SCIENTIFIC OPINION

Scientific Opinion on Dietary Reference Values for iodine[1]

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

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ABSTRACT

Following a request from the European Commission, the Panel on Dietetic Products, Nutrition and Allergies (NDA) derived Dietary Reference Values (DRVs) for iodine, which are provided as Adequate Intake (AI). Iodine is essential for the synthesis of thyroid hormones. Through these hormones, iodine has an important role in energy-yielding metabolism and many other physiological processes. Iodine deficiency is associated with an increased frequency of goitre and hypothyroidism in a population. The AI for iodine is based on a large epidemiological study in European school-aged children showing that goitre prevalence is lowest for a urinary iodine concentration above around 100 µg/L. From this study, a urinary iodine concentration of ≥ 100 µg/L has been accepted as the threshold indicating sufficient iodine intake of school-aged children. In the absence of similar suitable data for other age groups it is proposed that this threshold also be applied for adults, infants and young children. Taking into account urinary volume and an absorption efficiency for iodine of 92 %, an AI of 150 µg/day is proposed for adults. For infants aged 7–11 months and for children, AIs range between 70 µg/day and 130 µg/day. For pregnant women, an AI of 200 µg/day is proposed, taking into account additional needs due to increased maternal thyroid hormone production and the iodine uptake by the fetus, placenta and amniotic fluid. The proposed AI for lactating women of 200 µg/day takes into account the existence of large iodine stores in conditions of adequate iodine status before pregnancy and considers that a full compensation for the iodine secreted in breast milk is not justified for the derivation of an AI for iodine for lactating women.

KEY WORDS

iodine, goitre, Adequate Intake, Dietary Reference Value

SUMMARY

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

Iodine is an essential nutrient for mammals, required as a mandatory structural and functional element of thyroid hormones. Through these hormones, iodine has an important role in energy-yielding metabolism and on the expression of genes that impact many physiological functions, including embryogenesis and growth, and the development of neurological and cognitive functions.

The clinical effects of iodine deficiency, referred to as iodine deficiency disorders, are the result of insufficient intakes leading to insufficient thyroid function. Iodine deficiency disorders are seen at all stages of development and are particularly of concern in pregnancy and infancy. Chronic iodine deficiency may lead to compensatory thyroid hypertrophy with an enlargement of the thyroid gland denoted as goitre.

Intestinal absorption efficiency of ingested iodine is considered to be high (> 90 %). The thyroid is the major storage site for iodine in the body. Goitrogenous substances in foods, drinking water or cigarette smoke may inhibit the thyroidal uptake of iodide or its incorporation into the tyrosine precursors of thyroid hormones. The synthesis of normal quantities of thyroid hormones requires an adequate dietary intake of iodine. The kidney is the main route of excretion of iodine. In a steady state, the urinary iodine (UI) excretion represents more than 90 % of the dietary intake and is therefore a good indicator of recent iodine intakes. UI concentration has also been used to define the iodine status of a population. Concentrations of thyroglobulin, thyroid hormone T4 (thyroxine or 3,5,3′,5′-tetraiodothyronine) and thyroid-stimulating hormone in serum are also considered useful biomarkers of iodine status depending on age and population group and their iodine status. Thyroid volume and goitre prevalence are useful long-term clinical indicators of iodine status.

Iodine occurs in food and water mainly as iodide. The iodine concentration of water and foods is highly variable. The richest iodine sources are marine products, eggs, milk, and food products derived from them, and iodised salt. Dietary assessment methods do not accurately quantify habitual iodine intakes.

Studies of iodine balance have provided highly variable results, with null balances observed at very different levels of intakes. In addition, balance studies performed in countries with a higher habitual iodine intake compared with most European countries are difficult to extrapolate to the European context. The same is true for results on iodine accumulation by the thyroid. Insufficient evidence is available to determine iodine requirements by a factorial approach taking into account iodine needs for hormone production and iodine storage in the thyroid as well as basal iodine losses in urine, faeces and sweat.

Health outcomes such as cognitive function in children, cancer and sub-clinical thyroid dysfunction in older adults were also considered but were found not to be suitable for deriving DRVs for iodine.

For the setting of DRVs for iodine it was considered that the prevalence of thyroid volume enlargement in a population can be used to define a threshold of UI excretion and UI concentration above which the prevalence of abnormal increases of thyroid volume is minimised. This threshold is based on observational studies of goitre prevalence in Central America in the 1960s and in European school-aged children. In the latter study, a prevalence of goitre below 5 % was almost systematically observed in all study areas when the UI concentration was above 100 µg/L. Even though this threshold has been established in school-aged children, the Panel also accepted it for adults. A UI concentration of 100 µg/L corresponds to an approximate iodine intake of 150 µg/day in adults. It was concluded that an Adequate Intake (AI) for iodine for adult men and women can be set at 150 µg/day. Accepting the threshold for UI concentration of 100 µg/L also for infants aged 7–11 months and for children and

taking into account age-specific urinary volumes and body weights, AIs of 70 µg/day to 130 µg/day were derived.

For pregnant women, T4 production is estimated to be increased by a mean of 37 µg/day, corresponding to an additional iodine demand of 25 µg/day for hormone synthesis in the thyroid. The additional requirements due to the development of the fetus, placenta and amniotic fluid were considered very low when related to the whole pregnancy (equivalent to a net transfer of 1 µg iodine/day). Adding to this requirement the iodine needed for fetal synthesis of thyroid hormones, the total additional iodine reqirement is rounded to 50 µg/day. Provided that thyroid status and iodine stores before pregnancy are adequate, an AI of 200 µg/day is proposed for pregnant women. The Panel considered that the information available on the relationship between iodine intake or status of pregnant women and clinical outcomes, such as maternal thyroid function, infants being born small for gestational age or infants' neurobehavioural impairment, cannot be used for setting DRVs for pregnant women.

The Panel noted that iodine concentrations in breast milk of European women vary widely and that large iodine stores exist in conditions of adequate iodine status before pregnancy and lactation. The Panel therefore considered that a full compensation for the iodine secreted in breast milk may not be justified for the derivation of DRVs for iodine for lactating women. Therefore, for lactating women the same AI is proposed as for pregnant women, i.e. 200 µg/day.

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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 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;

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

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[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.

- 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

Iodine is an essential nutrient for mammals, required as a mandatory structural and functional element of thyroid hormones. Through these hormones, iodine has an important role in energy-yielding metabolism and on the expression of genes that impact many physiological functions, including embryogenesis and growth, and the development of neurological and cognitive functions. Iodine deficiency remains a major public health concern in many countries, including some European countries (WHO/UNICEF, 2007a; Zimmermann and Andersson, 2011).

In 1993, the Scientific Committee for Food (SCF) derived for iodine a Lowest Threshold Intake (LTI), an Average Requirement (AR) and a Population Reference Intake (PRI) for adults and PRIs for infants, children and pregnant and lactating women (see Section 4).

2. Definition/category

2.1. Chemistry

Iodine is a halogen with an atomic mass of 126.9 Da. It exists in the oxidation states -1 (I^- anion or iodide) to $+7$ (IO_4^- anion or periodate). Iodides and iodates (IO_3^- anion, oxidation state $+5$) occur ubiquitously in igneous rocks and soils, are liberated by weathering and erosion, and leach by rainwater into surface water and the sea. In many areas of the world, the surface soil becomes progressively poorer in iodine through these leaching processes (SCF, 2002). Liberated elemental iodine evaporates into the atmosphere and is precipitated by rainfall onto the land surface. The iodides in the sea accumulate in marine organisms, whereas, on land, small amounts of iodine are taken up by plants that are subsequently ingested by herbivores. Of the known isotopes of iodine, only one is stable (^{127}I).

In this Opinion, the term iodine is used in a generic way when the precise nature of the chemical species of iodine is either not known/specified or not relevant.

2.2. Functions of iodine

2.2.1. Biological functions

Iodine is an obligatory constituent of thyroid hormones. The biological function of the thyroid hormones T4 (thyroxine or 3,5,3′,5′-tetraiodothyronine) and T3 (3,5,3′-triiodothyronine) encompasses the regulation of mitochondrial energy metabolism as well as cellular oxidation, thermoregulation, intermediate metabolism, carbohydrate, lipid and protein metabolism and nitrogen retention. They are particularly necessary during early growth, development and maturation of most organs (SCF, 2002). The target organs are, in particular, the developing brain, affecting the development of hearing and vision (Morreale de Escobar et al., 2004; Williams, 2008), muscles, the heart (Kahaly and Dillmann, 2005), the pituitary gland and the kidney, but also the reproductive system (Krassas et al., 2010) and the bones.

The biological actions of thyroid hormones are considered as genomic through binding to T3 nuclear receptors or as non-genomic through binding of T3 to plasma membrane receptors or cytoplasmic proteins (Cheng et al., 2010).

2.2.2. Health consequences of deficiency and excess

According to their thyroid function, individuals are classified as euthyroid (i.e. having normal thyroid function), hypothyroid or hyperthyroid. Various mechanisms can lead to thyroid disorders, and hypo- and hyperthyroid status can be observed in cases of both insufficient and excessive iodine intakes.

2.2.2.1. Iodine deficiency disorders

The clinical effects of iodine deficiency, referred to as iodine deficiency disorders (IDD), are the result of insufficient intakes leading to insufficient thyroid function (hypothyroidism). The latter can also be induced by thyroiditis and exposure to antithyroid compounds.

IDD are seen at all stages of development and are particularly of concern in pregnancy and infancy because of the risk of developmental brain damage (WHO/UNICEF/ICCIDD, 1996; WHO, 2004; WHO/UNICEF, 2007b; Zimmermann, 2009; Bougma et al., 2013). On a population level, iodine intake can be assessed by measuring UI concentration and the following criteria based on UI concentration in school-aged children have been suggested: median UI < 20 µg/L, insufficient iodine intake and severe iodine deficiency; median UI 20-49 µg/L, insufficient intake and moderate iodine deficiency; median UI 50-99 µg/L, insufficient intake and mild iodine deficiency; median UI 100-199 µg/L, adequate iodine intake (WHO, 2004). This mode of evaluating iodine deficiency has been questioned because of insufficient proof that the iodine concentration in spot urine samples allows precise estimation of daily UI excretion (Andersen et al., 2008b). In 2011, it was estimated that 44 % of the population in Europe, i.e. 393 million inhabitants, had insufficient iodine intakes as evidenced by a UI concentration < 100 µg/L (Andersson et al., 2012). In addition, it was estimated that the prevalence of insufficient iodine intakes in European school-aged children has been reduced by about 30 % since 2003 but that insufficient iodine intakes remain a public health problem in 14 European countries (Zimmermann and Andersson, 2011).

Chronic iodine deficiency may lead to compensatory thyroid hypertrophy/hyperplasia with goitre (enlarged thyroid gland). Goitre is initially diffuse but later may become nodular with the appearance of autonomous nodules, which may subsequently cause hyperthyroidism. Goitre also increases the risk of thyroid cancer. A large goitre may cause obstruction of the trachea and the oesophagus. Mild iodine deficiency is associated with goitre in 5–20 % of school children in the world (WHO/UNICEF/ICCIDD, 2007), appearing more frequently in girls. According to WHO, the severity of iodine deficiency can be evaluated by assessing the prevalence of goitre (i.e. number with goitres of grades 1 and 2 divided by total number examined) in school-aged children: if the proportion of total goitre is less than 5 %, it corresponds to iodine sufficiency within the population: 5.0 – 19.9 % refers to mild deficiency; 20.0 – 29.9 % refers to moderate deficiency; whereas a proportion of goitre above 30 % indicates severe iodine deficiency (WHO/UNICEF/ICCIDD, 2007). However, goitre prevalence shows a slow adaptation to long-term changes in iodine intake (WHO, 2004). In 2003, 16 % of the European population had goitre (WHO/UNICEF, 2007a).

Hypothyroidism (myxoedema), observed with severe IDD, also results from hormone deficiency and is associated with reduced metabolic rate, cold intolerance, weight gain, puffy face, oedema, hoarse voice and mental sluggishness.

Maternal iodine deficiency during pregnancy results in fetal iodine deficiency. It is accompanied by higher rates of stillbirths, abortions and congenital abnormalities. It constitutes a threat to early brain development with consequent physical and mental retardation and lower cognitive and motor performance in later life (Zimmermann, 2012).

In areas with severe iodine deficiency cretinism, i.e. a condition of severely stunted growth and retarded physical and mental development owing to untreated congenital deficiency of thyroid hormones, may be endemic. The most common neurological type of cretinism is characterised by cognitive impairment, deaf mutism and spastic diplegia; the less common myxoedematous type is characterised by apathy, hypothyroidism, puffy features, growth retardation, delayed bone maturation, retarded sexual maturation and dwarfism (Delange, 1994; Chen and Hetzel, 2010; Skeaff, 2011; Zimmermann, 2012).

2.2.2.2. Iodine excess

Chronic excessive iodine supply can also lead to goitre, as has, for example, been observed following chronic excessive iodine intakes through water in China (Zhao et al., 2000). Long-term follow-up suggests that chronic excessive iodine intakes may accelerate the development of sub-clinical thyroid disorders to overt hypothyroidism or hyperthyroidism, increase the incidence of autoimmune thyroiditis and increase the risk of thyroid cancer (Laurberg et al., 1998; Teng et al., 2006).

The SCF (2002) adopted the value of 600 µg/day as a Tolerable Upper Intake Level (UL) for adults including pregnant and lactating women (i.e. approximately half of the value of 1 100 µg/day adopted by IOM (2001)), on the basis of dose-response studies of short duration (two weeks) and in a small number of subjects (n = 10–32). For iodine intakes of about 1 700–1 800 µg/day, the studies showed an increased response of thyroid-stimulating hormone (TSH) concentrations to thyrotropin-releasing hormone (TRH) provided intravenously (Gardner et al., 1988; Paul et al., 1988), but these changes were considered marginal and not associated with any clinical adverse effects. A study by Stockton and Thomas (1978) covering a five-year exposure to approximately similar iodine intakes in which no clinical thyroid pathology occurred was also considered, and an uncertainty factor of 3 was selected to derive the UL for adults. The ULs for children were derived by adjustment of the adult UL on the basis of metabolic weight (body weight$^{0.75}$).

2.3. Physiology and metabolism

2.3.1. Intestinal absorption

Ingested iodine in forms other than iodide is reduced to iodide in the gut. Iodide is almost completely absorbed by the small intestine, whereas the absorption and metabolism of iodised oils is not entirely known. The absorption efficiency of oral inorganic iodide and T3 is > 90 %; that of oral T4 is around 70–80 % (Fish et al., 1987; Hays, 1991).

Iodide absorption is reduced in the presence of humic acids in drinking water (Gaitan, 1990), and of thiocyanates, isothiocyanates, nitrates, fluorides, calcium, magnesium and iron in food and water (Ubom, 1991). IOM (2001) considered an absorption efficiency of 92 %; the few papers published thereafter are consistent with this conclusion (Jahreis et al., 2001; Aquaron et al., 2002).

The Na/I symporter is present in brush border membranes and mediates active iodine accumulation. Genetic expression of the symporter is down-regulated by iodide (Nicola et al., 2009).

2.3.2. Transport in blood

In blood, inorganic iodide and organic iodine are found. Total plasma iodine concentrations (inorganic and organic iodine) in euthyroid subjects range from 40 to about 80 µg/L (Allain et al., 1993; Michalke et al., 2000). Concentrations between 80 and 250 µg/L are generally associated with hyperthyroidism, whereas concentrations above 250 µg/L generally result from iodine overload with iodinated drugs.

Most organic iodine is present as T4, which accounts for more than 10 times the iodine content of T3, reverse T3 (rT3), mono-iodotyrosine (MIT) and di-iodotyrosine (DIT) (Michalke et al., 2000). T4 occurs either free (fT4) or bound to proteins, mainly to thyroxine-binding globulin (TBG) and to a lower extent to transthyretin (TTR or pre-albumin) and albumin. Less than 1 % of T3 and T4 is free in plasma (see Section 2.4.2.2).

The concentration of plasma inorganic iodide is proportional to dietary intake and ranges from 2 to 6 µg/L for usual intakes below 200 µg/day (Vought and London, 1965).

2.3.3. Distribution to tissues

Plasma iodide is actively taken up through the basal membrane of the thyroidal follicular cells using the Na/I symporter (Dohan and Carrasco, 2003; Bizhanova and Kopp, 2009) and concentrated 20–50 times in these cells. It is then transferred to the follicle lumen at the apical membrane by pendrin and possibly by an additional human apical iodine transporter (Twyffels et al., 2011).

The activity of the Na/I symporter is sensitive to inhibition by the contaminants perchlorate, thiocyanates, isothiocyanates and nitrates, to an extent which might be relevant at the population level when iodine intake is low (FAO/WHO, 2011; Mendez and Eftim, 2012).

Thiocyanate is abundant in cigarette smoke and exerts goitrogenic effects by competitively inhibiting iodine transport and organification (Colzani et al., 1998; Knudsen et al., 2002). Other goitrogens present in foods that inhibit the thyroidal uptake of iodide are cyanoglycosides (liberating cyanide upon enzymatic hydrolysis in the gut, which is subsequently metabolised to thiocyanate) and glucosinolates (goitrogenic thioetherglycosides yielding upon hydrolysis, among others, the aglycones isothiocyanate, nitriles or thiocyanate). Clinical consequences of intake of goitrogens are more easily observed in iodine deficiency.

Extrarenal clearance of iodide is assumed to represent thyroid clearance, corresponding to the capture of iodine by the thyroid gland. It is in the range of 3–40 mL of serum/minute in euthyroid subjects (McConahey et al., 1951; Berson et al., 1952), which corresponds to a capture by the thyroid of an average of 33 % (range 12–68 %) of the administered dose. There is an inverse relationship between thyroid uptake and dietary iodine intake or urinary excretion (McConahey et al., 1951; Berson et al., 1952; Fisher and Oddie, 1969b). The percentage of capture by the thyroid can change within 12–14 weeks, and sometimes faster, in response to changes in iodine intake in euthyroid subjects (Fisher and Oddie, 1969b).

Other tissue sites for iodide uptake from plasma are the salivary glands, the choroid plexus, the mammary gland, the kidneys and the gastric mucosa. Within the range of usual intakes, iodine flux in saliva is up to 10 µg/hour, depending on the level of intake (Vought and London, 1965).

2.3.4. Storage

In adults with adequate iodine status, average total body iodine amounts to about 10–20 mg, of which 70–80 % is found in the thyroid containing, on average, 8–15 mg of iodine. In Germany, a mean thyroid iodine content of 10 mg was found in thyroid glands of 20 euthyroid subjects at autopsy (Reinwein et al., 1981). A study using X-ray fluorescence in 37 subjects aged 60–65 years who had lived in an area of adequate iodine supply throughout their lives (average UI concentration 210 ± 50 µg/L) indicated that a wide variation in thyroid iodine content from 0.9 to 20.2 mg (mean 5.2 mg) is compatible with euthyroidism (Milakovic et al., 2006). These figures for thyroid iodine content are similar to thyroid iodine contents of 2–16 mg observed in Belgium (Jonckheer, 1987).

The thyroid iodine content at birth is around 100–300 µg and increases progressively to around 0.8–1 mg at four to six years (Widdowson and Spray, 1951).

2.3.5. Metabolism

In the thyroid, the follicular cells synthesise intracellularly the glycoprotein thyroglobulin (Tg), which is then transferred to and stored in the colloidal follicle lumen. At the cell-colloid interface, iodide is oxidised and attached to the phenyl ring of Tg tyrosyl residues. This so-called organification is catalysed by thyroid peroxidase (TPO), an iron-containing enzyme, and results in the formation of MIT and DIT. Further action of TPO leads to the coupling of two DIT to give T4 or of MIT and DIT to give T3. All these iodothyronines remain attached to the Tg. About one-third of the iodine present is in the form of T3 and T4; the rest is present as MIT and DIT. When needed, T3 and T4 are released into the circulation from Tg by endosomal and lysosomal cellular proteases. Released MIT and DIT

are deiodinated by a iodotyrosine deiodinase providing an efficient intrathyroidal recycling of iodide (Rokita et al., 2010).

Soy isoflavones inhibit TPO and goitre and hypothyroidism have been observed in infants fed entirely on soy-based infant formula low in or devoid of iodine (Doerge and Sheehan, 2002). These formulae, as is the case for all infant and follow-on formulae in the EU, are now enriched to contain 10 to 50 µg iodine/100 kcal.[6] In addition to their action on iodine uptake by the thyroid, some of these compounds block the incorporation of iodine into the tyrosine precursors of thyroid hormones and suppress T4 secretion (Doerge and Sheehan, 2002; EFSA, 2008). Water from wells containing humic substances may also block the iodination process. Goitrins, glucosinolate-derived oxazolidinethiones present in vegetables of the brassica family and some other vegetables, also inhibit TPO.

The thyroid hormone T4 contains 65 % by weight of iodine, and its active form T3 contains 59 %. The synthesis of normal quantities of thyroid hormones requires an adequate dietary intake of iodine, but excessive intakes may inhibit thyroid function either by inhibition of iodide organification (Wolff-Chaikoff effect) or by inhibition of Tg proteolysis with reduction in hormone secretion.

Thyroid function is regulated by a feedback process: in response to a decrease in circulating T3 and T4 concentrations, TRH is secreted by the hypothalamus and stimulates the secretion of thyrotropin (or TSH) by the anterior pituitary gland. Within 15 to 20 minutes, TSH stimulates the secretion of thyroid hormones and causes an increased iodide uptake by the thyroid and an increased Tg breakdown. The thyroid gland is also controlled by interaction between growth factors, their receptors and signal transduction pathways. Epidermal and insulin-like growth factors may stimulate follicular cells to synthesise Tg (Nordic Council of Ministers, 2002). Persistent action of TSH causes hypertrophy and hyperplasia of the thyroid gland, and reduces the colloid and the stored iodine. TRH secretion is also stimulated by α-noradrenergic impulses and inhibited by dopaminergic impulses. An autonomous regulation of thyroidal iodine metabolism also occurs independent of TSH (Forth et al., 1987).

T4 is produced only by the thyroid gland, whereas T3 is primarily produced by extrathyroidal deiodination of T4 in liver and kidney, brain, pituitary gland and brown fat tissue, with some (20 % in humans) deiodination taking place also in the thyroid. Removal of iodine occurs via specific iodothyronine deiodinases (Maia et al., 2011). Deiodinases show reduced activity in selenium deficiency, with consequently impaired activity of thyroid hormones (Forth et al., 1987). The deiodinases forming the active hormone T3 are inhibited by some drugs (thiouracil, propylthiouracil, propranolol and glucocorticoids).

The iodine liberated when T4 is enzymatically deiodinated to its active form T3 enters the plasma pool as iodide and is either re-used by the thyroid or excreted in the urine. T3, which is less tightly bound to proteins, enters the cells more easily.

2.3.6. Elimination

2.3.6.1. Urine

The kidney is the main route of excretion of iodine. In adults with adequate iodine intake, the excess iodine not taken up by the thyroid is excreted in the urine (more than 90 % of dietary iodine) (Vought and London, 1967; Nath et al., 1992), with partial reabsorption occurring in the renal tubules. The renal iodide clearance is 30–36 mL/minute in euthyroid subjects and is significantly decreased either in impaired renal function or in myxoedema (McConahey et al., 1951; Berson et al., 1952). In comparison with habitual fluid intakes, an increase in fluid volume intake can lead to additional iodine losses: for an increase in urinary volume of one litre, additional iodine losses of around 15 µg/day were predicted for adolescents and adult women, respectively (Johner et al., 2010).

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[6] 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.

On an individual basis, daily iodine excretion is variable from day to day in line with variable daily intake (Vought and London, 1964; Rasmussen et al., 2001) (see Section 5.1). For populations or population groups, UI excretion as a marker of usual intake and status requires some time to reach a steady state when the usual intake is modified. In iodine-replete subjects (UI concentration > 100 µg/L according to WHO), it takes one to two weeks for UI concentrations to reflect an increase in usual iodine intake (for a supplemental intake of 250–1 500 µg/day) and to reach null balance (Paul et al., 1988). In contrast, in infants and young children (six months to three years) living in a mildly iodine-deficient area (median UI concentration 50–99 µg/L) and receiving supplemental iodine (90 µg/day five times per week), UI progressively increased, and up to 30 weeks were needed for the stabilisation of UI concentrations at around 210 µg/L (Delange et al., 2001). In adults with goitre (average UI concentration 35 µg/L), it took nine months for UI to reflect an increased iodine intake via supplements (200 µg/day) and to reach null balance (Kahaly et al., 1997); for a higher dose of 500 µg/day it took six months until null balance was reached (Kahaly et al., 1998).

2.3.6.2. Faeces

The amount of iodine measured in faeces varies, with most values being between 10 and 30 µg/day (Vought and London, 1964). A part of faecal iodine consists of thyroid hormones metabolised in the liver to glucuronide or sulphate conjugates that are excreted in the bile (enterohepatic circulation) (Wu et al., 2005).

2.3.6.3. Sweat

Early studies were in disagreement about the extent of iodine losses via sweat (Cole and Curtis, 1935; Spector et al., 1945; Harden and Alexander, 1963). Spector et al. (1945) found an iodine concentration in sweat of around 9.5 µg/L, which increased to 31.8 µg/L after a single dose of 2 mg potassium iodide, whereas Harden and Alexander (1963) concluded that iodine elimination in sweat was negligible (average 1.67 µg/L).

More recent studies confirmed that profuse sweating may result in significant iodine losses. A one-hour soccer game induced a mean iodine loss of around 50 µg (Mao et al., 2001). Despite some adaptation by a decrease in urinary excretion, profuse sweating (induced by exercise or warm environment) may lead, in the long run, to a depletion of iodine stores (Smyth and Duntas, 2005). Compared with UI concentrations, iodine concentrations in sweat appeared to be relatively constant, i.e. from 24.9 to 46.5 µg/L, compared with a range from 8.7 to 110.4 µg/L in urine of the same subjects (Mao et al., 2001). In a hot environment, total body iodine losses with sweat can reach an average of 150 µg/day (Consolazio et al., 1966), the flux ranging from 4.3 µg/hour during sleep at 33 °C to 13 µg/hour at 38.5 °C and 35 % relative humidity. Suzuki and Tamura (1985) and Mao et al. (1990; 2001) reported a value of 37 µg/L. Overall, iodine sweat concentrations appear to be relatively constant at around 35–40 µg/L over a large range of iodine intakes (UI concentration from 8 to 280 µg/L) and in various climatic conditions, meaning that, in contrast to urinary excretion, iodine losses via sweat are mostly determined by the volume of sweat produced.

2.3.6.4. Breast milk

The expression of the Na/I symporter is up-regulated in the lactating mammary gland allowing a preferential uptake of iodine and thereafter secretion in breast milk, with the concentration in milk being 20 to 50 times higher than in plasma (Azizi and Smyth, 2009). More than 80 % of iodine is in the form of inorganic iodide, whereas T4 is < 2 µg/L and T3 is < 0.05 µg/L.

In iodine sufficiency, average breast milk iodine concentrations may be up to 150–180 µg/L (Semba and Delange, 2001; Dorea, 2002). Azizi and Smyth (2009) reported a moderate (r = 0.40) linear relationship between breast milk iodine concentration and UI concentration ranging from 50–400 µg/L. Andersen et al. (2014) also found only a moderate (r = 0.28, p < 0.015) linear relationship between UI concentration and breast milk iodine concentration; the relationship was stronger (r = 0.48, p < 0.001) when UI concentration was adjusted by urinary creatinine (to account for differences in

fluid intake) and expressed as 24-hour UI excretion and 24-hour breast milk iodine excretion. In Korean women, a strong linear relationship was observed between maternal iodine intake (range 61–3 813 µg/day as estimated by 24-hour recalls and measurement of iodine in foods consumed) and the iodine concentration of mature breast milk (range 60–3 838 µg/L) (r = 0.82, p < 0.0001) (Moon and Kim, 1999). A high intra- and interindividual variability (25–87 % and around 90 %, respectively) in iodine concentration of breast milk has been reported (Kirk et al., 2007).

In colostrum, iodine concentrations ranging from 200–400 µg/L have been reported (Semba and Delange, 2001), which provides the iodine for the peak T4 production that takes place in the newborn some hours after birth. Thereafter, iodine concentration in breast milk decreases (Costeira et al., 2009).

Iodine concentrations in breast milk of mothers of term infants in Europe are shown in Appendix A. However, most of the reported values are difficult to interpret, because sample sizes were small and not representative and information as to maternal intake of iodine supplements or smoking status is often lacking. There is a large overlap of breast milk iodine concentrations between countries classified as iodine-sufficient and iodine-deficient (Zimmermann, 2007). The SCF considered that the iodine concentration of breast milk in Europe varies between 10 and 300 µg/L; assuming an average iodine concentration of 75 µg/L and a breast milk secretion of 0.8 L/day, a mean iodine loss of 60 µg/day was calculated (SCF, 2003).

Thiocyanate is known to inhibit the function of the Na/I symporter (see Section 2.3.3). In smoking Danish women who had similar UI concentrations but significantly higher serum thiocyanate concentrations than non-smoking women, milk iodine concentration on day five after delivery was only half that of non-smoking women (26 vs. 54 µg/L) (Laurberg et al., 2004).

2.3.7. Modifications of iodine metabolism during pregnancy

Adaptations of iodine metabolism during pregnancy include stimulation of the TSH receptor by chorionic gonadotropin (Yoshimura and Hershman, 1995), which is associated with a decrease in TSH (Glinoer, 1997); reduced hepatic clearance of T4-binding globulin Tg because of higher sialylation (preventing binding and internalisation through the hepatic asialoglycoprotein receptor) induced by high oestrogen concentrations (Ain et al., 1987); increase of the peripheral metabolism of thyroid hormones (placental de-iodination of T4 to the inactive reverse T3 form) (Roti et al., 1981); increased renal clearance of iodine by 30–50 % (Glinoer, 2007) with a fast return to pre-pregnant values after delivery (Dafnis and Sabatini, 1992; Smyth et al., 1997); and transfer to the fetus of a not yet well-defined amount of iodine and thyroid hormones (Glinoer, 2001, 2007; Patel et al., 2011). During gestation, maternal thyroid size slightly increases in iodine-deficient areas, whereas it remains constant in areas adequate for iodine (Berghout and Wiersinga, 1998). The Panel notes that more recent studies indicate that thyroid enlargement can also be observed in areas of adequate iodine intake (Fister et al., 2009), that at least a part of this increase could be linked to haemodynamic changes and that the increase is rapidly reversed, being no longer apparent four months after delivery. The extra demand for iodine might explain the decrease in UI concentration with the progression of gestation in areas of mild iodine deficiency (Stilwell et al., 2008). However, studies in pregnant women living in iodine-deficient or iodine-adequate areas produced conflicting results (Caron et al., 1997; Smyth et al., 1997; Elnagar et al., 1998; Smyth, 1999; Kung et al., 2000; Ainy et al., 2007; Alvarez-Pedrerol et al., 2009; Fumarola et al., 2009; Andersson et al., 2010).

In general, serum T4 increases, whereas free T4 decreases progressively and, at least in iodine-sufficient regions, serum iodide concentrations are not modified during pregnancy (Liberman et al., 1998). The multiple possibilities for adaptation render the picture complex: recently, in New Zealand, where there is a long history of iodine deficiency, a survey in pregnant women did not show abnormal modifications of thyroid hormones, thyroid volumes and TSH or anomalies in infant growth and development, despite a median maternal UI of around 35 µg/L (Pettigrew-Porter et al., 2011; Skeaff, 2012). In iodine-sufficient areas, thyroid hormone concentrations at the end of pregnancy are not correlated with UI concentrations (Fister et al., 2011).

The placenta transfers maternal T4 to the fetus (Patel et al., 2011). In newborns with a genetic defect of thyroid organification or thyroid agenesis, the serum concentration of T4 can be up to 35–70 nmol/L, suggesting that up to 40 % of T4 in fetal blood at term could originate from the mother (Vulsma et al., 1989).

2.3.8. Interaction with other nutrients

Iodine metabolism can be impaired by deficiencies of vitamin A, selenium, zinc, copper or iron. Owing to the importance of seleno-enzymes in thyroid hormone metabolism, the influence of selenium status has been extensively studied (Köhrle and Gärtner, 2009). These interactions are significant only when there is concomitantly a chronic high intake of goitrogens and/or a low habitual iodine intake.

The nuclear receptors for thyroid hormones belong to a superfamily together with steroid hormones, vitamin D and retinoid receptors, which may explain overlapping effects and interactions with some nutrients (Davis et al., 2011).

2.4. Biomarkers

The iodine status of an individual or a population can be assessed using various indicators, and their suitability may differ according to age and population group of interest (SCF, 2002; Ristić-Medić et al., 2009; Ristić-Medić et al., 2013).

2.4.1. Biomarkers of intake

In a steady state, UI excretion represents more than 90 % of dietary iodine intake and is therefore an excellent indicator of recent iodine intake. UI is preferably determined in 24-hour samples and can be expressed as 24-hour excretion (µg/day), as a concentration (µg/L), or in relationship to creatinine excretion (µg iodine/g creatinine) (Laurberg et al., 2007). Owing to the difficulty of 24-hour urine collections in a large number of people, urine spot samples are preferred at the population level and the median value is used to characterise the iodine status of a population (WHO/UNICEF, 2007a). At the individual level, 10 repeated collections of spot or 24-hour urinary samples are needed to assess iodine status with a 20 % precision (Andersen et al., 2008b). Introducing the 24-hour urine volume in an equation and also taking into account the absorption efficiency of dietary iodine, the iodine intake corresponding to a UI concentration can be calculated (IOM, 2001). In adult populations, a median UI concentration of 100 µg/L corresponds to an iodine intake of 150 µg/day (WHO/FAO, 2004).

2.4.2. Biomarkers of status

2.4.2.1. Urinary iodine concentration

UI concentration is usually used as an indicator of usual iodine intake, but has also been used to define the iodine status of a population. WHO/UNICEF/ICCIDD (2007) adopted thresholds of median UI concentrations to define the iodine status of a population. In addition to the classification of insufficient iodine intakes mentioned in Section 2.2.2.1, a UI concentration of 200–299 µg/L was considered likely adequate for pregnant/lactating women but possibly to indicate a slight risk of excess for other groups, and a UI concentration of ≥ 300 µg/L was considered to reflect excessive iodine intake with risk of adverse health consequences (iodine-induced hyperthyroidism, autoimmune thyroid diseases).

2.4.2.2. Serum concentration of thyroid hormones

All hormone determinations assess in the first place thyroid function, and only secondarily iodine status.

Although serum TSH is a suitable biomarker of thyroid function, it may sometimes be used as an indirect marker of iodine status. The normal serum TSH range is 0.1–5 mU/L, but a concentration of 1.0 to 1.9 mU/L was associated with the lowest incidence of abnormal thyroid function during a five-year follow-up in subjects above 13 years of age at enrolment (Teng et al., 2006).

Serum Tg concentration is a useful biomarker of iodine status in children and adolescents. In iodine adequacy, the concentration of Tg is below 10 µg/L.

Serum concentrations of T4 and T3 are less sensitive for assessing iodine status, except for T4 in pregnancy. The normal serum concentrations are around 100 nmol/L (80 µg/L) for total T4 and around 1.8 nmol/L (1.2 µg/L) for total T3; concentrations of the free forms are in the ranges 11–18 pmol/L and 3.5–5 pmol/L, respectively.

2.4.2.3.   Thyroid volume

Goitre prevalence and thyroid volume are useful long-term clinical indicators of iodine status. In adults, chronic iodine deficiency causes hypothyroidism and, in the case of severe deficiency, up-regulation of thyroid iodine utilisation (iodide autoregulation), with an increase in uptake and many other processes including H_2O_2 generation. Secondary to these changes, goitre and multinodularity tend to develop, and many elderly people will develop multinodular goitre, because of increased concentrations of TSH, leading to hyperplasia of the thyroid.

Thyroid volume is best determined from ultrasound measurements rather than by palpation which is less sensitive in the case of mild or moderate iodine deficiency. A thyroid volume exceeding 18 mL in adult women and 25 mL in adult men is considered to represent a goitre (Gutekunst et al., 1988). However, this generic health outcome can be measured and expressed in different ways at the population level. Thyroid size can be determined by palpation and expressed in percentages of the different stages at population level (from 0 (no goitre) to 2); thyroid volume can be given as mL, determined by thyroid ultrasonography. The results can also be expressed as the epidemiological prevalence of abnormal thyroid volume, such as the "total goitre rate" (WHO/UNICEF/ICCIDD, 2007).

2.5.   Effects of genotype

Although mutations in proteins involved in iodine metabolism have been described and induce various forms of thyroid diseases, there are few known polymorphisms related to iodine and thyroid hormone metabolism. Genotype differences that predict differences in requirements have not yet been identified as being important at the population level (Ristić-Medić et al., 2013).

3.   Dietary sources and intake data

3.1.   Dietary sources

Iodine occurs in food and water mainly as iodide. Iodine can also enter the food chain via sanitising solutions and iodophores, which may provide significant amounts of iodine but are difficult to control (Phillips, 1997).

The iodine concentration of water is highly variable (e.g. from 2–140 µg/L in tap water in Denmark; from 0.2–15.5 µg/L (median 2.6 µg/L) and decreasing from north to south in 26 regions of Germany (Bittermann, 1999)). Iodine absorption efficiency from water is influenced by the content and nature of humic substances in water (Andersen et al., 2008a).

Sodium iodide, sodium iodate, potassium iodide and potassium iodate may be added to foods and food supplements.[7] Iodine readily binds to double bonds in fatty acids, allowing the preparation of iodised oils that are used for supplementation outside the EU (EFSA ANS Panel, 2013).

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[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; 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.

The iodine content of foods is highly variable between food categories as well as within each category. The richest sources are marine products (such as fish, shellfish, molluscs, seaweed), eggs and milk, as well as their derivatives and iodised salt. Iodine content of milk and eggs is influenced by feeding and hygienic practices (EFSA, 2005; Flachowsky et al., 2014). According to WHO/UNICEF (2007a), iodine fortification of salt has been implemented in 40 European countries, being mandatory in 13 countries, voluntary in 16 and not regulated in the remaining countries; the amount of iodine added varies from 10–75 mg/kg salt with a majority of values in the range 15–30 mg/kg. The iodine content of certain foods for healthy people is regulated, for example of infant and follow-on formulae.[8]

3.2. Dietary intake

"Classical" dietary assessment methods do not accurately quantify habitual iodine intakes. Food frequency questionnaires targeted and validated for iodine intake can be used (Rasmussen et al., 2001; Combet and Lean, 2014), as well as simulation and modelling methods (Verkaik-Kloosterman et al., 2009), which improve the correlation of intake with UI excretion. The lack of accuracy in measuring iodine intake from iodised salt is a major limitation of dietary assessment. In addition, the quality of iodine data in food composition tables is often poor, and depends on whether the food iodine analysis is up-to-date and to what extent natural variability in iodine content is taken into account. Food composition databases contain information on the salt content of foods, but they rarely specify if the salt used in processed foods is iodised or not. Because of these limitations, UI excretion as a valuable marker of iodine intake (see Section 2.4.1) is listed for various European countries in Appendix B.

4. Overview of Dietary Reference Values and recommendations

4.1. Adults

Because of insufficient iodine intake in some regions and for some life stages in Germany and Austria, and considering influencing factors such as iodine content in food or drinking water, the German-speaking countries (D-A-CH, 2013) decided to retain the previous recommended value of 200 µg/day for adults for these countries, but chose for Switzerland the value recommended by WHO/UNICEF/ICCIDD (1996) of 150 µg/day, considering the Swiss programme of salt fortification with iodine that has been in place for decades and the consequently better iodine status in this country. For Germany and Austria, but not for Switzerland, recommended intakes differ according to age, being 200 µg/day for adults below 51 years of age and 180 µg/day from 51 years onwards.

The World Health Organization/Food and Agriculture Organization (WHO/FAO, 2004) considered that, in adults and adolescents (13 years and over) with adequate intakes of iodine, most dietary iodine finally appears in the urine (Stanbury, 1960; Delange, 1994). Median UI concentrations below 100 µg/L were associated with increases in median thyroid size and possibly in serum TSH and Tg concentrations. WHO/FAO described data investigating the relationship between UI concentration and thyroid size (Delange et al., 1997), or serum TSH and Tg concentrations (Moulopoulos et al., 1988; Buchinger et al., 1997), or goitre prevalence, radioiodine uptake and thyroidal organic iodine content (Delange et al., 1993). WHO/FAO finally set a daily recommended intake of 150 µg/day (2.0 µg/kg body weight per day) for adolescents and adults of both sexes. The recommended intake corresponded to the daily UI excretion in non-endemic areas (Bottazzo, 1981; Delange, 1994), as well as the intake needed to maintain both the plasma iodide concentration above the average value (1 µg/L), which is most likely associated with the onset of goitre (Wayne et al., 1964) and the iodine stores of the thyroid above the value (10 mg) below which an insufficient iodination of Tg may lead to disorders in thyroid hormone synthesis (Delange, 1994).

The Nordic countries (NNR, 2004) estimated the AR to be 100 µg/day for both adult men and adult women. This iodine intake corresponds to a plateau of iodine concentration in the thyroid gland and to

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[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.

iodine turnover in euthyroid subjects (IOM, 2001). The recommended intake was derived as 150 µg/day and included a safety margin for any goitrogenic substances in foods. The lower level of intake in adults was set at 70 µg/day for both sexes. In the 2012 update, the Nordic countries did not change the previous recommendations for adults, since there were no new data supporting changes (Nordic Council of Ministers, 2014).

The US Institute of Medicine (IOM, 2001) used evidence on thyroidal radioiodine accumulation to estimate the average requirement of iodine. IOM considered studies investigating iodine turnover in euthyroid adults (DeGroot, 1966; Fisher and Oddie, 1969a, 1969b), a study investigating the basal amount of excreted iodine (Vought and London, 1967), balance studies (Dworkin et al., 1966; Harrison, 1968) as well as other data (Delange et al., 1993; Dunn et al., 1998). IOM also stated that there was no evidence to suggest that the average iodine requirement was altered with ageing, or differed according to sex in adults, and no reason to adjust recommended values for smaller body weight in women. IOM therefore set an Estimated Average Requirement (EAR) of about 95 µg/day for adults. A coefficient of variation (CV) of 20 % was chosen based on half of the CV of 40 % observed in the study by Fisher and Oddie (1969b), assuming that half of the variation observed in this study was a result of the complex experimental design and calculations. This CV of 20 % was added twice to the EAR to cover the needs of 97 to 98 % of the individuals in the group. Thus, the Recommended Daily Allowance (RDA) was derived as 150 µg/day (rounded value to the nearest 50 µg) for adults of all age groups and both sexes.

The SCF (1993) concluded that most adults maintain iodine balance and normal thyroid function with intakes between 40 and 100 µg/day. The SCF indicated that a plateau concentration of iodine in the thyroid was achieved at an iodine intake of 100 µg/day, and that increasing intakes to 300 or 500 µg/day had no further effect on this or on reducing the incidence of goitre. An AR of 100 µg/day and a PRI of 130 µg/day were proposed, as well as an LTI of 70 µg/day, below which there may be a risk of thyroid dysfunction or "sub-optimal operation" of the thyroid (Stanbury et al., 1974; Lamberg, 1986; Phillips et al., 1988).

The UK Committee on Medical Aspects of Food Policy (COMA) (DH, 1991) did not calculate an EAR but concluded that an intake of 70 µg/day appeared to be the minimum necessary to avoid signs of goitre in a population (Stanbury et al., 1974; Lamberg, 1986) and considered this value as a Lower Reference Nutrient Intake (LRNI). To provide a margin of safety and to allow for the possible effects of different dietary patterns, the Recommended Nutrient Intake (RNI) was set at 140 µg/day.

In the Netherlands, there are no official DRVs for iodine (Health Council of the Netherlands, 2008).

An overview of DRVs for iodine for adults is presented in Table 1.

Table 1: Overview of Dietary Reference Values for iodine for adults

	D-A-CH (2013) (Germany, Austria)	D-A-CH (2013) (Switzerland)	WHO/FAO (2004)	NNR (2012)	Afssa (2001)	IOM (2001)	SCF (1993)	DH (1991)
Age (years)	19–51	≥ 19	≥ 13	≥ 18	≥ 19	≥ 19	≥ 18	≥ 19
PRI Males (µg/day)	200	150	150 (i.e. 2.0 µg/kg per day)	150	150	150	130	140
PRI Females (µg/day)	200	150	150 (i.e. 2.0 µg/kg per day)	150	150	150	130	140
Age (years)	≥ 51							
PRI Males (µg/day)	180							
PRI Females (µg/day)	180							

4.2.   Infants and children

According to WHO/FAO (2004), the iodine concentration of human milk varies markedly according to the iodine intake of the population. Positive iodine balance was achieved only at an iodine intake of at least 15 µg/kg body weight per day in term infants (Delange et al., 1993). Based on an assumed average body weight of 6 kg for an infant of six months of age, this value corresponded to about 90 µg/day. Therefore, WHO/FAO recommended an iodine intake of 15 µg/kg body weight per day, i.e. 90 µg/day for infants, in coherence with previous recommendations of WHO/UNICEF/ICCIDD (2001). WHO/FAO also explained that high concentrations of serum TSH, indicating sub-clinical hypothyroidism with the risk of brain damage, occurred at an intake of about one-third of the recommended value, and neonatal hypothyroidism resulting in endemic cretinism occurred at an intake of about one-tenth of this value. WHO/FAO (2004) stated that the daily iodine requirement on a body weight basis decreases progressively with age. For children aged 1-5 and 6-12 years, respectively, the recommendations were 90 µg/day (6 µg/kg body weight per day) and 120 µg/day (4 µg/kg body weight per day), based on an average body weight of a 10-year-old child (25 kg), and a study by Tovar et al. (1969) correlating 24-hour thyroid radioiodine uptake and UI excretion in 9- to 13-year-old school children in rural Mexico. Recommendations for adolescents aged 13 years and older were the same as those for adults.

The Nordic countries (NNR, 2004) recommended intakes of 90 µg/day for children aged 2-5 years, 120 µg/day for children aged 6-9 years and 150 µg/day for children aged 10 years and over. The recommendations were based on data on goitre prevalence and UI excretion in European children (Delange et al., 1997) and extrapolations from adults based on energy and growth requirements. These recommendations were kept unchanged in the 2012 update, as there were no new data supporting changes (Nordic Council of Ministers, 2014).

The IOM (2001) concluded that no functional criteria of iodine status had been demonstrated to reflect response to dietary intake in infants. Thus, for infants from birth to six months of age, an AI was derived based on an estimated iodine intake in infants exclusively fed human milk. An AI of 130 µg/day for infants aged 7-12 months was derived extrapolating from the AI for younger infants. Recommended values for older children were extrapolated from adult data or derived from balance data for a specific age group. For children aged 1-3 years, a four-day balance study on children (1.5-2.5 years) previously malnourished and then nutritionally rehabilitated (Ingenbleek and Malvaux, 1974) was considered. For children aged 4-8 years, a balance study undertaken in children aged eight years (Malvaux et al., 1969) was considered. For children aged 1-8 years, an EAR of 65 µg/day was set. The RDA of 90 µg/day was derived by adding twice a CV of 20 %. For children aged 9-18 years, the EAR was extrapolated down from adults considering metabolic weight (kg$^{0.75}$): 73 µg/day for children aged 9-13 years and 95 µg/day for children aged 14-18 years. For these age ranges, IOM then derived RDA values of 120 µg/day and 150 µg/day, respectively, considering a CV of 20 % and after rounding. For children aged 9-13 years, data on the prevalence of goitre in European boys and girls aged 6-15 years (Delange et al., 1997), and its relationship with UI excretion, were also discussed.

The SCF (1993) calculated PRIs for children from adult values on the basis of energy requirements.

The UK COMA (DH, 1991) set RNIs and LRNIs for children and which were extrapolated from the adult values using EARs for energy, as extrapolating on a body weight basis would have resulted in values similar to those estimated in areas with a high incidence of goitre.

An overview of DRVs for iodine for children is presented in Table 2.

Table 2: Overview of Dietary Reference Values for iodine for children

	D-A-CH (2013) (Germany, Austria)	D-A-CH (2013) (Switzerland)	WHO/FAO (2004), WHO Secretariat et al. (2007)	NNR (2012)	IOM (2001)	Afssa (2001) [c]	SCF (1993)	DH (1991)
Age (months)	4–<12	4–<12	0–<24	6–11	7–12	6–12	6–11	7–12
PRI (µg/day)	80	50	90	50	130 [a]	90	50	60
Age (years)	1–<4	1–<4	2-5	1–<2	1–3	1–3	1–3	1–3
PRI (µg/day)	100	90	90 (i.e. 6 µg/kg per day)	70	90 [b]	80	70	70
Age (years)	4–<7	4–<7	6–12	2–5	4–8	4–6	4–6	4–6
PRI (µg/day)	120	90	120 (i.e. 4 µg/kg per day)	90	90 [b]	90	90	100
Age (years)	7–<10	7–<10	≥ 13	6–9	9–13	7–9	7–10	7–10
PRI (µg/day)	140	120	150	120	120 [b]	120	100	110
Age (years)	10–<13	10–<13		10–13	14–18	10–19	11–14	11–14
PRI (µg/day)	180	120		150	150 [b]	150	120	130
Age (years)	13–<19	13–<19		13–17			15–17	15–18
PRI (µg/day)	200	150		150			130	140

(a): Adequate Intake.
(b): Recommended Dietary Allowance.
(c): Based on values provided in the final summary table in Afssa (2001).

4.3. Pregnancy

D-A-CH (2013) considered the increased renal clearance and the increased iodine excretion in urine during pregnancy and recommended an intake of 230 µg/day for Germany and Austria and of 200 µg/day for Switzerland.

In 2004, WHO/FAO indicated that the iodine requirement during pregnancy should provide for the needs of the fetus and should compensate for the increased loss of iodine in the urine because of an increased renal clearance of iodine (Aboul-Khair et al., 1964). WHO/FAO concluded that the iodine intake required to prevent the onset of sub-clinical hypothyroidism of mother and fetus during pregnancy, and thus to prevent the possible risk of brain damage of the fetus, was approximately 200 µg/day (Roti and Vagenakis, 2000), i.e. 3.5 µg/kg body weight per day (WHO/FAO, 2004), in agreement with previous recommendations by WHO/UNICEF/ICCIDD (2001). In 2007, an expert consultation evaluated whether this amount is sufficient to prevent brain damage or thyroid function disorders due to iodine deficiency during pregnancy and proposed to increase the recommended intake to 250 µg/day (WHO Secretariat et al., 2007).

The Nordic countries (NNR, 2004) recommended an extra 25 µg/day for pregnant women to cover the needs of the fetus. Thus, the recommended intake was 175 µg/day and was unchanged in the 2012 update of the Nordic Nutrition Recommendations (Nordic Council of Ministers, 2014).

The IOM (2001) set an EAR of 160 µg/day for pregnant women. This was based on studies of the thyroid iodine content of newborns (Delange et al., 1989; Braverman and Utiger, 1991) suggesting a daily thyroid iodine uptake of approximately 75 µg/day by the fetus, on balance studies in full-term

infants (Delange et al., 1984) and pregnant women (Dworkin et al., 1966) suggesting a mean iodine retention of a fetus with a mean weight of 3 kg of about 22 µg/day and a balance observed in pregnant women at about 160 µg/day, and on studies on iodine supplementation during pregnancy (Romano et al., 1991; Pedersen et al., 1993; Berghout and Wiersinga, 1998; Glinoer, 1998). The RDA of 220 µg/day was derived by adding twice a CV of 20 % and rounding to the nearest 10 µg.

The SCF (1993) and the UK COMA (DH, 1991) did not recommend an increment for pregnant women. Therefore, the PRI for pregnancy was the same as for non-pregnant women, i.e. 130 µg/day according to the SCF and 140 µg/day according to the UK COMA. The SCF (1993) considered that, provided the pre-pregnancy iodine intake was adequate, there was no evidence that an increased dietary intake was needed during pregnancy.

4.4.   Lactation

The German-speaking countries (D-A-CH, 2013) considered the amount of iodine secreted in human milk and recommended an intake of 260 µg/day for Germany and Austria, and 200 µg/day for Switzerland.

In 2004, WHO/FAO proposed as RNI the value recommended by WHO/UNICEF/ICCIDD (2001), i.e. 200 µg/day or 3.5 µg/kg body weight per day (WHO/FAO, 2004). A subsequent expert consultation proposed to increase the recommended intake to 250 µg/day (WHO Secretariat et al., 2007).

The Nordic countries (NNR, 2004) recommended an additional supply of 50 µg/day for lactating women to provide sufficient iodine in human milk, thus resulting in a recommended intake of 200 µg/day. In the 2012 update of the Nordic Nutrition Recommendations, this value was kept unchanged (Nordic Council of Ministers, 2014).

For lactating women, the IOM (2001) considered the average daily loss to be 114 µg of iodine in human milk (Gushurst et al., 1984) (considering an average milk volume of 0.78 L/day and an average concentration of 146 µg/L), thus deriving an EAR of 209 µg/day and an RDA of 290 µg/day, considering a CV of 20 % and after rounding to the nearest 10 µg.

The SCF (1993) derived a PRI of 160 µg/day for lactating women to replace iodine losses in milk. The SCF noted that the PRI increase for lactating women was based on the needs of the infant rather than the amount actually secreted in the milk.

The UK COMA (DH, 1991) did not recommend any increment for lactating women; thus the RNI was 140 µg/day as for non-lactating women.

An overview of DRVs for iodine for pregnant and lactating women is presented in Table 3.

Table 3:   Overview of Dietary Reference Values for iodine for pregnant and lactating women

	D-A-CH (2013)	WHO Secretariat et al. (2007)	NNR (2012)	Afssa (2001)	IOM (2001)	SCF (1993)	DH (1991)
Pregnancy (µg/day)	230 (Germany, Austria), 200 (Switzerland)	250	175	200	220	+0, i.e. 130	+0, i.e. 140
Lactation (µg/day)	260 (Germany, Austria), 200 (Switzerland)	250	200	200	290	160	+0, i.e. 140

5. Criteria on which to base Dietary Reference Values

From the data on biomarkers of intake and status (Section 2.4), the Panel concludes that these markers change with iodine intake, but cannot be used as such and in isolation as a basis for setting DRVs for iodine. Other possible criteria include physiological data (such as balance studies, iodine accumulation in the thyroid and iodine requirement for thyroid hormone synthesis) or health consequences of iodine intake.

5.1. Iodine balance

Several balance studies are available in adults (Cole and Curtis, 1935; Vought and London, 1964; Harrison et al., 1965; Malamos et al., 1967; Vought and London, 1967; Harrison, 1968), as well as some in children (Malvaux et al., 1969; Ares et al., 2008) and pregnant women (Dworkin et al., 1966).

Balance studies are based on the assumption that a healthy subject on an adequate diet maintains equilibrium or a null balance between nutrient intake and nutrient losses; at this null balance, the intake perfectly matches the requirement corresponding to the given physiological state of the individual. When intake exceeds losses (positive balance), there is nutrient accretion that may be attributable to growth or to weight gain, anabolism or repletion of stores. When losses exceed intake (negative balance), nutrient stores are progressively depleted resulting, in the medium-term, in biological signs and, in the long term, in clinical symptoms of deficiency. When performed at different levels of intakes, balance studies enable the quantification of basal (or obligatory) losses (i.e. losses that occur with zero intake) by regression to zero. In addition to numerous methodological concerns about the accuracy and precision in the determinations of intake and losses (Baer et al., 1999), the validity of balance studies for addressing requirements has been questioned; they might possibly reflect only either adaptive changes before reaching a new steady state (Young, 1986) or reflect only the conditions for maintenance of nutrient stores in the context of a given diet (Mertz, 1987).

In the case of iodine, these methodological and conceptual limitations are of particular concern for a number of reasons: the iodine content of foods is highly variable resulting in large day-to-day variation, i.e. day-to-day differences of 10 to 90 times (Vought and London, 1964; Malamos et al., 1967); the pre-study status is often not precisely reported, limiting the possibility of extrapolation to habitual intakes in many European countries; high pre-study habitual intakes may lead to overestimate basal losses; sweat losses are generally not taken into account; and the duration of studies is often too short for iodine status to reach a new equilibrium owing to thyroid regulation. In addition, in the absence of measurement of specific markers of thyroid function, it is difficult to relate results of balance studies to thyroid status.

The Panel notes that negative balances are observed in most of the studies in euthyroid subjects, who, despite a low intake, do not display goitre. The Panel also notes that the results of balance studies are highly variable and that balances may be null at very different levels of intakes. The Panel considers that balance studies performed in countries with a higher habitual iodine intake compared with most European countries are difficult to extrapolate to the European context. Taking into account the limitations of balance studies, especially in the case of iodine, the Panel concludes that iodine balance studies cannot be used for setting DRVs, although some of their results may contribute to informing other choices for setting DRVs for iodine.

5.2. Iodine accumulation in the thyroid

To set the EAR in adults, IOM (2001) used the results from two studies on the thyroidal radioiodine accumulation in euthyroid adults (Fisher and Oddie, 1969a, 1969b).

In the first study (Fisher and Oddie, 1969a), 21 healthy euthyroid US adults were given radio-labelled iodine (^{131}I) intravenously. Using a complex study design, mean UI excretion was measured as 411 µg/day, mean thyroid accumulation was 96.5 µg/day and mean thyroid pool size was 14.6 mg. In the second study (Fisher and Oddie, 1969b), similar measurements were conducted in 274 euthyroid US subjects. The (geometric) mean UI excretion was 281 µg/day and the mean thyroid iodine

accumulation was 91.2 µg/day. There was a correlation between thyroid iodine accumulation and iodine intake estimated as UI excretion; the two parameters were positively correlated and the association is described by the following equation (correlation coefficient r = 0.64):

$$\log(\text{iodine accumulation in the thyroid [µg/day]}) = 0.2456 + 0.7001 \times \log(\text{UI excretion [µg/day]}).$$

Similar to medium-term iodine accumulation, short-term iodine capture by the thyroid is down-regulated with increasing intake (generally assessed through UI) and reaches a plateau for intakes above 80–100 µg/day (Bernard et al., 1970; Hooper et al., 1980). In school children, iodine uptake by the thyroid gland was reported to decrease with increasing iodine intake, reaching a plateau at around 20 % (Tovar et al., 1969) or 30 % (Follis et al., 1962) of the administered dose of above 60–80 µg/day calculated from UI excretion. In Europe, down-regulation of iodine uptake by the thyroid has also been documented (Milakovic et al., 2006): iodine uptake in the year 2000 was around 14–30 % (median 21 %) in adults aged 60–65 years having spent their adult lives in a situation of iodine adequacy (UI in 2000: 190 µg/L), whereas the uptake was higher 50 years earlier (median uptake 31 %, range 10–70 %).

The Panel notes that the average iodine accumulation by the thyroid obtained from the two studies of Fisher and Oddie (1969a, 1969b) was measured at an average UI excretion of about 410 and 280 µg/day, respectively; therefore, these results on iodine accumulation do not reflect the European situation. The Panel concludes that the values of 96.5 and 91.2 µg/day for mean iodine accumulation cannot be used for deriving DRVs for the European context.

5.3. Iodine requirement for thyroid hormone synthesis in euthyroid adults

The major part of iodine is released from the thyroid in the form of T4. The production of T4 has been measured in several studies with healthy euthyroid subjects: it was 88.5 ± 11.5 µg/day in eight subjects (Nicoloff et al., 1972), 102 ± 4.9 µg/day in 10 subjects (Chopra, 1976), 77 µg/day (range 66–110) in eight subjects (Kirkegaard et al., 1990) and 75.5 µg/day (range 50–103) in 14 subjects (Bregengard et al., 1987). These hormone production values would require 49–66 µg/day of available iodine.

The production of T3 in healthy euthyroid subjects is lower; values of 27.6 ± 3.99 µg/day (Nicoloff et al., 1972), 33.5 ± 3.7 µg/day (Chopra, 1976), 20 µg/day (Bregengard et al., 1987), 23 µg/day (Cardoso and Rosenthal, 1987), 20 µg/day (Faber et al., 1988), 24.2 µg/day (Gavin et al., 1977) and 34.6 µg/day (24.4–41.2 µg/day) (Kirkegaard et al., 1990) have been reported. The range of average total T3 production therefore would require 20–35 µg/day of available iodine. Part of this T3 is formed from T4 by deiodination in the periphery whilst T3 production in the thyroid gland only accounts for around 20 % of total T3 production. This corresponds to 4–7 µg/day of T3 produced in the thyroid gland or to approximately 2–4 µg of iodine needed to be incorporated.

The Panel concludes that thyroid hormone production in adult euthyroid subjects would require 50–70 µg/day of iodine, to be taken up by the thyroid or released from thyroid stores. According to the equation developed by Fisher and Oddie (1969b) (see Section 5.2), the average daily requirement for thyroid hormone synthesis of 60 µg iodine is associated with an intake leading to a calculated UI excretion of 155 µg/day.

5.4. Factorial approach in adults

The main factor driving iodine requirement is the iodine needed by the thyroid to produce hormones for maintaining an euthyroid state and to ensure an adequate level of iodine stored in the thyroid, to which basal losses from urine, faeces and sweat should be added. In addition, transfer to the fetus and secretion in human milk need to be considered in pregnant and lactating women, respectively.

As noted in the previous section, thyroid hormone production requires 50–70 µg of iodine/day.

Faecal losses comprise unabsorbed iodine from ingested iodine (taking into account the figure of 92 % for absorption efficiency), unabsorbed iodine from the saliva cycle (6 µg/hour in the saliva for usual intakes meeting current recommendations, assuming 92 % absorption efficiency) and undegraded hormones and different metabolites (for which iodine absorption is around 50 %). Faecal losses are highly variable from day to day, with most values being between 10 and 30 µg/day in the study by Vought and London (1964); a median value of 27 µg/day provided by this study may be assumed in the situation of iodine sufficiency.

Urinary losses can adapt to the level of intake within weeks or months (the actual duration depending on the initial iodine status) and, in a steady state, are considered to reflect intake. The Panel notes that the value of 57 µg considered as basal UI excretion by IOM (2001) (obtained by regression to a null intake by Vought and London (1967)) was determined in a population with relatively high iodine intakes (more than adequate according to the terminology of WHO/FAO (2004)). Similarly, basal losses in faeces and urine from the data of Vought and London (1964) probably also represent an overestimation but, being lower and obtained in free-living conditions, they are possibly more reflective of the European situation; in this study of iodine balance, the intercept of losses (urinary + faecal) for a null dietary intake is 41.1 ± 47.5 µg/day for subjects with a wide range of dietary intakes (56–729 µg/day; 50 % of the subjects had iodine intakes above 200 µg/day). The Panel notes that this value was obtained in a population of adults and children.

From the limited number of available data (see Section 2.3.6.3), sweat iodine concentration is relatively constant at a wide range of intakes. At usual iodine intakes, losses in sweat may be around 20 µg/day, assuming an iodine concentration of sweat of 37 µg/L and a sweat volume of 0.5 L/day (Shirreffs and Maughan, 2005; Subudhi et al., 2005).

Assuming a demand of 60 µg iodine/day for thyroid hormone production, a need of 40 µg iodine/day for the sum of urinary and faecal losses, a need of 20 µg iodine/day for sweat losses, and an absorption efficiency of 92 %, an iodine intake of 130 µg/day ((60+40+20)/0.92) would be required to cover the losses and provide iodine for thyroid hormone production. Estimations stem from small-scale studies with rather high CVs (e.g. 13–41 % for hormone production in two studies with 18 subjects (Nicoloff et al., 1972; Chopra, 1976), 18–27 % for sweat losses in two studies with 17 subjects (Suzuki and Tamura, 1985; Mao et al., 2001)).

The Panel concludes that the factorial approach, based on insufficient data on the size of iodine basal losses, and subject to many uncertainties related to the values of the CV and to the extrapolation of the results to the conditions of habitual iodine intakes in Europe, is not suited for the setting of DRVs for iodine for adults in the EU, although it can provide some support to other approaches.

5.5. Iodine intake and health consequences

Iodine deficiency or excess has been linked to various clinical outcomes such as goitre, thyroid cancer or sub-clinical and overt thyroid disorders. At a population level, the association of thyroid disorders with iodine intakes appears to be U-shaped and the range for the lowest prevalence of thyroid disorders could be relatively narrow (Laurberg et al., 2010).

5.5.1. Goitre

Thyroid volume has been recognised as an integrative marker of medium- to long-term iodine status at the population level (see Section 2.4.2.3).

In observational studies, goitre prevalence has been associated with UI excretion. Ascoli and Arroyave (1970) measured UI excretion (µg/day) and thyroid size by palpation in people living in 186 rural localities in Central America between 1965 and 1967. Presence or absence of goitre was assessed using WHO criteria. In each locality, members of approximately 20 randomly selected families were investigated. A total of 21 611 people from 3 712 families were investigated for goitre and the concentrations of iodine and creatinine were measured in a late morning spot urine sample in 3 181

randomly chosen participants. The daily UI excretion was estimated from iodine and creatinine concentrations using an equation correcting for body weight and age- and sex-dependent differences in 24-hour urinary creatinine excretion. The Panel notes that the use of such an equation introduces some uncertainty in the precision and accuracy of the values of daily UI excretion. Goitre prevalence was inversely associated with UI excretion following a sigmoidal curve and, above a UI excretion of 100 µg/day, the prevalence of goitre was below 10 % (the level used to define endemic goitre) in all but one locality. For a UI excretion below 100 µg/day, the disparity in goitre frequency with apparently identical iodine intakes as observed in this study has been explained by other dietary factors (irregular iodine intake, intakes of other essential nutrients, intake of goitrogens) and genetic factors (Laurberg et al., 2010). Delange has pointed out that the threshold of UI excretion of 100 µg/day is also supported by data on 24-hour ^{131}I uptake by the thyroid as well as a thyroidal iodine content within the limits of normal, i.e. 10–20 mg (Delange and Ermans, 1991; Delange, 1994).

During the ThyroMobil project, in 7 599 European school-aged children (6–15 years), normal thyroid volume determined in areas of iodine sufficiency was around 8 mL in 15-year-old boys and girls at the 50th percentile and 16 mL at the 97th percentile. Upper limits of normal thyroid volume were also established as a function of body surface area, calculated from measured body weights and heights (Delange et al., 1997). Goitre was defined as a thyroid volume exceeding the upper limit of normal, expressed in relation to age or body surface area. An inverse non-linear relationship was observed between median UI concentration and goitre prevalence in 57 study sites in 12 European countries and a prevalence of goitre below 5 % was almost systematically observed in all study sites for a UI concentration above 100 µg/L (Figure 1). On the basis of the daily urine volume, it is thus possible to calculate the corresponding iodine intake for the different age groups.
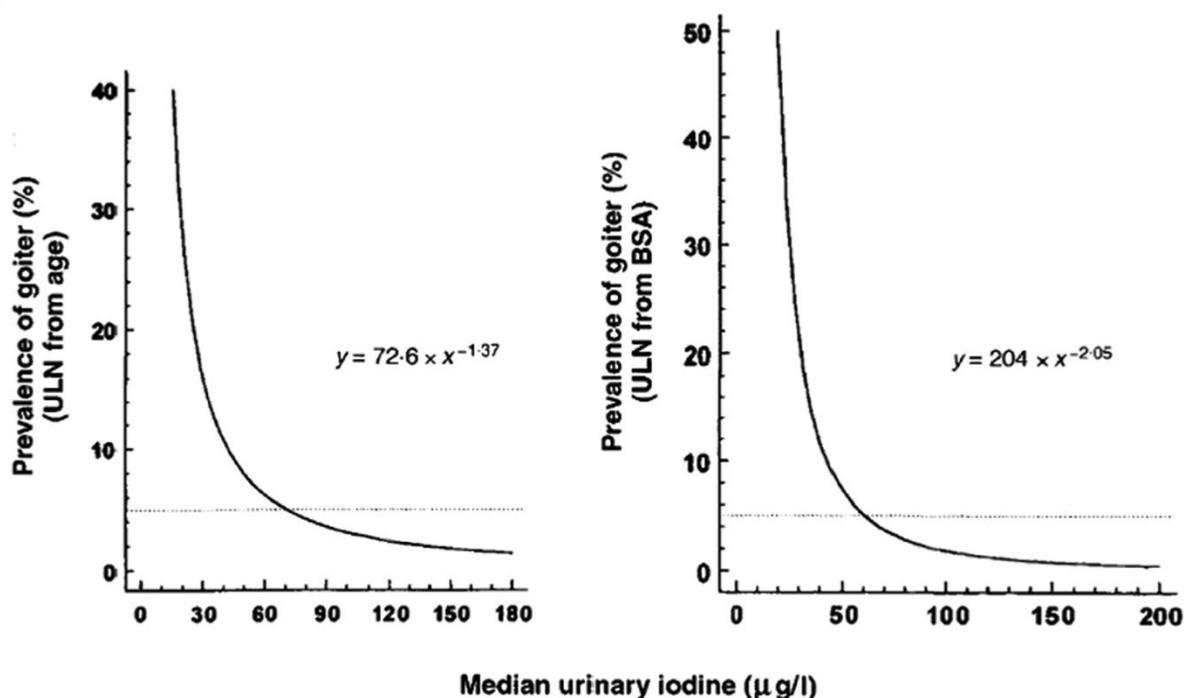
Figure 1: Relationship between urinary iodine concentration and goitre prevalence in school-aged children (adapted from Delange et al., 1997). ULN, upper limit of normal, BSA, body surface area

Subsequently, the threshold value for classification of iodine intakes (into "sufficient" or "insufficient") by population groups other than pregnant women was given as iodine concentration in urine, i.e. 100 µg/L (WHO/UNICEF, 2007a). However, the shift from using a UI excretion of 100 µg/day to a UI concentration of 100 µg/L, for population groups other than school children and pregnant women, as the lower threshold indicating sufficient iodine intake, resulted in an increase in

the recommended iodine intake for many population groups without any real evidence that this was necessary to avoid IDD (Laurberg et al., 2007).

Ristić-Medić et al. (2013) performed several meta-analyses on the relationship between iodine intake and the risk of goitre. Owing to the diversity of measurement methods and expression of the results, as well as the limited duration of the observation/intervention periods contrasting with the time required for observing changes in goitre prevalence in a population (Laurberg et al., 2010), the Panel considers that the pooling of these data in a meta-analysis does not provide a dose-response curve that could be used for deriving DRVs for iodine.

In 65 infants born at term, there was an inverse polynomial relationship between thyroid volumes three months after birth and UI concentrations; infants with a UI concentration above about 150 µg/L had thyroid volumes below 1 mL, whereas thyroid volumes of some infants with lower UI concentrations were up to about 4 mL. The upper limit of normal thyroid volumes is, however, unclear in this age group (Böhles et al., 1993). Chanoine et al. (1991) observed a median thyroid volume of 0.76 mL in 85 euthyroid neonates in an area with a median UI concentration of 97 µg/L and a volume of 1.25 mL for the 90th percentile.

The Panel considers that the prevalence of thyroid volume enlargement in a population can be used to define a threshold of UI excretion (adults) and UI concentration (children) above which the prevalence of abnormal values for thyroid volume is minimised. The Panel notes that the slow modification of this parameter provides a valuable medium- to long-term health outcome in relation to usual iodine intakes at the population level. In comparison with other approaches, where sources of variability and uncertainty are not fully identified and/or controlled for, the major source of uncertainty originates from the estimation of a daily iodine intake from the UI excretion or concentration.

5.5.2. Cognitive function in children

The role of iodine insufficiency in the impaired development of cognitive function, with the most severe form expressed as cretinism (see Section 2.2.2), was recognised a long time ago, and was followed by therapeutic measures using iodine (Anonymous, 1869). Mass prevention of cretinism in areas of severe iodine deficiency has shown that the most efficient prevention was achieved by improving maternal iodine status before pregnancy (Pharoah et al., 1971).

Ristić-Medić et al. (2013) undertook a systematic review of the literature for studies relating iodine intake to cognitive function in children with goitre and/or iodine deficiency; 13 studies (five randomised controlled trials (RCTs), four cross-sectional studies and four nested case-control studies) were selected. In most intervention studies, children aged between 1 and 14 years were given a single dose of iodised oil (400–540 mg), with a follow-up of 4–22 months. Only one study used daily doses of 150 µg/day as tablets of potassium iodide versus placebo, but the intervention lasted 28 weeks and was therefore too short and not relevant for this outcome. Different tests for evaluation of cognitive function were used. The Panel notes that the results from the included RCTs were inconsistent, probably as a result of heterogeneity of the studies and high or moderate risk of bias in most of the included studies. The number of included studies for moderate iodine deficiency was generally small and the studies were methodologically weak. Observational studies in severely iodine-deficient groups (median UI concentration < 20 µg/L) indicated a strong relationship between iodine intake or status and cognitive impairment. Data in infants were unavailable. Due to the existence of many confounding factors and the absence of a clear dose-response relationship, the Panel concludes that data on iodine intake and cognitive function cannot be used to derive DRVs for iodine.

5.5.3. Cancer

According to WCRF/AICR (2007), iodine deficiency (via higher serum TSH concentrations) is a "probable" cause and iodine excess is a "possible" cause of thyroid cancer.

The Panel considers that data on the relationship between iodine deficiency or excess and cancer cannot be used to derive DRVs for iodine.

5.5.4. Sub-clinical thyroid dysfunction

The availability of precise and accurate methods with a high analytical sensitivity allowed the recognition of the existence of sub-clinical thyroid dysfunction characterised by serum concentrations of thyroid hormones within the normal range in the presence of abnormal TSH concentrations; in sub-clinical hypothyroidism, TSH increases to above 5 mU/L, whereas in sub-clinical hyperthyroidism it decreases to below 0.3 mU/L. The prevalence of sub-clinical hypothyroidism is higher (up to more than 15 %) in groups of older adults in most of the surveys addressing this issue. The causes of this high prevalence in the elderly are multiple, and include high iodine intakes: sub-clinical thyroid dysfunction is more prevalent (up to five times) in areas of high iodine intake compared with areas of low intake (Biondi and Cooper, 2008). Although sub-clinical hypothyroidism may be transient in older adults, the risk of evolving to overt hypothyroidism is important in sub-clinical thyroid dysfunction-affected subjects with the highest concentrations of TSH (> 10 mU/L) (Somwaru et al., 2012). Sub-clinical thyroid dysfunction may be associated with an increased risk of cardiovascular disease and mortality (Rodondi et al., 2010), an increased risk of depression (Chueire et al., 2007) or of impaired functional mobility (Simonsick et al., 2009).

The Panel considers that data on iodine intake and prevalence of sub-clinical thyroid dysfunction are insufficient to support the necessity for deriving DRVs specific for older adults.

5.6. Additional iodine requirement for pregnancy

Recent studies of iodine in pregnancy have focused on the relationship of thyroid function (assessed through the determination of maternal hormone concentrations and autoantibodies) to various clinical outcomes rather than on the relationship of these outcomes with iodine intakes and/or status (Gunnarsdottir and Dahl, 2012). In the absence of a clear dose-response relationship between obstetrical or paediatric outcomes and iodine intakes, the requirement during pregnancy may be derived by a factorial approach, taking into account extra needs owing to modification of iodine metabolism during pregnancy and to the development of the fetal thyroid and fetal hormone synthesis. The results of supplementation studies may provide additional information. The definition of reference values implies that iodine status before pregnancy is adequate.

5.6.1. Thyroid function, urinary iodine excretion and clinical outcomes

The prevention of cretinism in areas of severe iodine deficiency has been suggested to be more efficient before conception than during pregnancy (Pharoah et al., 1971), though an increase in iodine intake during the first and second trimester can still have a beneficial impact, contrary to an increase of iodine intake only during the last trimester (Cao et al., 1994).

The relationship between iodine intake of pregnant women (generally assessed through UI concentration or excretion) and various outcomes, such as maternal thyroid function or infants' neurobehavioural impairment and being born small for gestational age, has been investigated in several studies (Alvarez-Pedrerol et al., 2009; Henrichs et al., 2010; Costeira et al., 2011; Karagiannis et al., 2011; van Mil et al., 2012; Bath et al., 2013a; Hynes et al., 2013). The Panel notes that available studies are observational and that most of them do not provide data on pre-pregnancy iodine status. The Panel considers that the information available on the relationship between iodine intake or status of pregnant women and these clinical outcomes cannot be used for setting DRVs for pregnancy.

5.6.2. Supplementation studies during pregnancy

It is well established that iodine supplementation before or during early pregnancy has an impact on cognitive function in the offspring in areas of severe or moderate iodine deficiency (Bougma et al., 2013; Zhou et al., 2013), although the impact of this public health measure in areas of mild deficiency,

as it is still present in Europe, remains to be studied by high-quality intervention studies (Bath et al., 2013b; Rebagliato et al., 2013).

Iodine supplementation during pregnancy is generally effective at minimising an increase in maternal thyroid size in iodine-deficient areas (Pedersen et al., 1993; Glinoer et al., 1995; Berghout and Wiersinga, 1998; Antonangeli et al., 2002; Zimmermann and Delange, 2004; Zimmermann, 2009; Rebagliato et al., 2010; Zimmermann, 2012). However, these studies usually lack important information, such as the iodine status before pregnancy or the total iodine intake of pregnant women. Therefore, the Panel concludes that results from the available supplementation studies cannot be used for setting a DRV for iodine for pregnant women.

5.6.3.   Additional requirement owing to modifications of maternal iodine metabolism

Maternal thyroid hormone production increases during pregnancy because of several physiological adaptations and this is reflected in the need of women on thyroid hormone substitution therapy to increase the dose of thyroxine (by 40–50 % and on average 47 %) to maintain their normal pre-pregnancy concentrations of T4 and TSH during pregnancy (Mandel et al., 1990; Alexander et al., 2004). In the study by Alexander et al. (2004), the average thyroxine dose was 133 µg/day; thus, using the above data, the required increase can be calculated (133 µg/day × 47 %) as 63 µg T4/day. In the study by Kaplan (1992), the extra need for exogenous T4 during pregnancy was 41 µg for women with TSH concentrations below 10 mU/L. Based on these studies, the study by Yassa et al. (2010) used increases in thyroxine doses of 29 % or 43 % and showed that only 3 women out of 48 did not maintain a serum TSH concentration below the upper bound value of 5 mU/L, and thus confirming the validity of the determinations in the previous studies.

The Panel considers that this extra need of exogenous thyroxine of 40–60 µg/day in fully T4-substituted patients may be used to estimate the additional iodine demand for hormone synthesis in pregnancy. Assuming an absorption efficiency of oral thyroxine of around 75 % (see Section 2.3.1), 30-45 µg of T4 would be absorbed with an iodine content of 20-29 µg.

5.6.4.   Additional requirement owing to the development of the fetus, placenta and amniotic fluid

At the beginning of pregnancy, maternal T4 is the only source of hormone for the fetus, and this hormone is required at a very early fetal age for normal corticogenesis in the brain (Morreale de Escobar et al., 2004). Thereafter, iodine supply to the mother and its transfer to the fetus must be adequate to prevent fetal goitre formation (Glinoer et al., 1995), inducing a growing need of iodine for hormone synthesis by the fetal thyroid gland and for storage in the fetal thyroid, placenta and amniotic fluid.

5.6.4.1.   Fetal and neonatal thyroid

The interpretation of studies on neonatal iodine status should take into account the iodine status of the mother and the time elapsed between birth and the biological determinations in the newborn; these characteristics are not always reported and might explain the very different figures provided in the literature. For a similar gestational age (around 30 weeks), thyroid iodine content increases from 60 µg/g (at around 10 hours after birth) to 93 µg/g (at around 30 hours) and 263 µg/g (after more than 10 days) (Etling, 1977); the impact of postnatal age on the characteristics of the neonatal thyroid has been confirmed by Savin et al. (2003).

Costa et al. (1986) measured a thyroid weight of 0.37 g at week 23 and 0.71 g at week 26 that remained practically constant up to term (0.74 g), with an iodine content of 60 µg/g thyroid at term (maximum of 123 µg/g) for a group of 52 newborns having a UI concentration of 64 ± 29 µg/L (the corresponding concentration for the mothers being 74 ± 37 µg/L). For late-preterm and term newborns of 2.5 ± 0.6 kg body weight, Savin et al. (2003) found a thyroid weight of 0.93 ± 0.4 g and an iodine content of 95.5 ± 34.4 µg/g. Higher iodine contents in the thyroid have been reported for countries

with more than adequate maternal iodine intakes, for example around 300 µg in Toronto (UI excretion in adults being 600–800 µg/day) (Delange and Ermans, 1991).

Fetal hormonal synthesis becomes significant at the 12th week of gestation and increases linearly with fetal size up to the 24th gestational week when the postnatal total T4 concentration in serum of around 60 µg/L is reached (Greenberg et al., 1970; Thorpe-Beeston et al., 1991). The theoretical turnover of the intrathyroidal T4 pool in preterm infants born after six months of gestation has been determined (early after birth) to be 1–10 times per day (van den Hove et al., 1999).

The Panel also notes that a thyroid iodine content of 100–300 µg at birth, accumulated during the two last trimesters, would approximately correspond to a net iodine transfer of 1–2 µg/day to the fetal thyroid. Evans et al. (1967) determined that iodine transfer to the fetal thyroid is starting at around three months of gestation and accounts for 1 % of the dose ingested by the mother at six months and for 2 % at nine months. Iodine uptake by the thyroid reached a maximum of 5 % of the dose consumed by the mother per gram of thyroid tissue at six months of gestation, which suggests that iodine turnover of the fetal thyroid is rather low. The iodine uptake by the thyroid of the mothers was in the range of 10–35 %, indicating a near-to-adequate iodine status. Contrary to some other mammals, the human fetus does not concentrate iodide (Rayburn et al., 2008).

In fetal blood, T4 is the prominent form. According to Thorpe-Beeston et al. (1991), total T4 is on average 77 µg/L in the fetus at 36 weeks of gestation; the postnatal serum total T4 concentration of a term newborn is around 120 µg/L, corresponding to a total amount of organic iodine in serum of around 10 µg,[9] part of which (up to 40 %, Vulsma et al. (1989)) is from maternal hormone, which has already been considered in Section 5.6.3.

5.6.4.2. Placenta and amniotic fluid

The placenta traps maternal serum iodide through the Na/I symporter, the expression of which remains constant during pregnancy, suggesting no specific adaptation through this symporter (Di Cosmo et al., 2006). The placenta has an iodine content of 30 ng/g compared with the content of below 2 ng/g for the myometrium. Uptake and storage by the placenta are dependent on maternal iodine intake (Burns et al., 2011b); a total storage capacity of around 18 to 100 µg iodine could play a significant role in fetal iodine economy (Burns et al., 2011a).

Amniotic fluid also contains iodine and its concentration is weakly correlated with maternal UI excretion (r = 0.11); the concentration of iodine in amniotic fluid has been reported to be around 15 µg/L in an area with median UI concentrations of 118 µg/L and to be independent of the ingestion of iodine supplements (Garcia-Fuentes et al., 2008). Considering a volume of amniotic fluid of around one litre at 32–36 weeks of gestation (Queenan et al., 1972), the impact on the maternal requirement for iodine can be considered as negligible.

5.6.5. Conclusions on additional iodine requirement for pregnancy

The total amount of iodine deposited in the placenta (18–100 µg), amniotic fluid (15 µg), fetal thyroid (100–300 µg) and fetal blood (10 µg) is very low when related to the whole pregnancy (equivalent to a net transfer of 1 µg/day). The main additional requirement seems, therefore, to be the result of the increased synthesis of thyroid hormones by the mother, corresponding to a need for an additional iodine capture by the thyroid of 25 µg/day. Assuming that the equation of Fisher and Oddie (1969b) derived in non-pregnant adults remains valid in pregnancy (see Section 5.2), this amount may be accumulated in the thyroid by an additional iodine intake of 44 µg/day. In addition, the iodine needed for fetal synthesis of thyroid hormones, which is likely to be low considering the limited iodine

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[9] 3.25 kg [mean weight of newborn boys and girls at 50th percentile (WHO Multicentre Growth Reference Study Group, 2006)] × 8 % [proportion of body weight as blood (Usher et al., 1963)] equals 0.26 kg or about 260 mL, corresponding to around 135 mL of serum at a haematocrit of 48 % according to Usher et al. (1963). Assuming a serum total T4 concentration of 120 µg/L, the amount of T4 in 135 mL of serum is about 16 µg. As the iodine content in T4 is 65 %, an iodine content of 10 µg can be calculated.

transfer to the fetal thyroid gland of around 2–4 µg/day (Evans et al., 1967), leads to a total additional iodine intake rounded up to 50 µg/day.

The Panel concludes that the many physiological regulations taking place during pregnancy lead to an increase in iodine requirement during gestation of around 50 µg/day, provided that thyroid status and iodine stores before pregnancy are adequate.

5.7.   Additional iodine requirement for lactation

Breast milk iodine concentrations are more a reflection of maternal iodine intake than of the infant's needs (see Section 2.3.6.4).

Azizi and Smyth (2009) reported a linear relationship between breast milk iodine concentration and maternal UI concentration in the range of 50–400 µg/L, although the correlation coefficient in a cohort of 142 lactating women was relatively low (r = 0.40). In 127 lactating women in Denmark, the correlation between UI concentration ranging from about 8-400 µg/L and milk iodine concentration was r = 0.28. In these lactating women either taking (n = 60) or not taking (n = 67) iodine supplements, median iodine concentration in mature breast milk was 112 µg/L in supplemented women with a median UI excretion of 87 µg/day and it was 72 µg/L in unsupplemented women with a UI excretion of 60 µg/day (Andersen et al., 2014).

In conditions of adequate iodine stores in the thyroid (10–15 mg), iodine stores would theoretically allow several months of iodine secretion in milk. In conditions of maternal iodine deficiency, the iodine secretion in milk can lead to thyroid stimulation in the mother as evidenced by modifications of thyroid markers (TSH, thyroid hormones, Tg, thyroid volume). Without changes in iodine intake, these modifications can be reversed 6 to 10 months after delivery, although the reversibility of thyroid volume may only be partial within this timeframe (Glinoer et al., 1992; Eltom et al., 2000). The Panel notes the existence of large physiological iodine stores in conditions of adequate iodine status before pregnancy and lactation.

6.   Data on which to base Dietary Reference Values

The Panel considers that thyroid volume/prevalence of goitre is an integrative marker of medium- to long-term iodine status of a population, for which a large database collected in males and females with very different iodine intakes is available. Moreover, this marker is insensitive to short-term modifications of iodine intake, and thus eliminates many sources of variability and uncertainties inherent in short-term metabolic or balance studies. The Panel selected this association as the basis for deriving DRVs for iodine. From the available evidence and taking into account the inherent uncertainties the Panel considers that it is not possible to derive an AR and a PRI and instead decided to set an AI. The values obtained using other criteria appear to support the proposed AI. From the data available, there is no indication that iodine requirements differ by sex.

6.1.   Adults

At population level, a UI excretion of 100 µg/day or higher was associated with a goitre prevalence of up to 10 % in Central America in the 1960s. During steady state more than 90 % of dietary iodine is excreted in the urine (see Section 2.3.6.1); thus, it can be calculated that a daily UI excretion of 100 µg/day is equivalent to an iodine intake of 110 µg/day. The Panel notes that this threshold implies that up to 10 % of the population may still develop goitre, possibly resulting from iodine deficiency, and that this approach may underestimate the iodine needs of up to 10 % of the population.

For the population of school-aged children, a UI concentration of 100 µg/L or higher has been shown to be associated with the lowest prevalence of goitre (see Section 5.5.1). Although this threshold concentration has been established in school-aged children, the Panel also accepts it for adults. A UI concentration of 100 µg/L corresponds to an approximate iodine intake of 150 µg/day in adults (Laurberg et al., 2007).

This is based on an average daily urinary volume of 1.5 L, which can be achieved by the AI for water for adults (EFSA NDA Panel, 2010).

The Panel considers that an AI for iodine for adult men and women can be set at 150 µg/day.

The Panel notes that other approaches, such as the approach based on thyroid hormone production and the factorial approach (Sections 5.3 and 5.4), support this value.

6.2. Infants and young children

For infants below one year of age, data on goitre prevalence in relation to iodine intake or UI excretion or concentration are unavailable.

Accepting the threshold for UI concentration of 100 µg/L (see Section 5.5.1) also for infants and taking into account a urinary volume of 637 mL/day based on a daily urine volume of 74.1 mL/kg body weight measured in 15 normal infants aged 6–12 months (Goellner et al., 1981) and a median body weight of 8.6 kg at nine months of age according to the WHO Multicentre Growth Reference Study Group (2006), a necessary iodine intake of 70 µg/day can be calculated (see Table 4). The Panel considers that the AI for iodine for infants is 70 µg/day.

Accepting the threshold for UI concentration of 100 µg/L also for young children and taking into account a urinary volume of 827 mL/day (average urinary volume of 69.5 mL/kg body weight per day for children aged 12–32 months according to Goellner et al. (1981)) and a median body weight of 11.9 kg at two years of age according to the WHO Multicentre Growth Reference Study Group (2006), a necessary iodine intake of 90 µg/day can be calculated (see Table 4). The Panel considers that the AI for iodine for young children is 90 µg/day.

Table 4: Reference body weight, urinary volume and Adequate Intake for iodine for infants and young children

Age	Average body weight (kg)	Urinary volume (mL/kg bw per day)	Urinary volume (L/day)	Calculated iodine intake (µg/day) [a]	AI (µg/day)
7–11 months	8.6 [b]	74.1	0.637	69.2	70
1–3 years	11.9 [c]	69.5 [d]	0.827	89.9	90

(a): Taking into account a threshold UI concentration of 100 µg/L and 92 % absorption efficiency according to the formula:

$$\text{Theoretical daily iodine intake [µg/day]} = (100 \text{ µg/L} \times \text{urinary volume [L/day]})/0.92.$$

(b): Mean of body weight for age at 50th percentile of male and female infants aged nine months (WHO Multicentre Growth Reference Study Group, 2006).
(c): Mean of body weight for age at 50th percentile of boys and girls aged 24 months (WHO Multicentre Growth Reference Study Group, 2006).
(d): Mean of volumes for three age groups, i.e. 80.6 mL/kg per day (12–18 months), 66.2 mL/kg per day (18–24 months) and 61.7 mL/kg per day (24–32 months) (Goellner et al., 1981).
bw, body weight.

6.3. Children

For children, a large study in European boys and girls aged 6–15 years found a wide range of median UI concentrations in groups living in regions with very different iodine environments (medians of UI concentrations ranging from 20 to 140 µg/L). The UI concentration at which goitre prevalence in this population was at 2–3 % was about 100 µg/L (Delange et al., 1997) (see Section 5.5.1). Taking into account urinary volume and iodine absorption efficiency, this concentration can be converted into an AI for children between 6 and 15 years of age. In the absence of data for children below six years or above 15 years of age, the same approach is chosen. Despite a large variability, the median urinary flow in this large age group is around 0.9 mL/hour per kg body weight (21.6 mL/day per kg body weight), being higher (around 1.4 mL/hour per kg body weight or 33.6 mL/day per kg body weight) for the youngest and lower (around 0.8 mL/hour per kg body weight or 19.2 mL/day per kg body

weight) for the oldest children (Mattsson and Lindstrom, 1995). The calculations using these urinary flows and reference body weights for European children (van Buuren et al., 2012) are shown in Table 5. Calculated daily urinary volumes are in line with 24-hour urine volumes observed in a cohort of 293 children aged 4–6 years and of 326 children aged 7–10 years (Montenegro-Bethancourt et al., 2013).

Table 5: Reference body weight, urinary volume and Adequate Intake for iodine for children

Age (years)	Average body weight (kg)	Urinary flow (mL/hour per kg bw) [a]	Calculated urinary volume (L/day)	Calculated iodine intake (µg/day) [b]	AI (µg/day)
4–6	19.0 [c]	1.4	0.638	69.4	90 [d]
7–10	28.7 [e]	1.2	0.827	89.8	90
11–14	45.7 [f]	1.0	1.097	119.2	120
15–17	60.3 [g]	0.8	1.157	125.8	130

(a): Estimated from the curve established by Mattsson and Lindstrom (1995), for ages defined in notes (e)–(g), and extrapolated from this curve for age five years.

(b): Taking into account a threshold UI concentration of 100 µg/L and 92 % absorption efficiency according to the formula:

$$\text{Theoretical daily iodine intake [µg/day]} = (100\ \text{µg/L} \times \text{urinary volume [L/day]})/0.92.$$

(c): Mean of body weight at 50th percentile of boys and girls aged five years (van Buuren et al., 2012).

(d): As there is no reason to assume that iodine needs are lower for this age group, the same AI is proposed as for the neighbouring age groups.

(e): Mean of body weight at 50th percentile of boys and girls aged 8.5 years (van Buuren et al., 2012).

(f): Mean of body weight at 50th percentile of boys and girls aged 12.5 years (van Buuren et al., 2012).

(g): Mean of body weight at 50th percentile of boys and girls aged 16 years (van Buuren et al., 2012).

bw, body weight.

6.4. Pregnancy

The factorial approach takes into account the AI in the pre-pregnant state (based on thyroid size and supported by other considerations, see Section 6.1) and the additional needs owing to increased thyroid hormone production during pregnancy and the iodine uptake by the fetus, placenta and amniotic fluid, which amount to 50 µg/day (see Sections 5.6.3 to 5.6.5). The Panel proposes to set an AI at 200 µg/day.

6.5. Lactation

The Panel notes that iodine concentrations in breast milk of European women differ widely. The Panel also notes that the SCF (2003) considered daily iodine losses with breast milk of 60 µg/day, assuming an average iodine concentration of 75 µg/L and a breast milk volume of 0.8 L/day, and that one study showed that women with a median UI excretion of 87 µg/day, and thus below the threshold of 100 µg/day, had a median breast milk iodine concentration of 112 µg/L (Andersen et al., 2014). Assuming an average milk volume of 0.8 L/day (Butte et al., 2002; FAO/WHO/UNU, 2004; EFSA NDA Panel, 2009), iodine losses with breast milk in these women would amount to 90 µg/day. The Panel notes the existence of large iodine stores in conditions of adequate iodine status before pregnancy and lactation and considers that a full compensation of the transitory loss of iodine secreted in breast milk is not justified for the derivation of DRVs for iodine for lactating women. The Panel therefore considers that the AI for lactating women is the same as for pregnant women, i.e. 200 µg/day.

CONCLUSIONS AND RECOMMENDATIONS

CONCLUSIONS

The Panel concluded that there is insufficient evidence to derive an AR and a PRI for iodine. Data on the relationship between iodine intakes and UI excretion in population groups without signs of thyroid dysfunction evidenced by a minimal prevalence of goitre were used to set an AI (Table 6). For adults and children, the AI is based on iodine intakes ensuring a UI concentration which has been associated with the lowest prevalence of goitre in school-aged children (≥ 100 µg/L). For children, age-specific urinary volumes and absorption efficiency of dietary iodine were taken into account to calculate the AI. It was considered unnecessary to give sex-specific values. An AI is also proposed for infants and young children based on the UI concentration which has been associated with the lowest prevalence of goitre in school-aged children. For pregnancy, a factorial approach was used, assuming that iodine intake is adequate before pregnancy. For lactation, the existence of large iodine stores in conditions of adequate iodine status was noted and it was considered that a full compensation of the transitory loss of iodine secreted in breast milk is not justified. Therefore, the same AI as in pregnant women was set.

Table 6: Summary of Adequate Intakes for iodine

Age	Adequate Intake (µg/day)
7–11 months	70
1–3 years	90
4–6 years	90
7–10 years	90
11–14 years	120
15–17 years	130
$\geq$ 18 years	150
Pregnancy	200
Lactation	200

RECOMMENDATIONS FOR RESEARCH

The Panel suggests that studies be undertaken on iodine requirements in all population groups, especially in pregnancy, lactation and infancy, relating iodine intakes to thyroid morphology and function and health outcomes more directly.

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APPENDICES

Appendix A.   Iodine concentration of human milk from healthy mothers of term infants in Europe

Reference	Number of women (n of samples)	Country	Total maternal intake		Stage of lactation	Iodine concentration (µg/L)			Information on iodine intake
			Measurement	Value		Mean ± SD	Median	Range (µg/L)	
Andersen et al. (2014)	67 (unsupplemented)	Denmark	Median (IQR) UI excretion (µg/day)	60 (44–83)	29 days		72	47–87 (IQR)	No information on the nature of supplementation and its duration
	60 (iodine-supplemented)			87 (55–144)	34 days		112	80–154 (IQR)	
Heidemann et al. (1986)	60	Sweden	Median (range) UI excretion (µg/g creatinine)	91.8 (34.5–316.1)	4–6 days		92.5	35–330	Healthy mothers under dietary iodine supplementation (no further information as to supplemented amounts etc.)
	41	Germany		32.6 (10.7–300)			25	12–195	
Costeira et al. (2009)	78	Portugal	Median (IQR) UI excretion (µg/L)	35 (15–98)	3 days		95	68–143 (IQR)	No women reported the use of iodine supplements or of iodised salt
	52			50 (28–84)	3 months		70	50–102 (IQR)	
Bader et al. (2005) [a]	12	Germany	Mean (µg/day)	116	1–10 days	184 ± 84	176		Iodised salt available and its use was promoted in the past
Kurtoglu et al. (2004)	70 (70)	Turkey	Not reported		5 days		73	9.50–355.6	Table salt is iodised but not industrial salt (it states that most families consume industrial salt)
Gokmen and Dagli (1995)	25	Turkey	Not reported		1–2 days	109 ± 50		45–208	No information on intake/ supplementation/iodised salt
Nohr et al. (1994) [a]	(20) (22) (16) (15)	Denmark	Not reported		5 days 5 days 5 days 5 days		54.0 36.0 54.5 28.7	12–117 7–89 19–178 9–39	No mention of iodisation but 36 % of mothers surveyed took supplements (not included in this table)
Böhles et al. (1993)	(10) (21)	Germany	Not reported		5–7 days 1 week 3 months	55 ± 19	37 125	20–88	None taking additional iodine supplements. No information on iodised salt

Reference	Number of women (n of samples)	Country	Total maternal intake		Stage of lactation	Iodine concentration (µg/L)			Information on iodine intake
			Measurement	Value		Mean ± SD	Median	Range (µg/L)	
Chierici et al. (1999)	10 (10)	Italy	Not reported		3 days 1 month 3 months	270 ± 140 150 ± 90 110 ± 40			No information on iodised salt. Dietary intake only reported for non-supplement and supplement users (the latter not included in this table)
Etling et al. (1986) [b]	(79)	Italy	Not reported		0–1 month	43.5 ± 2.5 [c]			No information on intake/supplementation/iodised salt
Etling and Gehin-Fouque (1984)	(68)	France	Not reported		Mature	81.6 ± 5.0 [c]			Young healthy women on an equilibrated diet (intake not given). No information on supplementation/iodised salt
Etling et al. (1983)	(77)	Italy	Not reported		1–28 days 1 day 5 days 16–52 days	54.0 ± 6.9 [c] 53.3 53.3 53.3–54.0			No information on intake/supplementation/iodised salt
Lahesmaa and Vilkki (1960)	42 (107) 18 (18)	Finland	Not reported		Not reported	53.3 ± 1.4 25.1 ± 1.6			The use of iodised salt was equally common in Turku and in Kuopio (~ 90 %). Kuopio (the second set of values) was an area where the incidence of endemic goitre was higher than the mean incidence for Finland. No information on supplementation

(a): Non-supplemented women only.
(b): Gestational age 37–42 weeks only.
(c): Mean ± standard error of the mean.
UI, urinary iodine; IQR, interquartile range.

Appendix B.   Urinary iodine concentrations in the European Union

The table below has been adapted from supplemental material by Andersson et al. (2012); VMNIS (online). The median UI concentration (µg/L) in school-aged children (6–12 years) in nationally representative surveys has been used to classify a population's iodine status (WHO/UNICEF/ICCIDD, 2007; Andersson et al., 2012). Hence, preference was given to studies carried out in school aged-children. In the review by Andersson et al. (2012), only surveys with a cross-sectional population-based sample frame were included, which used standard UI concentration assay techniques and reported at least on the following criteria: median and/or mean UI concentration (µg/L), prevalence of inadequate iodine intake, proportion (%) of the population with UI concentration < 100 µg/L, UI concentration distribution (proportion of the population within the categories < 20, 20–49, 50–99, 100–199, 200–299 and ≥ 300 µg/L). No data are available for Malta.

Country	Survey date	Survey level	Population group	Age range (years)	Sex	n	Median UIC (µg/L)	% with UIC < 100 µg/L	95 % CI	References
Austria	2000	Local (Carinthia)	Adults	NA	Men and women	430	191	21.4 [a]	17.6–25.3	Lind et al. (2002) [b]
Belgium	2010–2011	National	School-aged children	6–12	Boys and girls	1 507	113.1	39.4	36.9–41.9 [d]	Vandevijvere et al. (2012)
Bulgaria	2008	National	School-aged children	7–11	Boys and girls	355	182	11.2	7.9–14.5	Kovatcheva et al. (2011) [b]
Croatia	2009	National	School-aged children	6–10	Boys and girls	386	248	22.3	18.1–26.5	Kusic et al. (2012)
Cyprus	NA (published 2000)	Regional	School-aged children	9–10	Boys and girls	625	120	41.3 [a]	37.5–45.2	Erdogan et al. (2000) [b]
Czech Republic	2010	National	School-aged children	NA	Boys and girls	1 770	163	13.4	11.8–15.0	Zamrazil (2011) [b]
Denmark	2004–2005	Local	Adults	18–65	Men and women	3 554	101	48.1 [a]	46.5–49.8	Rasmussen et al. (2008) [b]
Estonia	1995	National	School-aged children	8–10	Boys and girls	1 840	65	67	64.9–69.1	Veinpalu et al. (1996) [b]
Finland	1997	Local	Adults	30–42	Men and women	342	164	28.3 [a]	23.5–33.0	Valsta et al. (2003) [b]
France	2006–2007	National	Adults	18–74	Men and women	1 867	136	33.2 [a]	31.1–35.3	Castetbon et al. (2009); Drees (2011) [b]

Country	Survey date	Survey level	Population group	Age range (years)	Sex	n	Median UIC (µg/L)	% with UIC < 100 µg/L	95 % CI	References
Germany	2003–2006	National	School-aged children	6–12	Boys and girls	6 635	122	38.8	37.6–40.0	Thamm et al. (2007) [b]
Greece	2001	Local	School-aged children and adolescents	12–18	Boys and girls	302	202	0	0–0	Zois et al. (2003) [b]
Hungary	1994–1997	National	School-aged children	7–11	Boys and girls	2 814	80	57.2 [a]	55.3–59.0	Farkas et al. (1997) [b]
Ireland	1999	Local	Adults	22–61	Men and women	132	82	56.2 [a]	47.7–64.7	Smyth (2002) (unpublished) [b]
Italy [e]	1999–2009	Regional, Local	School-aged children	NA	Boys and girls	4 911	96 [a]	50.2 [a]	48.8–51.6	Rapa et al. (1999b); Rapa et al. (1999a); Busnardo et al. (2003); Saggiorato et al. (2004); Marino et al. (2006); Saggiorato et al. (2006); Bonofiglio et al. (2009); Mazzarella et al. (2009) [b]
Latvia	2000	National	School-aged children	8–10	Boys and girls	599	59	76.8	73.4–80.2	Selga et al. (2000) [b]
Lithuania	1995	National	School-aged children	NA	Boys and girls	2 087	75	59.7 [a]	57.5–61.8	IDD Newsletter (2000) [b]
Luxembourg	2002	National	School-aged children	12–14	Boys and girls	498	148	32.7 [a]	28.6–36.8	Ministère de la Santé and Direction de la Santé (2002) [b]
Netherlands	1995–1996	Local	School-aged children and adolescents	6–18	Boys and girls	937	154	30.9 [a]	27.9–33.8	Wiersinga et al. (2001) [b]
Poland	2009–2011	Sub-national	School-aged children	6–12	Boys and girls	1 589	112	55	52.6–57.4	Szybinski (2011) [b]
Portugal	2010	National	School-aged children	NA	Boys and girls	3 680	105.5	47.1	45.5–48.7 [d]	Limbert et al. (2012)
Romania	2004–2005	National	School aged-children	6–7	Boys and girls	2 327	102	46.9	44.9–48.9	Alfred Rusescu Institute for Mother and Child Care (2005) [b]
Slovakia	2002	National	School aged-children	6–12	Boys and girls	1 744	183	15	13.3–16.7	Kostalova (2003) [b] (unpublished)

Country	Survey date	Survey level	Population group	Age range (years)	Sex	n	Median UIC (µg/L)	% with UIC < 100 µg/L	95 % CI	References
Slovenia	2003–2005	National	Adolescents	15–16	Boys and girls	2 464	140	23.5	21.8–25.2	Kotnik et al. (2006) [b]
Spain [e]	2000–2010	Local, district, state	School aged-children	NA	Boys and girls	7 314	141 [a]	34.8 [a]	33.7–35.9	Madueno Caro et al. (2001); Serra-Prat et al. (2003); Delgado et al. (2004); Santiago-Fernandez et al. (2004); Santiago et al. (2005); Zubiaur Cantalapiedra et al. (2007); Capdevila Bert et al. (2010) [b]
Spain	2009–2010	National	Adults	NA	Men and women	5 072 (total), 4 383 (with urine sample)	117.2			Soriguer et al. (2012)
Sweden	2006–2007	National	School-aged children	6–12	Boys and girls	857	125	30	26.9–33.1	Andersson et al. (2009) [b]
United Kingdom	2009	National	Adolescents	14–15	Girls	737	80.1	68.8	64.9–72.7	Vanderpump et al. (2011) [b]

(a): Data missing from the original study report and calculated by Andersson et al. (2012).
(b): Cited in Andersson et al. (2012).
(c): VMNIS (online).
(d): Calculated values (not in the original paper).
(e): Estimate based on pooled survey data (Andersson et al., 2012).
NA, not available; UIC, urinary iodine concentration; CI, confidence interval.

ABBREVIATIONS

Afssa	Agence française de sécurité sanitaire des aliments
AI	Adequate Intake
AR	Average Requirement
bw	Body weight
CI	Confidence interval
COMA	Committee on Medical Aspects of Food Policy
CV	Coefficient of variation
D-A-CH	Deutschland-Austria-Confoederatio Helvetica
DIT	Di-iodotyrosine
DRV	Dietary Reference Value
EAR	Estimated Average Requirement
EC	European Commission
EFSA	European Food Safety Authority
EU	European Union
FAO	Food and Agriculture Organization
fT4	Free thyroxine
ICCIDD	International Council for the Control of Iodine Deficiency Disorders
IDD	Iodine deficiency disorders
IOM	U.S. Institute of Medicine of the National Academy of Sciences
IQR	Interquartile range
LRNI	Lowest Reference Nutrient Intake
LTI	Lowest Threshold Intake
MIT	Mono-iodotyrosine
NNR	Nordic Nutrition Recommendations
PRI	Population Reference Intake
RCT	randomised controlled trial
RDA	Recommended Dietary Allowance

RNI	Recommended Nutrient Intake
rT3	reverse T3, or 3,3',5'-triiodothyronine
SCF	Scientific Committee for Food
T3	Triiodothyronine or 3,5,3′-triiodothyronine
T4	Thyroxine or 3,5,3′,5′-tetraiodothyronine
TBG	Thyroxine-binding globulin
Tg	Thyroglobulin
TPO	Thyroid peroxidase
TRH	Thyrotropin-releasing hormone
TSH	Thyroid-stimulating hormone, or thyrotropin
TTR	Transthyretin (pre-albumin)
UI	Urinary iodine
UIC	Urinary iodine concentration
UL	Tolerable Upper Intake Level
UNICEF	United Nations Children's Fund
WHO	World Health Organization