6	8.3 - 26.8	9.4 - 13.1
Products for non-standard diets, food imitates and food supplements or fortifying agents	0 - 0.5	<0.1 - 1	<0.1 - 0.4	<0.1 - 0.4	<0.1 - 0.3	0 - 0.4
Seasoning, sauces and condiments	0.2 - 0.9	0.3 - 1	0.3 - 1.6	0.4 - 1.8	0.5 - 1.8	0.4 - 1.5
Starchy roots or tubers and products thereof, sugar plants	0.5 - 2.1	0.7 - 3.1	0.7 - 3.5	0.4 - 2.7	0.5 - 1.9	0.4 - 1.9
Sugar, confectionery and water-based sweet desserts	0.2 - 1.1	0.3 - 3.7	0.3 - 2.7	0.2 - 1.3	0.2 - 0.9	0.2 - 0.5
Vegetables and vegetable products	0.5 - 3.9	0.5 - 5.6	0.7 - 6.6	0.9 - 7.4	0.8 - 6.8	0.9 - 7.1
Water and water-based beverages	0.5 - 1.3	0.4 - 1.4	1.2 - 1.5	0.8 - 1.5	0.5 - 1.4	0.4 - 1.4

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2232 **F. MINIMUM AND MAXIMUM % CONTRIBUTION OF DIFFERENT FOOD GROUPS TO SELENIUM INTAKES AMONG FEMALES**

Food groups	Girls 1–< 3 years	Girls 3–< 10 years	Girls 10–< 18 years	Women 18–< 65 years	Women 65–< 75 years	Women ≥ 75 years
Additives, flavours, baking and processing aids	0	0	0 - 0.1	0	0	0
Alcoholic beverages	0	<0.1	<0.1 - 0.1	<0.1 - 0.8	0.1 - 0.5	0.1 - 0.2
Animal and vegetable fats and oils	0.1 - 1.4	0.1 - 1.8	0.1 - 1.8	0.2 - 2.1	0.2 - 2.2	0.2 - 2.2
Coffee, cocoa, tea and infusions	<0.1 - 0.4	<0.1 - 1.2	0.2 - 1.2	0.4 - 2.3	0.4 - 2.4	0.4 - 1.6
Composite dishes	0.4 - 11.1	0.1 - 11.6	0.4 - 13.6	1.7 - 20.8	1.5 - 14.7	1.6 - 11.5
Eggs and egg products	0.7 - 6.3	0.4 - 8.5	0.3 - 8.3	0.3 - 5.5	0.4 - 6.2	0.3 - 6.7
Fish, seafood, amphibians, reptiles and invertebrates	2.1 - 29.5	2.2 - 19.8	3.6 - 28.7	8.2 - 26	10.4 - 27.1	15.7 - 25.8
Food products for young population	1.5 - 14.2	0 - 0.4	0	0	0	<0.1
Fruit and fruit products	0.8 - 3	0.7 - 2.3	0.8 - 2.6	0.8 - 2.1	1 - 3.1	1.4 - 2.6
Fruit and vegetable juices and nectars	0.1 - 1.6	0.5 - 1.7	0.6 - 1.8	0.4 - 1	0.3 - 0.8	0.2 - 0.6
Grains and grain-based products	11.3 - 27.8	14.4 - 31.5	15.2 - 32.8	12.8 - 27	10.1 - 24.8	11.2 - 24.4
Legumes, nuts, oilseeds and spices	0.1 - 4.3	0.4 - 3.4	0.7 - 3	0.9 - 3.5	0.9 - 2.7	0.6 - 2.3
Meat and meat products	11.7 - 19.5	15.4 - 31.2	16.7 - 35.2	17.5 - 35.6	19.3 - 32	16.5 - 32.1
Milk and dairy products	22.4 - 52.3	14.2 - 46.8	10.8 - 37.9	10.4 - 31.5	10.3 - 29.5	11.4 - 16.9
Products for non-standard diets, food imitates and food supplements or fortifying agents	0 - 0.2	<0.1 - 0.7	<0.1 - 0.5	0.2 - 1.2	0 - 1.4	0 - 1.9
Seasoning, sauces and condiments	0.2 - 1	0.2 - 1.2	0.3 - 1.8	0.5 - 1.8	0.6 - 1.3	0.5 - 1.2
Starchy roots or tubers and products thereof, sugar plants	1.1 - 1.9	0.7 - 3.5	0.7 - 3.3	0.3 - 2.2	0.3 - 1.7	0.3 - 1.5
Sugar, confectionery and water-based sweet desserts	0.1 - 1	0.3 - 3.5	0.3 - 2.7	0.3 - 1.3	0.2 - 0.8	0.3 - 0.8
Vegetables and vegetable products	0.4 - 4.2	0.6 - 6.6	0.9 - 6.3	1.2 - 7.5	1.2 - 7.7	1.1 - 7.1
Water and water-based beverages	0.5 - 1.4	0.5 - 1.4	0.5 - 1.5	0.3 - 2	0.8 - 1.8	0.8 - 2.3

ABBREVIATIONS

Afssa	Agence française de sécurité sanitaire des aliments
AI	Adequate Intake
ApoER2	Apolipoprotein E receptor 2
AR	Average Requirement
BMI	Body mass index
CI	Confidence interval
COMA	Committee on Medical Aspects of Food Policy
CV	Coefficient of variation
D-A-CH	Deutschland- Austria- Confoederatio Helvetica
DH	UK Department of Health
DIO	Iodothyronine deiodinase
DRV	Dietary Reference Value
EAR	Estimated Average Requirement
EC	European Commission
EFSA	European Food Safety Authority
ELISA	Enzyme-linked immunosorbent assay
EM	Excretory metabolites
EU	European Union
EVA	Epidemiology of Vascular Ageing study
FAO	Food and Agriculture Organization
FFQ	Food Frequency Questionnaire
GPx	Glutathione peroxidase
HR	Hazard ratio
I^2	Heterogeneity index
IOM	U.S. Institute of Medicine of the National Academy of Sciences
LOD	Limit of detection

LTI	Lowest Threshold Intake
mRNA	Messenger ribonucleic acid
n.a.	Not available
NDA	Panel on Dietetic Products, Nutrition and Allergies
NHANES III	US Third National Health and Nutrition Examination Survey
NNR	Nordic Nutrition Recommendations
NOAEL	No-Observed-Adverse-Effect-Level
NPC	Nutritional Prevention of Cancer
RDA	Recommended Dietary Allowance
RCT	Randomised controlled trial
RNI	Reference Nutrient Intake
RR	Risk ratio
SCF	Scientific Committee for Food
SACN	UK Scientific Advisory Committee on Nutrition
SD	Standard deviation
SECIS	Selenocysteine insertion sequences
SELECT	Selenium and Vitamin E Cancer Prevention Trial
SEPP1	Selenoprotein P
SNP	Single nucleotide polymorphism
T3	Triiodothyroxine
T4	Thyroxine
TPN	Total parenteral nutrition
tRNA	Transfer ribonucleic acid
Txnrd	Thioredoxin reductase
UGA	Uracil-Guanine-Adenine codon
UK	United Kingdom

UL	Tolerable Upper Intake Level
UNU	United Nations University
US	United States
WHAS	Women's Health and Aging Study
WHO	World Health Organization

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